



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Inactivated quadrivalent influenza vaccine (split virion) influenza virus haemagglutinin

Proprietary Product Name: Fluzone High-Dose
Quadrivalent

Sponsor: Sanofi-Aventis Pty Ltd

November 2020

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Common abbreviations

Abbreviation	Meaning
AAN	Australian Approved Name
Ab	Antibody
ACV	Advisory Committee on Vaccines
ADL	Activities of Daily Living score
AE	Adverse event
AESI	Adverse event of special interest
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific Annex
ATAGI	Australian Technical Advisory Group on Immunisation
BLA	Biological Licensing Application (United States)
BMI	Body mass index
CAS	Chemical Abstracts Service
CI	Confidence interval
CMI	Consumer Medicines Information
COPD	Chronic obstructive pulmonary disease
CPD	Certified Product Details
DLP	Data lock point
EMA	European Medicines Agency (European Union)
EMA	European Medicines Evaluation Agency (European Union; now known as European Medicines Agency)
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (United States)
GMR	Geometric mean ratio
GMT	Geometric mean titre

Abbreviation	Meaning
GMTR	Geometric mean titre ratio
GVP	Good Pharmacovigilance Practices
H1N1	Influenza A virus subtype H1N1
H3N2	Influenza A virus subtype H3N2
HA	Haemagglutinin
HAI	Haemagglutination inhibition
HAI GMT	Haemagglutination inhibition geometric mean titre
ICD	International Classification of Diseases (World Health Organization)
ILI	Influenza-like illness
IM	Intramuscular
MF59	An immunologic adjuvant
NA	Neuraminidase
NIH	National Institutes of Health (United States)
NIID	National Institute of Infectious Diseases (Japan)
NIP	National Immunisation Program
NSAID	Non-steroidal anti-inflammatory drug
PBAC	Pharmaceutical Benefits Advisory Committee
PBRER	Periodic benefit-risk evaluation report
PBS	Pharmaceutical Benefit Scheme
PCR	Polymerase chain reaction
PERR	Previous event rate ratio
Ph. Eur.	European Pharmacopoeia
PI	Product Information
PPAS	Per-protocol analysis set
PSUR	Periodic safety update report

Abbreviation	Meaning
QIV	Quadrivalent influenza vaccine
QIV-HD	High dose quadrivalent influenza vaccine
RCT	Randomised control trial
RMP	Risk management plan
RNA	Ribonucleic acid
RR	Relative risk
SAE	Serious adverse event
SC	Subcutaneous
TIV	Trivalent influenza vaccine
TIV-HD	High dose trivalent influenza vaccine
TIV-HD1	High dose trivalent influenza vaccine licensed as Fluzone High-Dose for the 2017-2018 Northern Hemisphere influenza season
TIV-HD2	High dose trivalent influenza vaccine containing an alternate strain of influenza B lineage (compared with TIV-HD1; see above)
TIV-SD	Standard dose trivalent influenza vaccine
US(A)	United States (of America)
VHA	Veterans Health Administration (United States)
VRBPAC	Vaccines and Related Biological Products Advisory Committee (United States)
WHO	World Health Organization
WSL	Working seed lots

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biological entity
<i>Product name:</i>	Fluzone High-Dose Quadrivalent (QIV); ¹
<i>Active ingredient:</i>	Inactivated quadrivalent influenza vaccine (split virion) influenza virus haemagglutinin
<i>Decision:</i>	Approved
<i>Date of decision:</i>	30 July 2020
<i>Date of entry onto ARTG:</i>	31 July 2020
<i>ARTG number:</i>	320962
<i>, Black Triangle Scheme:²</i>	No
<i>Sponsor's name and address:</i>	Sanofi-Aventis Australia Pty Ltd Talavera Corporate Centre, Building D 12 - 24 Talavera Road Macquarie Park, NSW, 2113
<i>Dose form:</i>	Suspension for injection
<i>Strength:</i>	240 µg/0.7 mL; ³
<i>Container:</i>	Pre-filled syringe (PFS)
<i>Pack sizes:</i>	5 x 0.7 mL single dose pre-filled syringes with needles; 5 x 0.7 mL single dose pre-filled syringes without needle; 10 x 0.7 mL single dose pre-filled syringes without needle.
<i>Approved therapeutic use:</i>	<i>Fluzone High-Dose Quadrivalent is indicated for active immunisation for the prevention of influenza disease. Fluzone High-Dose Quadrivalent is indicated for use in persons 65 years of age and older.</i>

¹ Note, as per the Delegate's approval letter 'Quadrivalent' will be expressed as 'QIV' in the tradename of the product in the ARTG for administrative purposes. Quadrivalent will be maintained in the approved Product Information (PI) and Consumer Medicines Information (CMI) documents.

² The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

³ This quadrivalent influenza vaccine contains a total of 240 µg influenza virus haemagglutinin per 0.7 mL pre-filled syringe (PFS), comprised of 4 (4 x 60 µg) different and specified seasonal strains of influenza virus haemagglutinin. See main body of text for details.

The use of Fluzone High-Dose Quadrivalent should be based on official recommendations.

See Section 5.1 Clinical Trials for information on the effects on influenza associated complications.

