Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Inactivated High-dose Trivalent Influenza Vaccine

Proprietary Product Name: Fluzone High-Dose

Sponsor: Sanofi-Aventis Australia

July 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AESI	Adverse Event of Special Interest
CDC	United States Centres for Disease Control and Prevention
GMT	Geometric Mean Titre
HA	Haemagglutinin component of the influenza virus capsule
HAI	Haemagglutinin Inhibition Test for the presence of antibodies against HA
IIV	Inactivated influenza vaccine
NIP	National Immunisation Program
SAE	Serious Adverse Event
SOC	System Organ Class
WHO	World Health Organisation

I. Introduction to product submission

Submission details

Type of submission:	New biological entity/New vaccine
Decision:	Approved
Date of decision:	20 December 2017
Date of entry onto ARTG:	21 December 2017
ARTG number:	285932
Active ingredients:	Inactivated high-dose trivalent influenza vaccine (split virion) containing a total of 180 µg haemagglutinin per 0.5 mL, comprised of the following: · 60 µg Type A/H1N1 like strain haemagglutinin; · 60 µg Type A/H3N2 like strain haemagglutinin; · 60 µg Type B-strain haemagglutinin (from Victoria or Yamagata lineages)
Product name:	Fluzone High-Dose
Sponsor's name and address:	Sanofi-Aventis Australia Talavera Road Macquarie Park NSW 2113
Dose form:	Solution for Injection
Strength:	0.5 mL
Container:	Pre-filled syringe without needle
Pack size:	Single-dose
Approved therapeutic use:	*Fluzone High-Dose is indicated 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 and older.*
Route of administration:	Intramuscular (IM)
Dosage:	Fluzone High-Dose should be administered as a single 0.5 mL injection by the intramuscular route in adults 65 years of age and older.

Product background

This AusPAR describes the application by the sponsor to register a new biological entity, Fluzone High-Dose. Fluzone High-Dose is an inactivated high-dose trivalent influenza vaccine (split virion) containing 180 µg of influenza virus haemagglutinin per 0.5 mL of solution in the form of a pre-filled syringe. It is proposed to be used for the prevention of

influenza in persons aged 65 years and above. The proposed dosing regimen involves the intramuscular (IM) administration of one 0.5 mL injection as a single dose.

Fluzone High-Dose is an inactivated split-virus vaccine containing three influenza virus components (TIV): two type A strains (subtypes H1N1 and H3N2) and one type B strain (from the Victoria or Yamagata lineages). Fluzone High-Dose contains 60 µg haemagglutinin (HA) of each of the three virus strains for a minimum of 180 µg of HA. This can be compared to 15 µg HA per strain in standard adult presentations. In Australia a quadrivalent inactivated influenza virus (split virion) is registered as FluQuadri, corresponding to Fluzone Quadrivalent approved in the United States (US).

While vaccination in the elderly is associated with a reduced rate of complications from influenza infection, this group has a lower rate of developing protective immunity when compared with younger adults. It has been estimated that the efficacy of influenza vaccines in adults > 65 years of age living in the community is only 43% when high levels of virus are circulating, compared to about 60% in younger adults.

Fluzone High-Dose is designed to enhance immune responses to influenza vaccines through higher HA antigen content in the elderly population and therefore reduce the disease burden.

Regulatory status

There are no forms of Fluzone High-Dose currently registered in Australia. One similar product called FluQuadri is registered on the ARTG. The 3 antigens included in Fluzone High-Dose are the same drug substances used in the manufacture of FluQuadri, inactivated quadrivalent influenza vaccine (ARTG Entry 213963).

Fluzone High-Dose was registered in the US and Canada in December 2009 and September 2015 respectively. The approved indications in these jurisdictions are:

> US: *'Fluzone High-Dose is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in the vaccine'.*
>
> Canada: *'Fluzone High-Dose is indicated for active immunization against influenza caused by the specific strains of influenza virus contained in the vaccine in adults 65 years of age and older'.*

The sponsor has not noted any other submissions to regulatory agencies.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Description	Date
Submission dossier accepted and first round evaluation commenced	31 March 2017
First round evaluation completed	31 August 2017
Sponsor provides responses on questions raised in first round evaluation	29 September 2017
Second round evaluation completed	27 October 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 November 2017
Sponsor's pre-Advisory Committee response	14 November 2017
Advisory Committee meeting	29 November 2017
Registration decision (Outcome)	20 December 2017
Completion of administrative activities and registration on ARTG	21 December 2017
Number of working days from submission dossier acceptance to registration decision*	162

*Statutory timeframe: 255 working days.

III. Quality findings

Drug substance (active ingredient)

Fluzone High-Dose is clear and slightly opalescent liquid that contains a zonal purified, sub-virion sterile suspension of the three strains: two type A strains (subtypes H1N1 and H3N2) and one type B strain (from the Victoria or Yamagata lineages). Fluzone High-Dose is formulated to contain 180 µg HA per 0.5 mL dose, in the ratio of 60 µg HA of each of the three strains. This vaccine contains three times more HA (180 µg HA) than the standard vaccine dose (60 µg HA).

There are number of similarities between the proposed product Fluzone High-Dose (also referred as Fluzone High-Dose) and the existing quadrivalent influenza vaccine (QIV) FluQuadri, many of which related to the manufacture of the drug substance. As Fluzone High-Dose contains three strains, it is also referred as trivalent high-dose influenza vaccine (TIV HD).

Structure

The drug substance is comprised of formaldehyde inactivated partially split viral particles propagated in embryonated chicken eggs. The influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is chemically disrupted using a non-ionic surfactant, Triton X-100, to produce a partially split virus, then split virus is further purified by diafiltration against phosphate buffered saline (PBS). The structure information is same for Fluzone High-Dose and QIV.

Physical and chemical properties

The drug substance is a clear colourless to opalescent liquid with a pH range of 7.3 to 7.9. Routinely monitored impurities are: formaldehyde, bioburden and endotoxin. Hydrocortisone is used during the inoculations stage of B strains and is removed by the downstream manufacturing process. Testing for hydrocortisone is conducted for the first five B strain lots produced each season.

Fluzone High-Dose differs from QIV in two aspects in this section:

1. General Description: Updated pH range from 6.9 to 7.4 to 7.3 to 7.9; and
2. Impurities: Triton X-100 is removed as an impurity but is categorised as an excipient.

Overall, supplied data is satisfactory and there are no further quality related concerns pertaining to this issue.

All analytical procedures have been validated.

There are no issues pertaining to the specifications.

Drug product

The following table (Table 1) summarises the ingredients in the drug product.

Table 1: Drug product

Active ingredients	Quantity/0.5 mL dose	Role in Formulation	Standards
Influenza drug substance without gelatin/pool (H1N1 strain)	60 µg	Active ingredient	WHO recommendations for strain
Influenza drug substance without gelatin/pool (H3N2 strain)	60 µg	Active ingredient	WHO recommendations for strain
Influenza drug substance without gelatin/pool (B strain)	60 µg	Active ingredient	WHO recommendations for strain

Proposed shelf life

Information provided in the first and second evaluation rounds supports the following stability of Fluzone High-Dose (TIV HD) vaccine or drug product:

- *Final Container storage conditions:* Final Container should be stored at 2 to 8°C.
- *Final Container shelf-life:* Final Container is stable for 9 months (52 weeks) at 2 to 8°C.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Stability studies have been conducted in accordance with relevant International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines.

Quality summary and conclusions

There are no objections to the registration of this product from sterility, endotoxin and container safety related aspects.

Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of Fluzone High-Dose inactivated trivalent influenza vaccine (split virion) have been controlled to an acceptable level.

Proposed conditions of registration for delegate

Batch release testing and compliance with the certified product details

It is a condition of registration that all independent batches of Fluzone High-Dose Inactivated Trivalent Influenza Vaccine (Split Virion) imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and you have received notification acknowledging release from the Laboratories Branch, TGA. For each independent batch of the product imported into Australia, the sponsor must supply the following:

- A completed Request for Release Form.
- Complete summary protocols for manufacture and QC, including all steps in production.
- At least 20 packaged doses of each first consignment of product lot with the Australian approved labels, PI and packaging. 10 packaged doses of any further consignment of already released product (including diluents) with the Australian approved labels, PI and packaging.
- Evidence that the consignment has been shipped under the approved storage conditions between the manufacturer and Australia e.g. plots of temperature recordings, summary of temperature monitoring and a summary of the maximum and minimum temperatures experienced during shipping. Excursions from the approved storage conditions should be detailed and justified. Please note that the data provided to support an excursion should meet with the current TGA guidance and that additional samples may be requested from the consignment.
- Certificate of Release from a regulatory agency acting for the country of origin such as an OMCL (if available).
- Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

Distribution of each shipment of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the Laboratories Branch acknowledging release.

All shipments (including reagents) must be sent to TGA from the Australian Sponsor/Agent who will be required to facilitate the import and customs clearance process.