<i>Route of administration:</i>	Intramuscular injection
<i>Dosage:</i>	<p>Fluzone High-Dose Quadrivalent should be given in accordance with the national recommendation as per the current Immunisation Handbook.</p> <p>The recommended dosage of Fluzone High-Dose Quadrivalent is 1 dose of 0.7 mL, annually, in persons 65 years of age and older.</p> <p>For further information refer to the Product Information.</p>
<i>Pregnancy category:</i>	<p>B2</p> <p>Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.</p> <p>Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.</p> <p>The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.</p>

Product background

This AusPAR describes the application by Sanofi-Aventis Australia Pty Ltd (the sponsor) to register Fluzone High-Dose Quadrivalent (QIV);¹ inactivated quadrivalent influenza vaccine (split virion) influenza virus haemagglutinin 240 µg, suspension for injection 0.7 mL pre-filled syringe.

Fluzone Quadrivalent High-Dose is indicated for active immunisation for the prevention of influenza disease and the associated complication of pneumonia-related hospitalisation. Fluzone Quadrivalent High-Dose is indicated for use in persons 65 years of age and older.

Fluzone High-Dose Quadrivalent is an inactivated split-virus quadrivalent influenza vaccine (QIV) containing four influenza virus components, two influenzavirus A strains (subtypes H1N1 and H3N2) and two influenzavirus B strains (one from each of the Victoria and Yamagata lineages). Fluzone High-Dose Quadrivalent contains 60 µg haemagglutinin (HA) of each of the four virus strains for a minimum of 240 µg of HA compared to 15 µg HA per strain in standard adult presentations. In Australia, Fluzone High-Dose is currently registered as a trivalent influenza vaccine (TIV) (an inactivated

influenza virus (split virion) vaccine).⁴ The antigens included in Fluzone High-Dose Quadrivalent are the same drug substances used in the manufacture of FluQuadri;⁵ inactivated quadrivalent influenza vaccine.

Influenza viruses are single-stranded ribonucleic acid (RNA) orthomyxoviruses. They are classified antigenically as types A, B or C. Generally, only influenza A and B cause severe disease in humans. Influenza viruses have 2 surface glycoprotein antigens: haemagglutinin (HA), which is involved in cell attachment during infection; and, neuraminidase (NA), which facilitates the release of newly synthesised virus from the cell. Influenza A viruses can be classified into subtypes based on differences in these surface antigens, but influenza B viruses cannot. There are 2 distinct influenza B lineages that co-circulate in varying proportions from year to year: B/Victoria and B/Yamagata. Antibodies against the surface antigens, particularly HA, reduce infection or severe illness due to influenza.

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);⁶ recommends annual influenza vaccination for all people over the age of 65 (as well as other vulnerable groups).⁷

Trivalent influenza vaccines (TIVs) have been used since the 1970s and contain 3 strains of influenza virus: 2 influenza A subtypes and 1 influenza B lineage. The 3 strains included are the same as those contained in quadrivalent influenza vaccines (QIVs), which contain an additional influenza B lineage. From 2018, two new formulations of TIVs (also known as 'enhanced TIVs') became available for use in adults aged ≥ 65 years only. One is Fluzone High-Dose, a TIV from the same sponsor; this is a high-dose vaccine that contains 60 μg HA per included virus strain per dose; this is 4 times the HA content of standard TIVs.⁴ The other contains an adjuvant, MF59;⁸ and the standard 15 μg of HA per strain per dose (Fluad). Both vaccines are formulated to induce a greater immune response than standard TIVs and are currently recommended for elderly Australian subjects (aged ≥ 65 years).⁹ At the time of evaluation, the high-dose (Fluzone High-Dose) and adjuvanted (Fluad) TIVs are recommended in preference to quadrivalent influenza vaccines for adults aged ≥ 65 years.

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

⁴ See the AusPAR for Fluzone High-Dose Inactivated high-dose trivalent influenza vaccine Sanofi-Aventis Australia PM-2017-00690-1-2 (published 20 August 2018).

⁵ See the AusPAR for FluQuadri, FluQuadri Junior Influenza virus haemagglutinin H1N1, H3N2, B Victoria lineage, B Yamagata lineage Sanofi-Aventis Australia Pty Ltd PM-2013-02401-1-2 (published 20 March 2015).

⁶ The **National Immunisation Program (NIP)** was set up by the Commonwealth and state and territory governments in 1997. It aims to increase national immunisation coverage to reduce the number of cases of diseases that are preventable by vaccination in Australia. The NIP provides free vaccines to eligible people to help reduce diseases that can be prevented by vaccination. This improves national immunisation coverage rates.

⁷ The **Australian Immunisation Handbook** provides clinical guidelines for healthcare professionals and others about the safest and most effective use of vaccines in their practice. The guidance is based on the best scientific evidence available, from published and unpublished literature. The Handbook contains information for all vaccines that are available in Australia at or near the time of publication. Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook, Australian Government Department of Health, Canberra. Available online at: <https://immunisationhandbook.health.gov.au>

⁸ **MF59** is an immunologic adjuvant that uses an oil-on-water emulsion of squalene oil. MF59 (not a component of the vaccine in this submission) is added to influenza vaccines to help stimulate the human body's immune response through production of CD4 memory cells.