Certified product details

An electronic copy of the Certified Product Details (CPD) as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) should be provided upon registration of the therapeutic good. In addition, an updated CPD, for the above products incorporating the approved changes is to be provided within one month of the date of approval letter. A template for preparation of CPD for biological prescription medicines and Vaccines can be obtained from the TGA website. The CPD should be sent as a single bookmarked PDF document to the TGA as soon as possible after registration/approval of the product or any subsequent changes as indicated above.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Influenza viruses are a group of highly contagious respiratory pathogens which cause regular community based outbreaks worldwide, most prominently in the winter months of temperate regions. Influenza viruses are also a significant cause of respiratory virus outbreaks in closed settings such as hospitals, aged care homes, prisons and cruise ships. In immune competent children and younger adults influenza infections are usually self-limiting and characterised by cough, fever and myalgia. However older adults, immune-compromised individuals and infants can develop severe complications of influenza infection which include pneumonia, bronchitis and exacerbations of chronic respiratory or cardiac disease. Influenza is estimated to cause approximately 3500 deaths, 18,000 hospitalisations and 300,000 general practice presentations in Australia each year.

Vaccination against influenza A and B is the main way to protect vulnerable people from the potential complications of influenza infection. In Australia, the National Immunisation Program (NIP) recommends annual influenza vaccination for all people over the age of 65 years (as well as other vulnerable groups).

Unfortunately, while vaccination in the elderly is associated with a reduced rate of complications from influenza infection, this group has a lower rate of developing protective immunity than younger adults. It has been estimated that the efficacy of influenza vaccine in adults > 65 years of age living in the community is only 43% when

high levels of virus are circulating compared to about 60% in younger adults. This has led to interest in improving rates of response of influenza vaccine in this group.

Fluzone High-Dose has been developed to deliver an increased dose of HA antigen of 60 µg per strain in each of the three viral strains included in the vaccine compared to 15 µg in the standard adult vaccine presentation. The sponsor anticipated that this would increase the proportion of recipients who develop protective titres against HA from vaccination and thus the efficacy of the vaccine in the > 65 year old group. As with all influenza vaccines, the HA antigen included in the vaccine must be assessed annually to match the continued genetic drift of viruses circulating in the community. The efficacy of vaccine varies between years where there is a 'good' match and those when antibodies elicited by the vaccine are less protective against circulating virus.

Formulation development

The sponsor conducted a Phase I dose ranging study (Study NIH-01-597) which compared the immune response of vaccine containing HA antigen at doses between 15 µg and 60 µg per strain. From this study the 60 µg dose was selected for the Phase II and III studies FIM01, FIM05, FIM07 and FIM12 respectively. The virus strain selected for each trial was based on the World Health Organization (WHO)/Centers for Disease Control and Prevention (CDC) recommendation for influenza vaccines during the year the trial was conducted.

The strains used in each study were as described in Table 2 below.

Table 2: Influenza strains included in investigational vaccines used in studies evaluated in this submission

		Influenza Vaccine Strains		
Study	**Season**	**A/H1N1**	**A/H3N2**	**B**
01-597	2001-2002	A/New Caledonia/20/99	A/Panama/2007/99	B/Victoria/504/2000
FIM01	2004-2005	A/New Caledonia/20/99	A/Wyoming/03/2003 (a A/Fujian/411/2002-like strain)	B/Jiangsu/10/2003 (a B/Shanghai/361/2002-like strain)
FIM05	2006-2007	A/New Caledonia/20/99/IVR-116	A/Wisconsin/67/2005/X-161	B/Malaysia/2506/04
FIM07	2009-2010	A/Brisbane/59/07	A/Uruguay/716/2007-X175C	B/Brisbane/60/2008
FIM12	Year 1: 2011-2012	A/California/7/2009	A/Victoria/210/2009	B/Brisbane/60/2008
	Year 2: 2012-2013	A/California/7/2009	A/Victoria/361/2001	B/Texas/6/2001 (a B/Wisconsin/1/2020-like virus)

Guidance

The evaluator is aware of the following guidance of relevance to this dossier:

- EMEA CHMP/VWP/164653/2005 Note for guidance on the clinical evaluation of vaccines.
- EMA/CHMP/VWP/457259/2014 Guideline on influenza vaccines non-clinical and clinical module.

Contents of the clinical dossier

Scope of the clinical dossier

The sponsor has provided four study reports in support of this application (Table 3). These all investigated ambulatory subjects > 65 years of age.

Table 3: Summary description of studies submitted in this dossier

Study	Number of Subjects	Design
FIM05	3,876	Double blind, active controlled, multicentre trial comparing immune reactivity of Fluzone High-Dose and Fluzone
FIM12	31,989	Double blind, active controlled, multicentre trial to determine relative vaccine efficacy of Fluzone High-Dose compared to Fluzone
FIM01	414	Double blind, multi-centre, trial comparing immune reactivity of Fluzone High-Dose and Fluzone
FIM07	9,172	Double blind, active controlled, multicentre trial to determine the relative vaccine efficacy of Fluzone High-Dose compared to Fluzone

Enrolment in Study FIM07 was prematurely discontinued due to the occurrence of the 2009 influenza pandemic and it was provided to support the safety analysis. Secondary efficacy endpoints for the trial were, however, also presented.

The clinical evaluator has reviewed Study NIH-01-597, which was provided as a literature reference.[1] This was considered significant as it was a dose-ranging study on which supported the selection of 60 µg HA per strain (180 µg total) in Fluzone High-Dose.

The sponsor provided 35 additional literature references, which the clinical evaluator reviewed but are not further discussed in this report.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

Trials were conducted according to principles of Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

No pharmacokinetic data were provided.

[1] Keitel WA, Campbell JD, Treanor JJ, Walter EB, Patel SM, He F, et al. Safety and immunogenicity of an inactivated influenza A/H5N1 vaccine given with or without aluminum hydroxide to healthy adults: results of a phase I-II randomized clinical trial. J Infect Dis. 2008;198(9):1309–16.

Pharmacodynamics

No pharmacodynamics data were provided.

Dosage selection for the pivotal studies

Study NIH-01-597

Study NIH-01-597 was a Phase I dose-ranging study which examined the immunological response of 202 ambulatory patients > 65 years of age to four doses of Fluzone. Subjects were randomised into equal groups to receive a single dose of trivalent influenza vaccine containing 0 µg (n = 50), 15 µg (n = 51), 30 µg (n = 51) or 60 µg (n = 50) of HA for each virus strain. The study was conducted in 2002 using the H1N1, H3N2 and influenza B strains current for that year's influenza vaccine. Oral temperature, infection site and systemic symptoms were observed for one week, with blood for serological analysis taken 1 month after the vaccine dose.

Serum haemagglutination inhibition (HAI) and neuraminidase (NA) were examined. The primary endpoints of the study were the geometric mean titre (GMT) for serum HAI and NA against each of the vaccine strains one month after immunisation.

Table 4: Comparative GMT of HAI antibodies and Neutralising Antibody in doses of Fluzone between 45 µg and 180 µg

Table 1. Geometric Mean Serum HAI and Neutralizing Antibody Responses Before and 1 Month After Immunization*

		Antibody Titer, Geometric Mean (95% CI)											
		Influenza A/H1N1				Influenza A/H3N2				Influenza B			
		HAI		Neutralizing		HAI		Neutralizing		HAI		Neutralizing	
Dose, µg	Participants, No.	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
0	50	20 (16-25)	23 (18-29)	15 (11-21)	12 (9-16)	33 (25-45)	43 (32-57)	45 (30-68)	49 (33-73)	11 (8-14)	10 (8-13)	62 (45-87)	59 (41-85)
15	51	20 (16-25)	37 (30-45)	14 (11-19)	28 (21-37)	45 (31-65)	86 (63-118)	52 (34-80)	101 (70-146)	8 (6-10)	14 (11-18)	57 (44-73)	129 (95-175)
30	51	20 (16-27)	50 (38-66)	15 (11-20)	35 (26-47)	39 (29-53)	91 (69-120)	45 (31-65)	106 (76-148)	8 (6-11)	18 (14-23)	60 (41-88)	152 (111-208)
60	50	22 (16-27)	61 (48-78)	19 (13-28)	50 (36-68)	53 (37-75)	125 (97-160)	58 (39-86)	160 (114-225)	9 (7-12)	24 (18-32)	64 (44-93)	199 (141-282)

Abbreviations: CI, confidence interval; HAI, hemagglutination inhibition.
*We tested for differences among the doses in the geometric mean titers before immunization using analysis of variance. None of these differences were statistically significant. Differences among doses after immunization were analyzed using linear regression models (Table 3).

The difference in GMT for HAI and NA between all dose levels was significant ($p < 0.01$). There was no significant difference between the dose groups in the frequency of systemic reactions reported. There was, however, a dose related increase in the incidence of injection site discomfort ($p < 0.01$) and redness/swelling ($p = 0.05$).

The 60 µg dose was chosen for further development in Phase II and III studies on the basis of demonstrating superior reactogenicity compared to the lower two doses with an acceptable safety profile. This was on the basis that increased reactogenicity was likely to be associated with high rates of protection from influenza among recipients of the 60 µg/strain vaccine.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies

The following submitted studies were considered pivotal efficacy studies:

- Study FIM05
- Study FIM 12
- Study FIM01
- Study FIM07

Evaluator's conclusions on efficacy

The pivotal studies FIM12 and FIM05 provide evidence of improved immune reactivity and clinical efficacy respectively of Fluzone High-Dose compared to Fluzone in the proposed target population. The number needed to treat to prevent a case of influenza with Fluzone High-Dose compared to using Fluzone is approximately 270 based on the primary endpoint for influenza A (rate of influenza of 1.56% and 1.19% in Fluzone and Fluzone High-Dose groups). This would potentially prevent a large number of cases of influenza if Fluzone High-Dose was used widely but may limit acceptance by the individual given the slightly higher rate of injection site reactions.

Study FIM12 confirmed greater relative efficacy of Fluzone High-Dose compared to Fluzone in preventing Influenza A and influenza B in subjects > 65 years of age. The subjects in this study were comparatively well and results from Study FIM12 provide little evidence of the comparative benefit of Fluzone High-Dose in settings such as aged care facilities where the population is very frail.

Table 5: Relative vaccine efficacy of Fluzone High-Dose compared to Fluzone in the prevention of laboratory confirmed influenza associated with protocol defined influenza like illness by age subgroups; Per-Protocol analysis

Efficacy Endpoint	Age (years)	Fluzone High-Dose N=10519 n (%)	Fluzone N=10518 n (%)	Relative Vaccine Efficacy of Fluzone High-Dose % (95% CI)
Laboratory confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	< 75 years	166 (1.47)	193 (1.83)	19.7% (0.3; 35.4)
Laboratory confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	75 to <85	64 (1.36)	96 (2.04)	33.1% (7.3; 52)
Laboratory confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	>85 years	8 (1.19)	11 (1.63)	26.8% (-99.7; 74.5)
Laboratory confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	< 75 years	47 (0.45)	72 (0.68)	34.73 (4.43; 55.79)
Laboratory confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	75 to <85	25 (0.53)	37 (0.78)	32.20 (-15.68; 60.88)
Laboratory confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	>85 years	1 (0.15)	4 (0.59)	74.85 (-154.1; 99.49)

An analysis of the effect by age was presented in the US FDA report of Fluzone High-Dose but was not included in the submitted dossier.[2] It does not suggest a strong effect of age on the efficacy of Fluzone High-Dose within the limited power of the sub-analysis.

The clinical evaluator notes that the modified-CDC defined influenza like illness used as a secondary efficacy endpoint is closer to the WHO surveillance definition of an Influenza Like Illness that is, a fever ≥ 38 degrees centigrade and cough. While all cases in Study FIM12 were laboratory confirmed, the clinical evaluator feels that the modified CDC definition is likely to better estimate the clinical syndrome which will be recognised as influenza and tested in the Australian clinical or public health setting than the protocol defined case definition.

The clinical evaluator notes that in the influenza seasons over which Study FIM12 was conducted H3N2 represented > 75% of the virus circulating in the US and Canada with comparatively little H1N1. This pattern was replicated in the adjacent Australian seasons. There were too few cases of H1N1 in Study FIM12 to effectively assess the clinical efficacy of the vaccine against this subtype. Study FIM07 does not provide supportive evidence because the vaccine was unmatched to the pandemic strain in that year. The clinical evaluator therefore feels that the immunological response demonstrated against H1N1 in Study FIM05 is the best evidence of a protective response against the H1N1 subtype. This study observed a higher rate of seroprotection in subject vaccinated with Fluzone High-Dose than in those who received Fluzone.

[2] Evaluation of STN 103914/5726 by Roshan Ramanthan MD MPH, 29 October 2014

Safety

Studies providing safety data

Safety data is available from Studies FIM01, FIM05, FIM07, FIM12 submitted in this dossier as complete reports. Study NIH-01-574 was included in the dossier as a literature reference and so analysis of safety endpoints in this study was not possible. However, this dose ranging study included only a low number of subjects who received the proposed dose of Fluzone High-Dose. No study assessed a safety as a primary endpoint.

Table 6 provides a summary of the safety endpoints collected in Studies FIM01, FIM07, FIM05 and FIM12.

Table 6: Safety endpoints from Studies FIM01, FIM07, FIM05 and FIM12

Safety Parameter	Time window for capture	FIM05	FIM12	FIM01 (NIH Study 04-100)	FIM07
Immediate Reactions*	Day 0† + 30 minutes	X‡	NC	NC	NC
	Day 0† + 20 minutes	NC	NC	X‡	NC
Solicited Injection Site Reactions	Day 0 + 7 days	X	NC	X	NC
Solicited Systemic Reactions	Day 0 + 7 days	X	NC	X	NC
Non-Serious Unsolicited AEs	Day 0 to Day 28	X	NC	X	NC
SAEs	Day 0 to end of study participant's follow-up	X	X	X	X
AESIs	Day 0 to end of study participant's follow-up	NC	X	NC	X
Additional clinical information	Day 0 - Month 6	X§	NC	NC	NC

* In FIM05 these were unsolicited events reported during the period; In FIM01 these were solicited events reported during the period.

† Day 0 = Immediately after vaccination.

‡ 'X' indicates that the parameter was documented in that particular study.

§ Study participant's Health Care Utilization was reviewed.

NC = Not collected

Patient exposure

Table 7 summaries the patient exposure to Fluzone and Fluzone High-Dose in the submitted studies.

Table 7: Patient exposure in studies submitted in support of this submission to the TGA

Study ID	Fluzone High-Dose	Fluzone	First visit of first subject	Last contact with last subject
FIM05	2588	1288	9 October 2006	9 July 2007
FIM12 (Year 1)	7254	7243	6 September 2011	31 May 2013
FIM12 (Year 2)	8738	8748		

Study ID	Fluzone High-Dose	Fluzone	First visit of first subject	Last contact with last subject
FIM01	206	208	11 April 2005	28 November 2005
FIM07	6018	3050	22 September 2009	28 May 2010
NIH-01-597	50 at proposed dose/202 at all doses		18 June 2002	April 2003

Postmarketing data

The sponsor has not provided Post Market Safety Update Reports (PSURs) or post-marketing data. They have noted that between February 2009 and February 2014 a total of 20,702,980 doses of Fluzone High-Dose were distributed in the US. The sponsor has referenced the US Product Information (Package Insert) regarding adverse events reported on the basis of this experience. The summary of post-marketing data provided does not reference post-marketing experience from Canada.

Evaluator's conclusions on safety

More injection site and systemic reactions were observed within one week of vaccination in subjected treated with Fluzone High-Dose than in those treated with Fluzone in Study FIM05. The majority of these occurred within 3 days of vaccination and lasted 1 to 3 days without sequelae.

The clinical evaluator notes that equivalence for solicited systemic reactions between Fluzone and Fluzone High-Dose by defining equivalence to be a relative risk of < 3. While this might reflected the limitations of the power of this study, the clinical evaluator does not feel that a relative risk of 3 is equivalent in a clinical sense and notes the higher point estimates for solicited systemic reactions in Fluzone High-Dose compared to Fluzone treated subjects.

Study FIM12 provides a very large population exposed to Fluzone High-Dose, including 7645 over two successive years. There is no indication of an imbalance in the incidence of adverse events reported after 30 days, the majority of which are consistent with the older population enrolled. There was no increase in adverse events of special interest (AESIs) observed among Fluzone High-Dose treated patients compared to those who received Fluzone.

The clinical evaluator notes that the sponsor's decision to report only serious adverse events (SAEs) potentially lowers the sensitivity of Studies FIM12 and FIM07 to detect adverse events which did not result in hospitalisation. While these are likely to include the more medically serious adverse events, a full analysis of all AEs reported in the period immediately following vaccination would be preferable for a vaccine which is intended for use in a large population. This is partially mitigated by the extensive post-marketing experience with Fluzone High-Dose in the USA and influenza vaccination generally but a full analysis of the post-marketing data has not been provided in this submission.

The clinical evaluator notes that sub-analyses of adverse events in immune-compromised subjects were included in the US FDA evaluation of Fluzone High-Dose.[3]

Table 8: Adverse events reported with Fluzone and Fluzone High-Dose

	Fluzone High-Dose (N=2892) n (%)	Fluzone (N=2835) n (%)
SAE[3]	51 (1.76)	52 (1.83)
Death	1 (0.03)	0 (0)
Adverse Event of Special Interest[2]	0 (0)	0 (0)
SAE leading to study discontinuation	4 (0.14)	0 (0)
Related SAE	1 (0.03)	0 (0)
Related SAE leading to study discontinuation	0 (0)	0 (0)

[1]Chronic Comorbid Immunodeficiency includes subjects with cancer, long-term systemic corticosteroid therapy, HIV/AIDS or potentially immunosuppressive therapy at baseline.
[2]Adverse Events of Special Interest (AESIs) include Guillain-Barré syndrome, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis
[3]SAE = serious adverse event

The clinical evaluator concurs with the FDA evaluator's conclusion that this limited post-hoc analysis does not indicate any particular safety concerns in this group. The supplemental tables on which this analysis was based were not, however, included in this submission.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Fluzone High-Dose in the proposed usage are:

- Improved protection from influenza than offered by standard adult dose influenza vaccine for example, Fluzone. The degree of benefit will differ as the match between circulating strains of influenza and the vaccine strains varies from year to year.
- It would be expected that decreased rates of influenza in the > 65 year old age group would produce lower rates of health care utilisation and secondary illness in this population.