⁹ <https://immunisationhandbook.health.gov.au/recommendations/adults-aged-65-years-are-strongly-recommended-to-receive-either-high-dose-or>

> 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.

Influenza A viruses (of subtypes H1N1 and H3N2) account for the majority of circulating influenza viruses in most countries and seasons; influenza B is common in all regions of the world with approximately 20% of the reported influenza cases. Influenza B often co-circulates with influenza A, although it is rarely dominant, and usually circulates later in the season than influenza A viruses. Influenza B outbreaks have been described among older adults and have led to excess mortality in some annual epidemics. Among the elderly, influenza B is associated with excess pneumonia and influenza hospitalisations, and while excess population-based hospitalisation rates associated with influenza B are lower than those associated with A/H3N2, they are twice as high as those associated with A/H1N1.

Fluzone High-Dose Quadrivalent 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

Australia

This product is considered a new biological entity for Australian regulatory purposes.

This product is similar to Fluzone High-Dose, a high dosed inactivated (split virion) TIV currently registered and supplied by the same sponsor containing a nominal 180 µg of HA antigen, with 60 µg of each of three strains (influenza A/H1N1 and A/H3N2, and a B strain of either Yamagata or Victoria lineage). Fluzone High-Dose was approved on 20 December 2017 and listed on the ARTG from 21 December 2017.⁴

Fluzone High-Dose Quadrivalent, covered in this submission, is a similarly high-dosed inactivated split-virion influenza vaccine, containing a nominal 240 µg of HA antigen, with 60 µg each of four influenza virus strains; two type A strains (subtypes H1N1 and H3N2) and two strains of influenza B lineage.

Overseas

At the time the TGA considered this application, a similar application for Fluzone High-Dose Quadrivalent had been submitted in the United States (US), as a supplement to the US Food and Drug Administration (FDA) Fluzone Biological Licensing Application (BLA) in January 2019. It was approved in November 2019 for:

'Fluzone High-Dose Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Fluzone High-Dose Quadrivalent is indicated for use in persons 65 years of age and older.'

Fluzone High-Dose Quadrivalent influenza vaccine has also been submitted in the European Union (EU) through the European Medicine Agency's (EMA) decentralised procedure (25 countries included) in April 2019 with proposed indications aligned to those proposed in Australia.

Fluzone Quadrivalent High-Dose was submitted in Canada in July 2019 with proposed indications aligned to those in the US.

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 timeline

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

Table 1: Timeline for Submission PM-2019-03202-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	2 September 2019
First round evaluation completed	31 January 2020
Sponsor provides responses on questions raised in first round evaluation	28 February 2020
Second round evaluation completed	14 April 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 May 2020
Sponsor's pre-Advisory Committee response	18 May 2020
Advisory Committee meeting	3 June 2020
Registration decision (Outcome)	30 July 2020
Completion of administrative activities and registration on the ARTG	31 July 2020
Number of working days from submission dossier acceptance to registration decision*	204 days

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

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

Quality

The quality summary identified no quality issues that would preclude the registration of Fluzone High-Dose Quadrivalent, inactivated quadrivalent influenza vaccine (split virion). Sufficient evidence has been provided to demonstrate that the risks related to the adventitious presence of infectious enveloped viruses, prion and mycoplasma agents in

the manufacturing of Fluzone Quadrivalent High Dose (HD) are controlled to an acceptable level to minimise infectious disease risks to patients.

Product will be registered in Australia in both a needle free presentation with and without needle supplied. Doses are presented in 5 or 10 dose cartons however these either of these pack sizes may not be marketed. The proposed indication for the product is for persons aged 65 years of age and older.

In conclusion, the product is recommended for approval. However, please note that there are post-approval commitments that should be met by the sponsor, prior to the lodgement of the Annual Strain Update for 2021, Southern Hemisphere Influenza Season. Refer to specific conditions of registration.

Nonclinical

Two nonclinical studies were provided in this submission; one repeat-dose toxicity study and one local tolerance study. Both studies were conducted in rabbits with the proposed QIV-HD.

Immunogenicity of QIV-HD against all 4 strains was demonstrated in rabbits in the toxicity study.

There was no systemic toxicity in rabbits administered 3 doses of QIV-HD with 2 weekly dosing intervals (16 times the human dose on a $\mu\text{g}/\text{kg}$ basis). The number of germinal centres of spleen was increased, probably associated with the pharmacological action of the vaccine. Minor inflammation was observed at injection sites.

Local tolerance reactions consisted of slight haematoma and inflammation after a single subcutaneous injection, and slight haematoma, very slight erythema and oedema, and slight to moderate muscle inflammation and necrosis following IM injections in rabbits.

Although the number of submitted nonclinical studies with QIV-HD is limited, the evaluated data raises no nonclinical objections to the registration of Fluzone Quadrivalent High-Dose. Evaluation of safety and efficacy will largely rely on clinical data.

Clinical

Content of the clinical dossier

The Australian clinical submission is based on the dossier submitted in the EU in April 2019.

The clinical dossier includes:

- 4 TIV-HD clinical studies
 - Study FIM01 (US National Institutes of Health (NIH) Study 04-100);
 - Study FIM05;
 - Study FIM12; and
 - Study FIM07
- (Note: the TIV-HD studies above have been previously evaluated by the TGA).
- 2 QIV-HD clinical studies
 - Study QHD00008

- § Study QHD0008 was a Phase I/II safety and immunogenicity study of QIV-HD (SP0178) administered by intramuscular or subcutaneous route in subjects aged 65 years and older in Japan.
 - Study QHD00013
- § Study QHD00013 was a Phase III safety and immunogenicity study of QIV-HD administered by intramuscular route in subjects aged 65 years and older compared to TIV-HD. This is the pivotal study in this submission.
- A supplementary analysis of data from Study FIM12 reported on observational and exploratory effectiveness analyses as did 2 cluster-randomised controlled clinical trials published conducted by Gravenstein et al. (2018);¹⁰ and other real world effectiveness studies (these evaluated TIV-HD versus TIV-standard dose (TIV-SD)) including Young-Xu et al. (2018).¹¹

Immunogenicity

Study QHD00013

Study QHD00013 was a randomised, modified double-blind, active-controlled, multicentre study conducted in 2670 healthy subjects aged 65 years and older. High-dose quadrivalent influenza vaccine (QIV-HD) was compared to one of the high-dose trivalent influenza vaccines (TIV-HD) containing either the B strain from the primary lineage (TIV-HD1, which was the licensed vaccine (Fluzone High-Dose) for the 2017-2018 Northern Hemisphere (NH) influenza season) or the B strain from the alternate lineage (TIV-HD2, which was an investigational TIV-HD containing an alternate B strain).

The primary objective was to demonstrate that QIV-HD induces an immune response (as assessed by HAI GMT;¹² and seroconversion rates) that is non-inferior to responses induced by the TIV-HD1 and TIV-HD2 for the 4 virus strains at 28 days post-vaccination in all subjects.

The secondary objectives were:

- to demonstrate that each B strain in QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-HD that does not contain the corresponding B strain in all subjects;
- to describe the immune response induced by QIV-HD, TIV-HD1 and TIV-HD2 by HAI measurement method in all subjects;
- to describe the immune response 28 days after vaccination by virus seroneutralisation measurement method;¹³ in a randomised subset of subjects from each study group; and
- to assess safety.

This study was conducted between September 2017 to April 2018 at 35 centres in the US.

¹⁰ Gravenstein S, Davidson HE, Taljaard M, 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* 2017; 5:738–46.

¹¹ Young-Xu Y, Van Aalst R, Mahmud SM, et al, Relative Vaccine Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among Veterans Health Administration Patients. *JID* 2018;217:1718–27.

¹² **HAI GMT = haemagglutination inhibition geometric mean titre**; the average haemagglutination inhibition antibody titre for a group of subjects calculated by multiplying all values and taking the n-th root of this number, where n is the number of subjects with available data.

¹³ The **virus seroneutralisation method** (or **serum virus neutralisation assay**) is a serological test to detect the presence and magnitude of functional systemic antibodies that prevent infectivity of a virus. The SVN assay is a highly sensitive and specific test that may be applied to influenza.

The study treatments were:

- High-Dose Influenza Vaccine Quadrivalent, (Zonal Purified, Split Virus) 2017 to 2018 Strains (QIV-HD). Each 0.7 mL dose of QIV-HD contained: Strains were based on World Health Organization (WHO) / Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommendations for the 2017 to 2018 Northern Hemisphere influenza season.
 - Active substances:
 - § A/Michigan/45/2015 X-275 (H1N1) strain 60 µg HA
 - § A/Hong Kong/4801/2014 (NYMC X-263B) (H3N2) strain 60 µg HA
 - § B/Brisbane/60/2008 strain 60 µg HA
 - § B/Phuket/3073/2013 strain 60 µg HA
- High-dose trivalent inactivated influenza vaccine (licensed Fluzone High-Dose, TIV-HD1). Each 0.5 mL dose of TIV-HD1 contained: Strains were based on WHO/VRBPAC recommendations for the 2017-2018 Northern Hemisphere influenza season.
 - Active substances:
 - § A/Michigan/45/2015 X-275 (H1N1) strain 60 µg HA
 - § A/Hong Kong/4801/2014 (NYMC X-263B) (H3N2) strain 60 µg HA
 - § B/Brisbane/60/2008 strain 60 µg HA.
- High-dose trivalent inactivated influenza vaccine (investigational TIV-HD with an alternate B strain, TIV-HD2). Each 0.5 mL dose of TIV-HD2 contained: Strains were based on WHO / VRBPAC recommendations for the 2017 to 2018 Northern Hemisphere influenza season.
 - Active substances:
 - § A/Michigan/45/2015 X-275 (H1N1) strain 60 µg HA
 - § A/Hong Kong/4801/2014 (NYMC X-263B) (H3N2) strain 60 µg HA
 - § B/Phuket/3073/2013 strain 60 µg HA.

The primary endpoint was immunogenicity assessed by the following:

- HAI antibody (Ab) titres obtained on Day 28: expressed as GMTs (with 95% confidence intervals (CI)) and pre/post vaccination ratios (geometric mean ratios (GMR))
- Seroconversion (titre < 10 (1/dil) at Day 0 and post-injection titre ≥ 40 (1/dil) at Day 28, or titre ≥ 10 (1/dil) at Day 0 and a ≥ 4-fold rise in titre (1/dil) at Day 28).