First round assessment of risks

The risks of Fluzone High-Dose in the proposed usage are:

- Increase immune mediated reactions such as site injection reactions and systemic reactions in the first week post vaccination compared to standard adult dose influenza vaccine, for example Fluzone
- Post-marketing data may include information regarding adverse events which were not reported in the clinical trials either due to the lower number of patients exposed or the reporting only of SAEs.

[3] Evaluation of STN 103914/5726 by Roshan Ramanthan MD MPH, 29 October 2014

First round assessment of benefit-risk balance

The benefit-risk balance of Fluzone High-Dose, given the proposed usage, is favourable based on the currently available trial data. However, given the large population of generally well people for which Fluzone is indicated in a preventative role, it is necessary to examine the largest body of safety information available to be certain of the incidence of potentially rare adverse events. This data is comprised of the significant post-marketing exposure to Fluzone High-Dose in the USA and an analysis of post-marketing adverse events reported to the sponsor should be evaluated before Fluzone High-Dose is registered in Australia.

First round recommendation regarding authorisation

The clinical evaluator recommends that Fluzone High-Dose be registered for the proposed indication provided:

1. Amendments to the Australian Product Information are made (the details of these are beyond the scope of this AusPAR).
2. Evaluation of post-marketing safety data does not provide additional information which would lead to a materially different assessment of the safety of Fluzone High-Dose from that which the clinical evaluator has formed on the basis of clinical trial data evaluated in this report.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

A noted in the first round evaluation, the benefit of Fluzone High-Dose in the proposed usage is protection from influenza that is greater than that offered by standard adult dose trivalent influenza vaccine (such as Fluzone). The extent of benefit will fluctuate as the match between circulating strains of influenza and the included vaccine strains varies from year to year.

Second round assessment of risks

The risks of Fluzone High-Dose in the proposed usage as previously noted are:

- Increased immune-mediated reactions, for example higher rates of injection site and systemic reactions in the first week post vaccination compared with the standard adult dose influenza vaccine (for example Fluzone).

Second round assessment of benefit-risk balance

The clinical evaluator notes that a quadrivalent inactivated influenza vaccine (Afluria Quad) is now included in the Australian National Immunisation Program (NIP) for adults aged 18 years and over (although it is not the recommended product for those aged 65 and over). As Fluzone has not been compared to any quadrivalent inactivated influenza

vaccine (IIV) in clinical studies, the benefits of Fluzone High-Dose against the three included strains have to balance against the lack of coverage of one of the B strain lineages.

Overall, however, the clinical evaluator considers that benefit-risk balance of Fluzone High-Dose for the proposed indication is favourable.

Second round recommendation regarding authorisation

In the view of the evaluator that the benefit-risk balance of Fluzone High-Dose for the proposed indication remains favourable and recommends that it be registered for the proposed indication.

VI. Pharmacovigilance findings

Risk management plan

The sponsor has submitted a core Risk management plan (RMP) version 2.0 dated May 2015; data lock point (DLP) 29 April 2014 and Australia Specific Annex version 1.0 dated 24 February 2017 in support of this application. The sponsor did not provide updated RMP documents in their response.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below (Table 9).

Table 9: Summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R*	A*	R*	A*
Important identified risks	None	–	–	–	–
Important potential risks	Thrombocytopenia	ü	–	ü	–
	Anaphylaxis	ü	–	ü	–
	Guillain-Barré syndrome (GBS)	ü	–	ü	–
	Convulsions	ü	–	ü	–
	Neuritis (including Bell's palsy)	ü	–	ü	–
	Encephalitis/myelitis	ü	–	ü	–
	Vasculitis	ü	–	ü	–
	Gastrointestinal disorders (nausea, vomiting, diarrhoea)	ü	–	ü	–
Missing	None	–	–	–	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R*	A*	R*	A*
information					

*Note: R = routine; A = additional.

Routine pharmacovigilance has been proposed to monitor all the safety concerns.

Outstanding pharmacovigilance requirement

The reactogenicity of seasonal influenza vaccine may vary each season; this is not monitored in the pharmacovigilance plan. The sponsor has not provided a study description and a commitment to conduct an '*enhanced safety surveillance study for reactogenicity*' in Australia, if the product is not included in the national safety surveillance program.

It is recommended to the Delegate that, as a condition of registration, the sponsor must provide either adequate post-market safety data with each annual strain update variation to demonstrate that the reactogenicity of that season's vaccine has been adequately characterised *or* a protocol satisfactory to the TGA and commitment to conduct an enhanced safety surveillance study in Australia, as requested.

Routine risk minimisation has been proposed by the sponsor to mitigate all the safety concerns.

Critical outstanding recommendation

The sponsor must provide a commitment to conduct an enhanced safety surveillance study in Australia, if requested by TGA. A protocol, for the proposed study will be required to be submitted with the annual strain update variation, if there is inadequate post-market safety data to demonstrate that the reactogenicity of that season's vaccine has been adequately characterised *and* the vaccine is not supplied on the National Immunisation Program in that season.

Other advice and recommendations

Administrative

The discussion of the additional EU requirements, which are not addressed in the ICH/Core RMP, and which were provided in the sponsor's response, should be included in the ASA.

Safety specification

Vaccine failure must be included as an important potential risk, to be monitored closely.

Anaphylaxis must be included as an Important identified risk.

RMP condition of registration

No wording can be provided, because a satisfactory response to the recommendation to conduct an enhanced safety surveillance study to assess reactogenicity, if requested by TGA, has not been provided.

Other advice to the delegate

If approval is recommended, the Delegate is requested to apply a condition of registration to the following effect: '*the sponsor must provide either adequate post-market safety data with each annual strain update variation to demonstrate that the reactogenicity of that*

season's vaccine has been adequately characterised or to conduct an enhanced safety surveillance study in Australia. A protocol, satisfactory to the TGA, must be submitted with the Annual Strain Update applications'.

It is recommended to the Delegate that the PI is revised as follows:

- The current contraindication for '*individuals with known hypersensitivity to egg*' is removed because this contradicts the best practice advice in the Immunisation Handbook. It should be replaced by a precaution that aligns with the Immunisation Handbook.

It is recommended to the Delegate that references to *'the official clinical guidelines'* should be included in the PI in the appropriate places to promote the quality use of medicines/vaccines and to align use of the product with Australian best practice.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluation recommends that there are no further objections to the registration of Fluzone High-Dose inactivated trivalent influenza vaccine (split virion). However, the summary report does not include viral safety issues which are still under negotiation between TGA viral safety unit and the sponsor. The TGA assessment concludes sufficient control of contamination with non-enveloped, non-haemagglutinating viruses was not demonstrated to conform with the European Pharmacopoeia (Ph. Eur.) General Monograph 01/2013:0153 Vaccines for human use. There is a specific PH. Eur. Monograph 0158 for egg–derived inactivated influenza vaccines which includes testing for freedom from extraneous agents.

Nonclinical

No nonclinical data were submitted based on the following information from the pre-submission documents sent to the TGA:

- Fluzone High-Dose incorporates the same drug substances (antigens) used in the manufacture of FluQuadri, marketed in the US as Fluzone Quadrivalent, and the components are the same as the US licensed Fluzone. The manufacturing process is also similar, but the phosphate concentration of the exchange buffer will increase from 6 to 30 mM to increase buffer capacity, and Triton X-100 will be reclassified from a residual to an excipient, although its bulk specification will remain the same at no more than (NMT) 500 µg/mL.
- Clinical data for Fluzone High-Dose are available for 17,100 subjects in Studies FIM05 and FIM12, and 54 million standard doses of Fluzone have been sold in the US over the past 3 decades.

Clinical

Immunogenicity

The sponsor conducted a Phase I dose ranging study (Study NIH-01-597) which compared the immune response of vaccine containing HA antigen at doses between 15 µg and 60 µg per strain. From this study the 60 µg per strain dose was selected for the Phase II and III Studies FIM01, FIM05, FIM07, and FIM12.

Study NIH-01-597 was a Phase I randomised, dose-ranging, placebo controlled study which examined the immunological response of 202 ambulatory patients > 65 years of age to four doses of Fluzone. Subjects were randomised into equal groups to receive a single dose of trivalent influenza vaccine containing 0 µg (n = 50), 15 µg (n = 51), 30 µg (n = 51) or 60 µg (n = 50) of HA for each virus strain. The study was conducted in 2002 using the H1N1, H3N2 and influenza B strains current for that year's influenza vaccine.

The primary endpoints of the study was the GMT for serum HAI and NA against each of the vaccine strains one month after immunisation, The difference in GMT for HAI and NA between all dose levels was significant ($p < 0.01$). There was no significant difference between the dose groups in the frequency of systemic reactions reported. There was, however, a dose-related increase in the incidence of injection site discomfort ($p < 0.01$) and redness/swelling ($p = 0.05$). The 60 µg dose was chosen for further development in Phase II and III studies on the basis of demonstrating superior reactogenicity to the lower two doses with an acceptable safety profile.

Study FIM05 was a Phase III randomised, double blind, active-controlled, multicentre study in subjects > 65 years of age which compared the immune response of subjects who received Fluzone High-Dose (n = 2588) to those who received Fluzone (n = 1288). The study had two main objectives. The first of these was to demonstrate the superiority of immune response in subjects receiving Fluzone High-Dose compared to those receiving Fluzone. The second main objective was to assess the lot consistency of immune response between subjects receiving Fluzone High-Dose from 3 different lots. Immune response was measured 28 days after subjects received a single dose of vaccine.