A sample size of 2616 was determined based on an overall power of 90% for demonstrating non-inferiority for both the HAI GMTs and seroconversion rates comparing QIV-HD versus TIV-HD1 and / or TIV-HD2 for all 4 virus strains. The non-inferiority margins were defined as 1.5 for GMTs and 10% for seroconversion rates.

A total of 2670 subjects were enrolled in the study and randomised to one of the 3 groups. All subjects were vaccinated and received the correct vaccine according to the group to which they were randomised. Of the 2670 randomised subjects, 16 (0.6%) subjects did not complete the study: 10 (0.6%), 3 (0.7%) and 3 (0.7%) subjects in the QIV-HD, TIV-HD1 and TIV-HD2 groups, respectively.

A total of 137 (5.1%) subjects had at least 1 protocol deviation with similar incidence across treatment groups.

The majority of subjects were female (58%), aged between 65 to 75 years (64.5%), Caucasian (91%) and obese (with 41% having a body mass index (BMI) > 30). Baseline demographics was similar across treatment groups. Overall, 1470 (55.1%) of all randomised subjects had at least one pre-specified medical history reported. Medical history data were similar across all study groups. Overall, approximately 74% of subjects received influenza vaccination in the previous year in the full analysis set (FAS) and per protocol analysis set (PPAS) populations.

The primary objective of non-inferiority of QIV-HD to TIV-HD as assessed by GMTs and seroconversion rates were met as the lower limit of the 95% CI was above 0.667 for the ratio of GMTs (see Table 2, below) and above -10% for the difference in seroconversion rates (see Table 3, below) for all influenza strains, in the PPAS.

Table 2: Study QHD00013 Non-inferiority of QIV-HD compared to TIV-HD1 and/or TIV-HD2 using geometric mean titres at Day 28 after vaccination (per-protocol analysis set)

	Antigen/strain	M	GMT	(95% CI)	QIV-HD/TIV-HDs*		
					GMT ratio	(95% CI)	Non-inferiority‡
QIV-HD	A/Michigan/45/2015 (H1N1)	1680	312	(292; 332)	--	--	--
	A/Hong Kong/4801/2014 (H3N2)	1679	563	(525; 603)	--	--	--
	B/Brisbane/60/2008 (B1)	1680	516	(488; 545)	--	--	--
	B/Phuket/3073/2013 (B2)	1680	578	(547; 612)	--	--	--
TIV-HD1	A/Michigan/45/2015 (H1N1)	423	387	(339; 442)	0.81	(0.697; 0.931)	--
	A/Hong Kong/4801/2014 (H3N2)	423	588	(513; 673)	0.96	(0.821; 1.115)	--
	B/Brisbane/60/2008 (B1)	423	476	(426; 532)	1.08	(0.958; 1.234)	Yes
TIV-HD2	A/Michigan/45/2015 (H1N1)	430	362	(317; 413)	0.86	(0.745; 0.993)	--
	A/Hong Kong/4801/2014 (H3N2)	430	600	(524; 687)	0.94	(0.805; 1.092)	--
	B/Phuket/3073/2013 (B2)	430	580	(519; 649)	1.00	(0.881; 1.129)	Yes
TIV-HD Pooled	A/Michigan/45/2015 (H1N1)	853	374	(341; 411)	0.83	(0.744; 0.932)	Yes
	A/Hong Kong/4801/2014 (H3N2)	853	594	(540; 653)	0.95	(0.842; 1.066)	Yes

Abbreviations: CI, confidence interval; GMT, geometric mean titer; QIV-HD, high-dose quadrivalent influenza vaccine; TIV-HD, high-dose trivalent influenza vaccine

M: number of subjects with available data for the considered endpoint

2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titres. Antilog transformations were applied to the results.

TIV-HD 1 does not contain B2 strain; TIV-HD2 does not contain B1 strain.

* Here TIV-HDs mean any one of the TIV-HD1, TIV-HD2, or TIV-HD pooled groups.

‡ Non-inferiority of GMTs is concluded if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups is > 0.667 for each of the comparisons applicable in this column.

Notation "--" is displayed in all non-applicable cells.

Table 3: Study QHD00013 Non-inferiority of QIV-HD compared to TIV-HD1 and/or TIV-HD2 using seroconversion rates at Day 28 after vaccination (per-protocol analysis set)