The study was conducted between October 2006 and July 2007 at 31 centres in the USA. Subjects received either Fluzone (15 µg HA per strain, 45 µg in total) or Fluzone High-Dose (60 µg per strain, 180 µg in total) as a single intramuscular injection of 0.5 mL.

The primary endpoint was the anti-HA GMT for each of the three viral strains in the vaccine measured 28 days post vaccination. This was used to assess the equivalence in anti-HA GMT between the three lots of vaccine used, where equivalence was defined as a ratio of GMT between two lots of vaccine between 0.67 and 1.50.

The secondary endpoint was the percentage of seroconversion among subjects measured one month post-vaccination. Seroconversion was defined as either:

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

Superiority was concluded if 95% confidence interval (CI) of difference was > 10%.

2588 subjects were randomised to receive Fluzone High-Dose (n = 859, 866 and 863) for Lots 1, 2 and 3 respectively. 1288 subjects were randomized to receive Fluzone. Participant flow is shown in Attachment 2, Table 4. More than 98% completed study up to Day 180 in each treatment arm.

Subjects were well matched between treatment arms and Fluzone High-Dose lots for age, sex and race. The average age of subjects in Study FIM05 was 72.9 years for both Fluzone

High-Dose and Fluzone treatment arms. The majority of subjects had received vaccination in the previous year (2005; 82.2%).

Results for the primary efficacy outcome: Results for the primary efficacy outcome are shown in Attachment 2, Table 5.

The 95% confidence interval of the difference in GMT for HAI antibodies between the three lots of Fluzone High-Dose used in Study FIM05 was between 0.67 and 1.5 for all comparisons. This met the predefined criteria for equivalence between the lots. The ratios for GMT values between lots observed were between 0.94 comparing Lot 1/Lot 2 for H1N1 antibodies, and 1.04 for comparing Lot 2/Lot 3 for H3N2 antibodies. The ratio of GMT values observed was 1 comparing Lot 1/Lot 2 and Lot 2/Lot 3 for B antibodies.

Results for other efficacy outcomes: Subjects who received Fluzone High-Dose achieved a significantly higher rate of seroconversion than those receiving Fluzone, the margin of superiority being 25.42%, 18.38% and 11.81% for the H1N1, H3N2 and B components of the vaccine respectively, as shown in Attachment 2 Table 6. Subjects who received Fluzone High-Dose had significantly higher GMT titres for HAI antibodies than those who received Fluzone as shown in Attachment 2, Table 8.

Study FIM01 is a supportive immunogenicity and reactogenicity study presented in Attachment 2. This randomised, double blind study enrolled 414 ambulatory and medically stable subjects > 65 years of age. The main objective of the study was to compare the immunogenicity of high dose trivalent influenza vaccine containing 60 μg of HA per strain with a vaccine containing the standard dose of 15 μg HA per strain in patients over 65 years of age. The study was conducted at 5 centres in the USA between April and November 2005.

Subjects received a single 0.5 mL IM dose of a trivalent influenza vaccine containing either 15 μg or 60 μg HA per strain of A/New Caledonia/20/99 (H1N1), A/Fujian/411/2002 (H3N2) and B/Jiangsu/10/2003.

The primary endpoint was proportion of subjects who achieved serum HAI titre at least 1:32 for each of the three vaccine antigens assessed 1 month after vaccination.

A total of 415 subjects were enrolled; 414 subjects were vaccinated and 413 completed the study. The demographic characteristics of the two treatment arms were well matched for gender, age and race. The average age of the treatment arms was 74 and 73 for the Fluzone High-Dose and Fluzone treatment arms respectively.

The primary efficacy outcome, HAI titre > 1:32, was observed against H1 antigen in 62.3% and 48.3% of subjects ($p < 0.01$) in the Fluzone High-Dose and Fluzone dose vaccine respectively. There was no significant difference between treatment groups for the H3 or B antigens. The results were similar between previously vaccinated or unvaccinated groups.

For other efficacy outcomes, the post-vaccination GMT was significantly higher for the Fluzone High-Dose (high dose) than the Fluzone (standard dose) vaccine for all three antigens at a 95% confidence level. There were a significantly higher proportion of subjects achieving a 4 fold increase in HAI antibody titres after vaccination for all 3 antigens in the Fluzone High-Dose compared to Fluzone treatment arms.

Clinical efficacy

Study FIM12 was a Phase IIIb/IV, randomised, double blind, active controlled, multicentre trial to determine relative vaccine efficacy of Fluzone High-Dose compared to Fluzone in subjects > 65 years of age. Study FIM12 was conducted between 6 September 2011 and 31 May 2013 at 126 centres in the USA and Canada.

Study FIM12 compared the clinical efficacy of Fluzone High-Dose and Fluzone in preventing influenza in subjects > 65 years of age over two consecutive seasons. Approximately 14,500 and 17,500 subjects were randomised 1:1 to receive either Fluzone High-Dose or Fluzone in the first and second study years respectively.

Vaccination of subjects was completed prior to 15 November in each study year.

Following vaccination, subjects were followed through active and passive surveillance to 30 April the following year. Passive surveillance was implemented by subjects being instructed to contact the study site if they experienced defined symptoms of influenza. Active surveillance consisted of all subjects being contacted by a call centre once or twice per week until 30 April to ask if they had experienced any symptoms of respiratory illness. Twice weekly calls were scheduled during the peak of the influenza season.

Nasopharyngeal swabs were taken from subjects who reported illness for confirmation of influenza by culture or polymerase chain reaction (PCR). The study site also collected history regarding concomitant illness such as pneumonia and systemic symptoms if illness. Subjects were followed for 30 days after reporting illness.

The primary endpoint of Study FIM12 was the occurrence of culture or PCR confirmed influenza in subjects > 14 days after vaccination who had a protocol defined influenza-like illness (ILI). This was used to calculate the relative vaccine efficacy of Fluzone High-Dose compared to Fluzone.

A protocol defined ILI was determined by at least one of sore throat, cough, sputum production, wheezing or difficulty breathing AND at least one of; fever > 37.2°C, shivering, fatigue, headache or myalgia. An alternate clinical endpoint, the Modified CDC defined ILI was also measured. A case of Modified-CDC-defined ILI was defined as the occurrence of a fever of > 37.2°C with cough or sore throat.

Several secondary endpoints examined the occurrence of influenza which was similar to the vaccine strains. 'Antigenic similarity' was concluded when a culture confirmed isolate was considered similar to the vaccine components when tested against a standardised panel of ferret HAI antibodies.

The rate of pneumonia, onset or exacerbation of cardio-respiratory conditions and occurrence of health care utilisation was defined as an observational endpoint.

The observed rate of influenza in the two treatment arms was used to calculate the relative vaccine efficacy of the Fluzone High-Dose and Fluzone by the following:

- Relative VE = 1 - ((CHD/NHD) / (CFL/NFL)) , where CHD is number of cases in the Fluzone High-Dose group, NHD is number of subjects in the Fluzone High-Dose group, CFL is the number of cases in the Fluzone group and NFL is the number of subjects in the Fluzone group.. Fluzone High-Dose would be considered superior to Fluzone if the lower bound of 95% two-sided confidence interval for relative VE was > 9.1%.

Subjects received one 0.5 mL dose of either Fluzone High-Dose or Fluzone containing 60 µg or 15 µg of HA respectively for each of the three influenza strains in the vaccine. The strains in the vaccine were as summarised below in Table 10.

Table 10: Strains in the vaccine in Year 1 and Year 2

Year 1	Year 2
A/California/7/2009 (H1N1)	A/California/7/2009 (H1N1)
A/Victoria/210/2009 (H3N2)	A/Victoria/361/2011 (H3N2)
B/Brisbane/60/2008	B/Texas/6/2011

Participant flow is summarised in Attachment 2, Table 9. A total of 31,989 subjects were enrolled with 31,983 vaccinated and 30, 467 (95.24%) completed the study overall.

Of the subjects enrolled, 43.4% were male and 56.6% female. The mean age was 73.3 years.

The treatment arms were balanced for race, sex and age. The proportion of subjects with at least one prespecified morbidity was similar between Fluzone High-Dose (67.22%) and Fluzone (67.24%) treatment arms.

The results for the primary efficacy outcome, relative rates of laboratory confirmed influenza according to protocol defined and modified CDC defined case definitions of influenza in PPAS set are shown in Attachment 2, Table 12. For protocol defined influenza like illness for Year 1 and 2 combined there were there were a total of 228 cases (1.43%) in the Fluzone High-Dose group and 301 (1.88%) in the Fluzone group with calculated relative vaccine efficacy of 24.24% (95% CI: 9.71, 36.5). Superiority of Fluzone High-Dose to Fluzone was demonstrated using the pre-specified margin of superiority of 9.1%. Results did not differ between per-protocol and Full Analysis Set (FAS) analyses.

Attachment 2 presents relative efficacy by strain. The relative efficacy of Fluzone High-Dose/Fluzone was higher for H3N2 influenza (23.30%) and Influenza B (25.48%) than for H1N1 influenza (11.09%), although there were low numbers of H1N1 cases. For protocol defined influenza like illness for Year 1 and 2 combined for influenza A there were there were a total of 190 cases (1.19%) in the Fluzone High-Dose group and 250 (1.56%) in the Fluzone group with calculated relative vaccine efficacy of 23.99% (95% CI: 7.84, 37.39).