	Antigen/strain	n/M	%	(95% CI)	QIV-HD minus TIV-HDs*		
					Difference of %	(95% CI)	Non-inferiority‡
QIV-HD	A/Michigan/45/2015 (H1N1)	841/1669	50.4	(48.0; 52.8)	--	--	--
	A/Hong Kong/4801/2014 (H3N2)	830/1668	49.8	(47.3; 52.2)	--	--	--
	B/Brisbane/60/2008 (B1)	610/1669	36.5	(34.2; 38.9)	--	--	--
	B/Phuket/3073/2013 (B2)	778/1669	46.6	(44.2; 49.0)	--	--	--
TIV-HD1	A/Michigan/45/2015 (H1N1)	236/420	56.2	(51.3; 61.0)	-5.80	(-11.05; -0.45)	--
	A/Hong Kong/4801/2014 (H3N2)	222/420	52.9	(48.0; 57.7)	-3.10	(-8.40; 2.25)	--
	B/Brisbane/60/2008 (B1)	164/421	39.0	(34.3; 43.8)	-2.41	(-7.66; 2.70)	Yes
TIV-HD2	A/Michigan/45/2015 (H1N1)	219/428	51.2	(46.3; 56.0)	-0.78	(-6.06; 4.52)	--
	A/Hong Kong/4801/2014 (H3N2)	206/428	48.1	(43.3; 53.0)	1.63	(-3.67; 6.90)	--
	B/Phuket/3073/2013 (B2)	207/428	48.4	(43.5; 53.2)	-1.75	(-7.04; 3.53)	Yes
TIV-HD Pooled	A/Michigan/45/2015 (H1N1)	455/848	53.7	(50.2; 57.1)	-3.27	(-7.37; 0.86)	Yes
	A/Hong Kong/4801/2014 (H3N2)	428/848	50.5	(47.1; 53.9)	-0.71	(-4.83; 3.42)	Yes

Abbreviations: CI, confidence interval; QIV-HD, high-dose quadrivalent influenza vaccine; TIV-HD, high-dose trivalent influenza vaccine

M: number of subjects with available data for the considered endpoint

2-sided 95% CI for the single proportion (%) is based on the Clopper-Pearson method. 2-sided 95% CI for the difference is based on the Wilson score method without continuity correction.

TIV-HD1 does not contain B2 strain; TIV-HD2 does not contain B1 strain;

* Here TIV-HDs mean any one of the TIV-HD1, TIV-HD2, or TIV-HD pooled groups.

‡ Non-inferiority in seroconversion is concluded if the lower limit of the 2-sided 95% CI of the differences of seroconversion rates between groups is > -10% for each applicable comparison.

Notation "--" is displayed in all non-applicable cells.

Non-inferiority between QIV-HD and TIV-HD (pooled) was shown for the A/H1N1 and the A/H3N2 strains in terms of both GMTs and seroconversion rates.

For the B/Brisbane/60/2008 strain, non-inferiority was shown between QIV-HD and TIV-HD1 in terms of both GMT and seroconversion rates. Non-inferiority was also shown between QIV-HD and TIV-HD2 for the B/Phuket/3073/2013 strain in terms of both GMT and seroconversion rates.

The secondary objective was also met: each B strain in QIV-HD induced an immune response (as assessed by HAI GMTs and seroconversion rates) that was superior to the response induced by the TIV-HD that does not contain the corresponding B strain in all subjects; the lower limit of the 95% CI was above 1.5 for the ratios of GMTs and above 10% for the seroconversion rates for both B influenza strains as shown in Tables 4 and 5 (below).

Table 4: Superiority of B strains in QIV-HD compared to either TIV-HD1 or TIV-HD2 using geometric mean titres at Day 28 post-vaccination (full analysis set)

Antigen/strain	QIV-HD			TIV-HD1			TIV-HD2			QIV-HD/TIV-HD*		
	M	GMT	(95% CI)	M	GMT	(95% CI)	M	GMT	(95% CI)	GMT ratio	(95% CI)	Superiority§
B/Brisbane/60/2008 (B1)	1763	515	(488; 543)	--	--	--	446	253	(227; 283)	2.03	(1.802; 2.288)	Yes
B/Phuket/3073/2013 (B2)	1763	573	(542; 605)	439	280	(249; 316)	--	--	--	2.04	(1.804; 2.315)	Yes

Table 5: Superiority of B strains in QIV-HD compared to either TIV-HD1 or TIV-HD2 using seroconversion rates at Day 28 post-vaccination (full analysis set)

Antigen/strain	QIV-HD			TIV-HD1			TIV-HD2			QIV-HD minus TIV-HD*		
	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference of %	(95% CI)	Superiority§
B/Brisbane/60/2008 (B1)	636/1751	36.3	(34.1; 38.6)	--	--	--	69/444	15.5	(12.3; 19.3)	20.78	(16.5; 24.61)	Yes
B/Phuket/3073/2013 (B2)	817/1751	46.7	(44.3; 49.0)	76/437	17.4	(14.0; 21.3)	--	--	--	29.27	(24.78; 33.29)	Yes

Abbreviations: CI, confidence interval; QIV-HD, high-dose quadrivalent influenza vaccine, TIV-HD, high-dose trivalent influenza vaccine

M: number of subjects with available data for the considered endpoint

2-sided 95% CI for the single proportion (%) is based on the Clopper-Pearson method. 2-sided 95% CI for the difference is based on the Wilson score method without continuity correction.

* Here TIV-HD means either TIV-HD1 or TIV-HD2 groups displayed in the column names.

For B1 strain, the immunogenicity of QIV-HD will be compared to TIV-HD2 group which does not contain B1 strain.

For B2 strain, the immunogenicity of QIV-HD will be compared to TIV-HD1 group which does not contain B2 strain.