Results were similar for the more restrictive modified CDC case definition of influenza like illness although statistical significant superiority was shown only for the overall and influenza B analyses.

The results for relative vaccine efficacy against culture confirmed influenza caused by viral types antigenically similar to those contained in the vaccine are shown in Attachment 2, Table 14. The relative vaccine efficacy for Fluzone High-Dose/Fluzone for influenza types which were antigenically similar to the vaccine strains was 31.44% indicating superior protection with Fluzone High-Dose to the standard dose vaccine.

The comparative rates of pneumonia, new onset or exacerbation of cardio-respiratory condition and health care utilisation in Fluzone High-Dose and Fluzone treated subjects are shown in Attachment 2, Table 15. The numbers of cases of pneumonia or onset/exacerbation of were lower in Fluzone High-Dose than Fluzone treated groups although the relative risk for these outcomes was not significantly different.

The clinical evaluation report presents a table of relative vaccine efficacy by age subgroups in Study FIM12 which does not suggest a strong effect of age on the efficacy of Fluzone High-Dose.

Study FIM07 was a double blind, active controlled study of relative efficacy with the same design as Study FIM12. Study FIM07 was prematurely discontinued in its first year due to occurrence of the 2009 influenza pandemic. The study has been submitted as part of the safety analysis.

Clinical safety

Safety data are available from Studies FIM01, FIM05, FIM07 and FIM12 submitted in this dossier as complete reports. A summary of safety endpoints is presented in Attachment 2 Table 22. Studies FIM12 and FIM07 analysed SAEs and AESI rather than all reported adverse events. Attachment 2, Table 24 summarises patient exposure in submitted studies.

Attachment 2, Table 26 presents solicited injection site reactions in the pivotal Study FIM05. Swelling, erythema and pain occurred approximately 1.4 times more frequently in subjects treated with Fluzone High-Dose than Fluzone. Severe swelling or erythema was uncommon in both groups but more frequent in Fluzone High-Dose (1.5% and 1.8% respectively) compared to Fluzone (0.6% and 0.6% respectively). Rates of severe pain at the injection site were similar between the two treatment arms.

In Study FIM01 a total of 57% Fluzone High-Dose and 44% of Fluzone subjects reported at least one solicited injection site reaction.

Attachment 2, Table 27 presents solicited systemic reactions in the pivotal Study FIM05.

The rates of solicited systemic reactions were similar between the two treatment arms, but generally more frequent in the Fluzone High-Dose than Fluzone treatment arms. The 95% confidence interval for the relative risk for of these adverse events between the two treatment arms fell within the protocol specified margin on non-inferiority of relative risk (RR) < 3. The clinical evaluator comments that a relative risk of 3 is not equivalent in a clinical sense and the higher point estimates of solicited systemic reactions in Fluzone High-Dose compared to Fluzone treated subjects.

In Study FIM01, a total of 41% of Fluzone High-Dose and 29% of Fluzone subjects reported at least one solicited systemic reaction.

SAEs reported in Study FIM05 to Day 180 follow-up were reported at a similar rate in Fluzone High-Dose (6.47%) and Fluzone (7.4%) treatment arms. Two SAEs in Study FIM05 were considered by investigators to be due to study treatment with one occurring in each treatment arm. These SAE described in Attachment 2 were myasthenia gravis in a male with an onset 19 days post-vaccination with Fluzone and exacerbation of Crohn's disease in a female requiring hospitalisation with symptoms commencing 2 days post-vaccination with Fluzone High-Dose.

In Study FIM05 no deaths were reported to Day 28. In follow-up to Day 180 there were 23 deaths, 16 (0.62%) in the Fluzone High-Dose and 7 (0.56%) in the Fluzone treatment arms. These were all considered unrelated to treatment.

SAEs reported in Study FIM12 are presented in Attachment 2, Table 28. A total of 8.27% of Fluzone High-Dose and 9.02% of Fluzone subjects experienced at least one SAE, a relative risk of 0.92 (95% CI 0.85, 0.99). The most frequently reported System Organ Class (SOC) for these SAEs was Cardiac Disorders. Three subjects in the Fluzone High-Dose group experience SAEs which were considered related to treatment and described in Attachment 2. These events were acute disseminated encephalitis 117 days after vaccination, left cranial VI nerve paralysis 1 day after vaccination and hypovolemic shock 1 day after vaccination.

Serious adverse events were reported in Study FIM01 with 14 SAE in the Fluzone High-Dose and 9 SAE in the Fluzone treated groups. None of these was considered related to treatment. There was one death from myocardial infarction 169 days post-vaccination which was not considered due to treatment.

Serious adverse events reported in Study FIM07 in 8.1% of Fluzone High-Dose treated subjects and 7.7% of Fluzone treated subjects. Among these cardiac failure and pneumonia were the most common conditions, occurring in 0.3% and 0.2% of Fluzone High-Dose subjects respectively. There were 3 SAEs considered related to treatment described (cardiac chest pain requiring hospitalisation, 1 day after vaccination with Fluzone High-Dose, Bells' palsy 34 days after vaccination with Fluzone, immune thrombocytopaenia 13 days after vaccination with in Fluzone).

Clinical evaluator's conclusions on clinical safety

More injection site and systemic reactions were observed within one week of vaccination in subjected treated with Fluzone High-Dose than in those treated with Fluzone in Study FIM05. The majority of these occurred within 3 days of vaccination and lasted 1 to 3 days without sequelae.

Study FIM12 provides a very large population exposed to Fluzone High-Dose, including 7645 over two successive years. There is no indication of an imbalance in the incidence of adverse events reported after 30 days; the majority of which are consistent with the older population enrolled. There was no increase in AESIs observed among Fluzone High-Dose treated patients compared to those who received Fluzone. The clinical evaluator notes that the sponsor's decision to report only SAEs and AESI potentially lowers the sensitivity of Studies FIM12 and FIM07 to detect adverse events which did not result in hospitalisation.

The clinical evaluator notes that sub-analyses of adverse events in immune-compromised subjects were included in the US FDA evaluation of Fluzone High-Dose. The clinical evaluator concurs with the FDA evaluator's conclusion that this limited post hoc analysis does not indicate any particular safety concerns in this group.

Post-marketing safety experience

The first round clinical evaluation report (CER) questioned the lack of post-marketing surveillance data in the submission. The most recent Global Pharmacovigilance Periodic Benefit-Risk Evaluation Report for September 2015 to September 2016 (PBRER) and most recent Data Safety Update Report (DSUR) for April 2016 to April 2017 were reviewed in the second round clinical evaluation. Evaluation of post-marketing safety data as detailed in Attachment 2 does not provide additional information which would lead to a materially different assessment of the safety of Fluzone High-Dose from that which the clinical evaluator has formed on the basis of clinical trial data evaluated in the first round evaluation.

Second round benefit-risk assessment

The clinical evaluator concludes the benefits of Fluzone High-Dose in the proposed usage are:

- Improved protection from influenza than offered by standard adult dose influenza vaccine for example Fluzone. The degree of benefit will differ as the match between circulating strains of influenza and the vaccine strains varies from year to year.

The CER concludes the risks of Fluzone High-Dose in the proposed usage are:

- Increased immune-mediated reactions, for example, higher rates of injection site and systemic reactions in the first week post vaccination compared with the standard adult dose influenza vaccine (for example Fluzone).

Second round assessment of benefit-risk balance

The CER notes that quadrivalent inactivated influenza vaccines are now included in the Australian National Immunisation Program (NIP) for adults aged 18 years and over. As Fluzone has not been compared to any quadrivalent inactivated influenza vaccine in clinical studies, the benefits of Fluzone High-Dose against the three included strains have to be balanced against the lack of coverage of one of the B strain lineages.

Overall, however, the clinical evaluator considers that benefit-risk balance of Fluzone High-Dose for the proposed indication is favourable.

Risk management plan

The sponsor has provided data in response to the clinical questions raised in the first-round evaluation report. The RMP second round evaluation report recommends the sponsor must provide a commitment to conduct an enhanced safety surveillance study in Australia, if requested by TGA. A protocol, for the proposed study will be required to be submitted with the annual strain update variation if there is inadequate post-market safety data to demonstrate that the reactogenicity of that season's vaccine has been adequately characterised and the vaccine is not supplied on the National Immunisation Program in that season.

The RMP recommends amendment of the PI to address discrepancies between the draft PI and the Australian Immunisation Handbook on persons with known egg allergy and inclusions of statements that use of Fluzone High-Dose should be based on official recommendations in appropriate places in PI.

Risk-benefit analysis

Delegate's considerations

Viral safety issues are still under negotiation between TGA viral safety unit and the sponsor.

The second round clinical evaluation report under 'Benefit-risk balance' notes that quadrivalent inactivated influenza vaccines are now included in the Australian National Immunisation Program (NIP) for adults aged 18 years and over. As Fluzone has not been compared to any quadrivalent inactivated influenza vaccine in clinical studies, the benefits of Fluzone High-Dose against the three included strains have to be balanced against the lack of coverage of one of the B strain lineages. The degree of benefits of Fluzone High-Dose will differ as the match between circulating strains of influenza and the vaccine strains varies from year to year.

Study FIM12 confirmed greater relative efficacy of Fluzone High-Dose compared to Fluzone in preventing Influenza A and influenza B in subjects > 65 years of age. The subjects in this study were comparatively well and Study FIM12 provides little evidence of the comparative benefit of Fluzone High-Dose in settings such as aged care facilities where the population is very frail.

In Study FIM12, the number needed to treat to prevent a case of influenza with Fluzone High-Dose compared to using Fluzone is approximately 270 based on the primary endpoint for influenza A (rate of influenza of 1.56% and 1.19% in Fluzone and Fluzone High-Dose groups). This would potentially prevent a large number of cases of influenza if Fluzone High-Dose was used widely but may limit acceptance by the individual given the slightly higher rate of injection site reactions.

In Study FIM12, the clinical evaluator considered that the modified CDC definition is likely to better estimate the clinical syndrome which will be recognised as influenza and tested in the Australian clinical or public health setting than the protocol defined case definition. Estimated relative efficacy of Fluzone High-Dose was lower using the modified CDC definition (overall 20.65% (95% CI: -4.6, 39.94)).

The clinical evaluator notes that in the influenza seasons over which Study FIM12 was conducted H3N2 represented > 75% of the virus circulating in the US and Canada with comparatively little H1N1. This pattern was replicated in the adjacent Australian seasons. There were too few cases of H1N1 in FIM12 to effectively assess the clinical efficacy of the vaccine against this subtype. The clinical evaluator considers the immunological response demonstrated against H1N1 in Study FIM05 is the best evidence of a protective response

against the H1N1 subtype. This study observed a higher rate of seroprotection in subjects vaccinated with Fluzone High-Dose than in those who received Fluzone.

Study FIM12 and Study FIM07 analysed SAE and AESI rather than all reported adverse events, which lowers sensitivity to detect adverse events which did not result in hospitalisation. The extensive post-marketing experience with Fluzone High-Dose in USA, evaluated in the second round clinical evaluation report partially mitigates this limitation.

The second round RMP evaluation report recommends the sponsor must provide a commitment to conduct an enhanced safety surveillance study in Australia, if requested by TGA. The TGA has not yet adopted Guideline on Influenza Vaccines Non-clinical and Clinical Module EMA/CHMP/VWP/457259/2014 (adopted in Europe 1 February 2017) but is considering adoption with annotation. The RMP evaluator's recommendation reflects the post-authorisation pharmacovigilance requirements for seasonal influenza vaccines and the need conduct of enhanced safety surveillance will be determined on a case to case basis.

Delegate's proposed action

The Delegate had no reason to say, at this time, that the application for inactivated high-dose trivalent influenza vaccine (split virion), Fluzone High-Dose, should not be approved for registration, subject to Advisory Committee on Vaccines (ACV) advice.

Request for ACV advice

The committee is requested to provide advice on the following specific issues:

1. Is the benefit-risk balance for Fluzone High-Dose favourable for registration? It should be noted that the benefits of Fluzone High-Dose against the three included strains have to be balanced against the lack of coverage of one of the B strain lineages and the degree of benefits of Fluzone High-Dose will differ as the match between circulating strains of influenza and the vaccine strains varies from year to year.
2. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor's comments on the issues for which the advice of the ACV is sought, as outlined in the Delegate's Overview of 2 November 2017, are presented below.

Sponsor's response to issues raised in the request for ACV advice

1. Is the benefit-risk balance for Fluzone High-Dose favourable for registration? It should be noted that the benefits of Fluzone High-Dose against the three included strains have to be balanced against the lack of coverage of one of the B strain lineages and the degree of benefits of Fluzone High-Dose will differ as the match between circulating strains of influenza and the vaccine strains varies from year to year.

Sponsor response

As for any influenza vaccine, the degree of benefits of Fluzone High-Dose may vary because of a range of factors such as the match between circulating strains and the vaccine compositions from year to year. Of note, the WHO makes recommendations on influenza vaccine composition each year based on the best available data at the time when the recommendation is made; these data are collected through the year- round work of the WHO Global Influenza Surveillance and Response System. The Australian Influenza Vaccine Committee (AIVC) meets at TGA each year to review and evaluates data related to epidemiology, antigenic and genetic characteristics of influenza strains circulating in

Australia before finalising the recommendation of influenza viruses to be used in the composition of the influenza vaccines for coming influenza season. Through these processes, the chance of vaccine compositions matching the circulating strains is maximised.

It is acknowledged that the seasonal influenza vaccines currently used under the National Immunisation Program are standard dose, quadrivalent inactivated vaccines (QIV) which include two A strains and two B lineages. However, among adults and the elderly, influenza A is more common than influenza B, is more likely to become epidemic and at the individual level is associated with substantially greater risk of morbidity or mortality. Whilst a QIV high dose vaccine is in development, the available data supports a favourable benefit risk profile to support approval of the TIV vaccine for use amongst Australians aged ≥ 65 years, based on the following considerations:

a. *Influenza A strains are responsible for the majority of influenza disease burden in Australians aged ≥65 years*

Most of influenza notifications in adults aged ≥ 65 years in Australia are due to influenza A strains, either A/H3N2 or A/H1N1. In a recent study using national notification data on laboratory confirmed influenza in Australia, the proportions of influenza notifications typed as influenza A during 2001 to 2014 were 89% in ≥ 85 years old and 85% in those aged 65 to 84 years, respectively.[4] Assuming two B lineages covered a similar proportion of the remaining influenza cases in adults ≥ 65 years during the same period;[5] the proportion of the influenza burden due to the alternative B lineage (in QIV but not in TIV) in adults aged ≥ 65 years is considered to be small.

Epidemiologically, A/H3N2 predominant seasons are associated with increased mortality and morbidity attributable to influenza.[6,7] In Australia, the highest incidence of death attributable to influenza among older adults (and most other age groups) during 2006 to 2013 (excluding 2009) was seen in A/H3N2 predominant seasons.[8] In 2012 for example, the incidence of death in those ≥ 75 years old peaked compared with other study years; 10.1 per 100,000 and this was almost three times of the average in the whole period (3.7 per 100,000).[8] The second highest incidence of death among older adults is seen in 2007, another A/H3N2-predominant season.[9] Therefore, when considering the optimal approach to improving influenza vaccine efficacy in those aged 65 years and older it was essential to ensure improved protection against A/H3N2 strains. Fluzone High-Dose has been formulated to contain four times the amount of A/H3N2 antigens as standard dose vaccine.

b. *Robust evidence of increased efficacy and effectiveness of Fluzone High-Dose compared with standard dose vaccine in adults aged ≥65 years*

Clinical data included in the registration dossier and extensive post marketing experience (68 million doses distributed) have demonstrated that Fluzone High-Dose has clinically and statistically significantly increased efficacy when compared with standard dose vaccines. This conclusion is supported by a number of independent, large-scaled (with sample size up to 6.1 million) cohort studies that confirm that the higher antigenic content

[4] Moa AM, Muscatello DJ, Turner RM, MacIntyre CR. Epidemiology of influenza B in Australia: 2001-2014 influenza seasons. Influenza Other Respi Viruses 2017; 11: 102-109
[5] Barr IG, Jelley LL. The coming era of quadrivalent human influenza vaccines. Drugs 2012; 72: 2177-2185.
[6] Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004; 292: 1333-1340.
[7] Centers for Disease Control and Prevention (CDC). Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. MMWR Morb Mortal Wkly Rep 2010; 59: 1057-1062.
[8] Li-Kim-Moy J, Yin JK, Patel C, et al. Australian vaccine preventable disease epidemiological review series: Influenza 2006 to 2015. Commun Dis Intell Q Rep 2016; 40: E482-495.
[9] Owen R, Barr IG, Pengilley A, Liu C, Paterson B, Kaczmarek M. Annual report of the National Influenza Surveillance Scheme, 2007. Commun Dis Intell Q Rep 2008; 32: 208-226.

in Fluzone High-Dose is associated with a reduction in the burden of influenza associated morbidity and mortality.[10,11]

c. Potential cross protection afforded by TIV against the alternative B lineage in QIV

There is a suggestion that TIV may induce cross-protection to the alternative B lineage that is only included in QIV.[12,13] While there are no data on adults aged ≥ 65 years or Australian setting, a systematic review of randomised control trials in all-age adults reported that cross protection (efficacy of TIV against mismatched B lineage) is up to 68% of the direct efficacy from TIV against the B lineage in TIV.[13]

In summary, the above supports the approval of Fluzone High-Dose for use in an elderly high risk population to elicit enhanced immune responses and reduce the burden of influenza associated morbidity and mortality.

RMP recommendations on Active Surveillance

The sponsor has noted the Delegate's comments regarding the second round RMP evaluation report recommendations for an enhanced safety surveillance study in Australia. As part of the sponsor's responses, the sponsor committed that if Fluzone High-Dose was unsuccessful in being included on the NIP and hence in AusVaxSafety's active surveillance, then an alternate approach would be discussed with the TGA prior to the launch of the vaccine.