§ Superiority in seroconversion is observed if the lower limit of the 2-sided 95% CI of the difference of seroconversion rates between groups is > 10% for each applicable comparison.

Notation '--' is displayed in all non-applicable cells.

Results for other immunogenicity endpoints included results in the FAS which were similar to the PPAS.

Immunogenicity data (GMTs, seroconversion rates and seroprotection rates) were assessed by various covariate factors. The subgroup analysis showed trends suggesting GMTs and seroconversion rates were lower in adults aged > 75 years, males and those with history of prior influenza vaccination in previous year.

As measured by the seroneutralisation assay, the GMTs (pre- and post-vaccination), geometric mean ratios (GMR) and fold rise (2- and 4-fold) were similar among all study groups for both influenza A strains and for each of the B strains when QIV-HD is compared with the corresponding TIV-HD which contains the same B strain.

Results of this study met the criteria provided by the TGA-adopted guidance.¹⁴ Seroprotection rates were 95 to 99%; the mean GMT increase between pre and post-vaccination was > 2-fold in 41 to 50% of the subjects (for A strains) and 23 to 26% of subjects (for B strains) with similar rates across all treatment groups. Seroconversion rates were > 30% against all strains included in the vaccine (for A/H1N1: 50.4%, 56.2% and 51.3% with QIV-HD, TIV-HD1 and TIV-HD2, respectively; H3N2: 49.8%, 52.9% and 48.1%, respectively; for B1: 36.5%, 39% and 15.2%, respectively; for B2: 46.6%, 17.6% and 48.4%, respectively).

Overall, this study provided immunological evidence to support the proposed QIV-HD.

Study QHD00008

Study QHD00008 was a Phase I/II, randomised, modified double-blind, multicentre study conducted in 175 healthy adults aged 65 years and older to assess the safety and immunogenicity of the high-dose quadrivalent influenza vaccine (QIV-HD) administered by intramuscular (IM) method and QIV-HD administered by subcutaneous (SC) method. The study was conducted from September to November 2017 at 2 sites in Japan.

The first 10 subjects enrolled were randomised 1:1 to receive either QIV-HD by IM route or QIV-HD by SC route (Cohort 1). After review of the local and systemic adverse events (AE) occurring for 7 days post-vaccination (Day 0 to Day 7) in Cohort 1, the remaining 165 subjects were randomised 1:1:1 to receive QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route (Cohort 2).

The study treatments were:

- High-Dose Influenza Vaccine Quadrivalent, (Zonal Purified, Split Virus) 2017-2018 Strains (QIV-HD) provided in a pre-filled single-dose syringe. Each 0.7 mL dose of QIV-HD contains: Strains determined based on World Health Organization (WHO) / Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommendations for the 2017-2018 Northern Hemisphere influenza season.
 - Active substances:
 - § A/Michigan/45/2015 (NYMC X-275) (H1N1) strain 60 µg haemagglutinin (HA)
 - § A/Hong Kong/4801/2014 (NYMC X-263B) (H3N2) strain 60 µg HA
 - § B/Phuket/3073/2013 strain 60 µg HA
 - § B/Brisbane/60/2008 strain 60 µg HA
- [Information redacted] Japanese licenced standard-dose influenza vaccine: Local standard-dose inactivated influenza vaccine quadrivalent, 2017-2018 strains (QIV-SD), provided in a pre-filled single-dose syringe. Each 0.5 mL dose of QIV-SD contains: Strains determined based on the National Institute of Infectious Diseases (NIID) of Japan recommendations for the 2017-2018 Northern Hemisphere influenza season.
 - Active substances:
 - § A/Singapore/GP1908/2015 (IVR-180) (H1N1) pdm09 strain 15 µg HA
 - § A/Hong Kong/4801/2014 (NYMC X-263) (H3N2) strain 15 µg HA
 - § B/Phuket/3073/2013 strain 15 µg HA
 - § B/Texas/2/2013 strain 15 µg HA.

Immunogenicity was evaluated by:

¹⁴ EMEA (European Medicines Evaluation Agency) Note for Guidance CPMP/BWP/214/96 for the immunological evaluation of influenza vaccines for adult and elderly populations.

- HAI antibody titres obtained on Day 0 and Day 28;
- individual titre ratios of HAI at Day 28/Day 0;
- seroconversion:
 - titre <10 (1/dil) at Day 0 and post-injection titre \geq 40 (1/dil) at Day 28; or
 - titre \geq 10 (1/dil) at Day 0 and a \geq 4-fold increase in titre (1/dil) at Day 28;
- seroprotection, titre \geq 40 (1/dil) at Day 0 and Day 28.

The FAS included all randomised subjects who received at least one dose of the study vaccine and had a post-vaccination blood sample HAI result for at least one strain.