Following the public health impact of the 2017 influenza season, the Department of Health (DoH) has identified the availability of a vaccine targeting the elderly population, who are at the highest risk of complications from influenza, as a priority. As a result, DoH has been working to facilitate a fast track registration and inclusion on the NIP for Fluzone High-Dose. On this basis the existing active surveillance scheme will address the concerns raised during the RMP evaluation and therefore the sponsor does not consider there are any outstanding issues precluding a recommendation for approval of the vaccine.

Viral safety

The sponsor has noted the Delegate's comment that the viral safety discussions are ongoing between the TGA and Sanofi.

The sponsor is working to address the control of non-enveloped, non-haemagglutinating viruses to ensure resolution of this issue before supply of the product in Australia.

Conclusion

In conclusion, significant post-marketing experience of Fluzone High-Dose has accumulated to support the benefit-risk in the elderly population. It has been used in the US since 2010 and is currently marketed in both the US and Canada with and more than 68 million doses distributed. These data support use in the Australia based on the similarity of patient populations, life expectancy, chronic disease burden, infectious disease burden and policy recommendations for the control of influenza.

The overall benefit-risk profile for Fluzone High-Dose supports its approval for use in persons 65 years of age and older as an option to elicit enhanced immune responses and

[10] Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard- dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis 2015; 15: 293-300.
[11] Shay DK, Chillarige Y, Kelman J, et al. Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among US Medicare Beneficiaries in Preventing Postinfluenza Deaths During 2012-2013 and 2013-2014. J Infect Dis 2017; 215: 510-517
[12] Diazgranados CA, Denis M, Plotkin S. Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: A systematic review with meta-analyses of controlled trials. Vaccine 2012; 31: 49-57
[13] Tricco AC, Chit A, Soobiah C, et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. BMC Med 2013; 11: 153.

efficacy against influenza and therefore reduce the disease burden including influenza-associated morbidity and mortality to address a significant unmet public health need.

Advisory Committee Considerations

The ACV, taking into account the submitted evidence of efficacy, safety and quality, considered Fluzone High-Dose inactivated trivalent influenza vaccine (split virion), containing 60 micrograms of influenza virus haemagglutinin from each of three strains (H1N1-like strain, H3N2-like strain, and B strain of either Yamagata or Victoria lineage), to have an overall positive benefit-risk profile for the indication:

> *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.*

In making this recommendation the ACV:

- Was of the view that the safety data were adequate. The types of adverse events were similar between Fluzone High-Dose and other influenza vaccines and the absolute rates of adverse events in the clinical trial populations for Fluzone High-Dose (compared to rates for trivalent influenza vaccines) were higher but acceptable.
- Was of the view that the efficacy data and immunogenicity data were sufficient and positive.
- Noted that the trivalent influenza vaccine was an acceptable comparator from a regulatory perspective, although current Australian practice is to use a quadrivalent vaccine.
- Noted that the clinical trial population excluded/omitted groups in which annual influenza vaccination is recommended (for example, immunosuppressed subjects; non-ambulatory patients; Aboriginal and Torres Strait Islander people; patients with significant co-morbidities).
- Noted that patients and healthcare practitioners will need education to assist in the comparison between and selection of influenza vaccine to use in a particular season.
- Noted that the vaccine has been approved in the USA and Canada, with use to date of over 80 million doses.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACV advised that the section '*Precaution – Immunosuppressive treatments or conditions*' should reflect that there are very limited data for this vaccine in this population. The advice '*vaccination of individuals with chronic immunodeficiencies is recommended*' appeared to be general advice from a public health perspective. Such advice should only appear in the Fluzone High-Dose PI if there is appropriate supporting evidence of safety and efficacy in this population administered this vaccine.

The committee noted that contraindications include '*anyone with a known systemic hypersensitivity … to any component of the vaccine (e.g. egg or egg products)*'. The ACV supported the approach of the Australian Immunisation Handbook and Australasian Society of Clinical Immunology and Allergy (ASCIA) on vaccination of egg-allergic individuals.

Specific advice

The ACV advised the following in response to the Delegate's specific question on the submission:

1. *Is the benefit-risk balance for Fluzone High-Dose favourable for registration? It should be noted that the benefits of Fluzone High-Dose against the three included strains have to be balanced against the lack of coverage of one of the B strain lineages and the degree of benefits of Fluzone High-Dose will differ as the match between circulating strains of influenza and the vaccine strains varies from year to year.*

The ACV advised that the clinical efficacy and safety data were sufficient to support registration of the vaccine.

Enhanced efficacy against H3N2 has to be weighed against the higher likelihood of pain, swelling and erythema at the injection site and systemic reaction (myalgia, malaise and headache) which can interfere with the activities of daily living and work.

The ACV noted that Shay et al.,[14] concluded that:

> *high-dose vaccine was significantly more effective (than standard dose) in preventing postinfluenza deaths in 2012–2013, when A(H3N2) circulation was common, but not in 2013–2014 (when 90% of A virus was H1N1).*

This study indicated that the relative advantage of Fluzone High-Dose against a trivalent influenza vaccine varied with the circulating A strain. In some seasons there will be a meaningful benefit of high-dose vaccine over standard dose vaccine while in years that H3N2 is not predominant there may be no advantage to the population.

The committee noted that Study FIM05 was the principal study that provided data on common adverse events not requiring hospitalisation. About 0.3% of subjects in both the Fluzone High-Dose and Fluzone treatment arms had one or more immediate adverse events. There were no significant differences in the type of reactions reported between treatment arms. A total of 559 (21.7%) of Fluzone High-Dose and 276 (21.9%) of Fluzone subjects reported unsolicited adverse events up to day 28. Studies FIM12 and FIM07 only analysed serious adverse events and adverse event of special interest (AESI). The ACV concluded that this was adequate, as some post-marketing data were provided in the second round assessment.

The committee also noted the work of Kaka et al.,[15] which concluded:

> *Thirty-seven percent of HD (high dose) recipients and 22% of SD [standard dose] recipients reported a local or systemic side effect (P < .001), most of which were mild to moderate. Only 7 of 547 (1.3%) HD recipients and 3 of 541 (0.6%) SD recipients reported a severe side effect (P = .34). There was no significant difference in healthcare visits between the groups.*

Overall, the benefit of improved vaccine effectiveness against H3N2 virus is expected to more than compensate for the lack of vaccine protection against the B strain that is not present in the vaccine.

2. *Any other issues that the ACV thinks may be relevant to a decision on whether or not to approve this application.*

The committee noted that data on Fluzone High-Dose would be captured under the AusVaxSafety active surveillance program, particularly if the vaccine is included within the National Immunisation Program. The sponsor intends to rely upon this for active surveillance. The number of patients aged over 65 years who would be enrolled in the

[14] Shay DK, Chillarige Y, Kelman J, et al. Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among US Medicare Beneficiaries in Preventing Postinfluenza Deaths During 2012–2013 and 2013–2014 *J Infect Dis* 2017: 215:512-517

[15] Kaka AS, Filice GA, Myllenbeck S, et al. Comparison of Side Effects of the 2015–2016 High-Dose, Inactivated, Trivalent Influenza Vaccine and Standard Dose, Inactivated, Trivalent Influenza Vaccine in Adults ≥65 Years. *Open Forum Infect Dis* 2017; doi: 10.1093/ofid/ofx001

AusVaxSafety program is uncertain (for comparison, the published 2017 AusVaxSafety influenza vaccine safety data included a cohort of 28,050 adults aged over 65 years who had received any of three influenza vaccines). The AusVaxSafety program does have some limitations: it relies on sentinel sites, and so does not cover the entire population; due to sample size it should detect events that are uncommon, but not rare; and patient-reported outcomes are currently only solicited at Day 3 post-vaccination. Differences between brands can be determined readily but subtle differences may not be detected. However, this surveillance has the capacity to provide near real-time safety signal detection and provides additional capacity to monitor adverse events, as compared with spontaneous reporting alone.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration Fluzone High-Dose inactivated trivalent influenza vaccine (Split Virion) 180 mcg influenza virus haemagglutinin 0.5mL suspension for injection in Pre-filled syringe (AUST R 285932), indicated for:

> *Fluzone High-Dose is indicated 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 and older*

Specific conditions of registration applying to these goods

1. It is a condition of registration that all independent batches of Fluzone High-Dose Inactivated Trivalent Influenza Vaccine (Split Virion) imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and you have received notification acknowledging release from the Laboratories Branch, TGA.

   For each independent batch of the product imported into Australia, the Sponsor must supply the following:

   - A completed Request for Release Form, available from Vaccines@tga.gov.au.
   - Complete summary protocols for manufacture and QC, including all steps in production.
   - At least 20 packaged doses of each first consignment of product lot with the Australian approved labels, PI and packaging. 10 packaged doses of any further consignment of already released product (including diluents) with the Australian approved labels, PI and packaging.
   - Evidence that the consignment has been shipped under the approved storage conditions between the manufacturer and Australia e.g. plots of temperature recordings, summary of temperature monitoring and a summary of the maximum and minimum temperatures experienced during shipping. Excursions from the approved storage conditions should be detailed and justified. Please note that the data provided to support an excursion should meet with the current TGA guidance (see https://www.tga.gov.au/guidance-14-stability-testing-prescription-medicines) and that additional samples may be requested from the consignment.
   - Certificate of Release from a regulatory agency acting for the country of origin such as an OMCL (if available).
   - Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

Attachment 1. Product Information

The PI for Fluzone High-Dose approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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