Majority of subjects were males (54.3%) with mean age of 70 years (28/175, 16% aged > 75 years) and mean BMI of 24kg/m². Almost all of the subjects had at least one ongoing significant diagnosis in the medical history. Baseline demographics and medical history was similar across treatment groups. The percentages of subjects who had received an influenza vaccination in the previous year (2016/2017 influenza season) were similar between the QIV-HD SC and QIV-SD SC groups (31.7% and 30.9%, respectively), but lower in the QIV-HD IM group (16.7%)

Post-vaccination, the seroconversion rate for both the QIV-HD IM and QIV-HD SC groups were higher than the QIV-SD SC group for all strains regardless of testing the subjects' sera with either the QIV-HD strains or QIV-SD strains. The difference (QIV-HD – QIV-SD) ranged from 17.9 to 42.9 for the QIV-HD IM group, and from 10.2 to 30.3 for the QIV-HD SC group. The seroconversion rates for the QIV-HD IM group were higher than the QIV-HD SC group for all strains, with the difference (QIV-HD IM – QIV-HD SC) ranging from 1.8 (95% CI: –15.6; 19.1) to 21.8 (95% CI: 5.5; 36.8).

Post-vaccination, high seroprotection rates (nearly 100%) were achieved for all strains in the QIV-HD IM and QIV-HD SC groups. In the QIV-SD SC group, seroprotection rates were over 90% for all strains.

Post-vaccination, the GMTRs (Visit 3 / Visit 1), and the seroconversion rates for the QIV-HD IM and QIV-HD SC groups were higher than the QIV-SD SC group for all strains regardless of whether sera was tested against the QIV-HD or QIV-SD strains.

It was observed that the GMTs at Visit 3 (post-vaccination), geometric mean titre ratios (GMTR) (Visit 3 / Visit 1), and seroconversion rates of subjects \geq 75 years in the QIV-HD IM group were lower compared with subjects < 75 years for any strain; however, there were limited numbers of subjects aged \geq 75 years.

Efficacy

In this submission, the sponsors state that evidence for efficacy of TIV-HD (compared to TIV-SD) in preventing '*associated complication of pneumonia-related hospitalisation*' was provided by the following 3 studies:

- supplementary analyses of data from pivotal TIV-HD Study FIM12;
- the cluster randomised control trial (RCT) published by Gravenstein et al. (2018);¹⁰ and
- the retrospective cohort study published by Young-Xu et al. (2018).¹¹

Study FIM12

Study FIM12 was a Phase IIIb/IV study which compared the clinical efficacy of Fluzone High-Dose and Fluzone Standard-Dose in preventing influenza in patients \geq 65 years of age over two consecutive seasons.

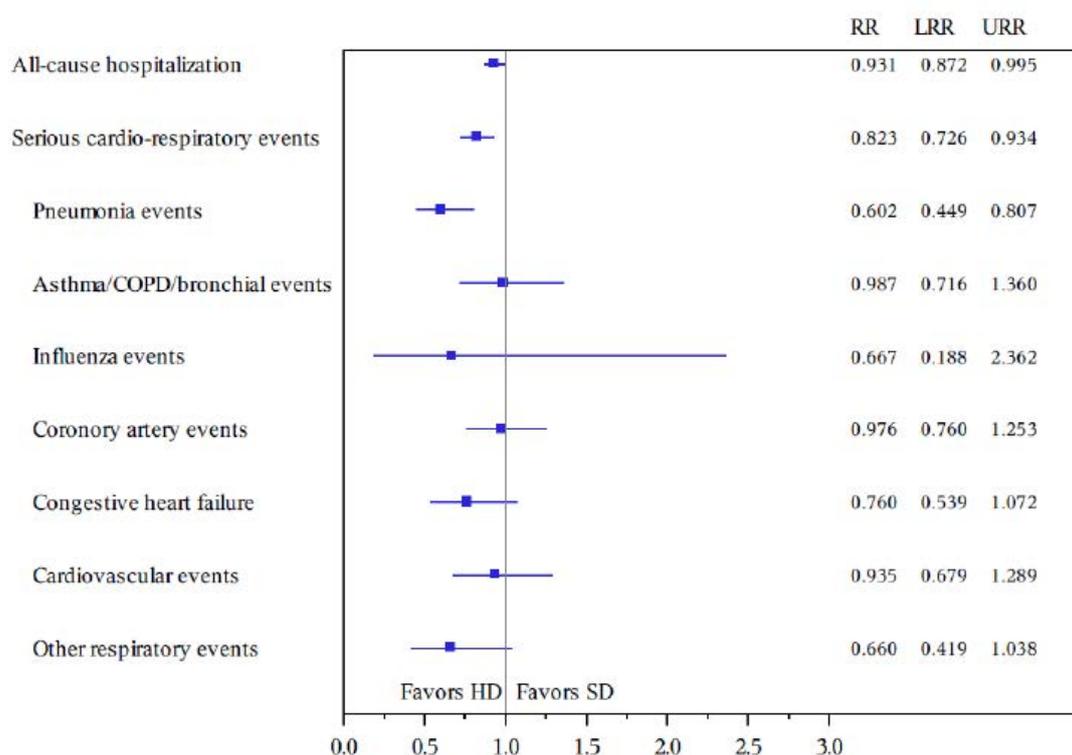
14,500 and 17,500 subjects were randomised 1:1 to receive either Fluzone High-Dose or Fluzone (standard-dose) in the first and second study years respectively. The primary endpoint of Study FIM12 was the occurrence of culture or polymerase chain reaction (PCR) confirmed influenza in subjects >14 days after vaccination who had a protocol-defined influenza-like illness (ILI). The number of cases of pneumonia or onset/exacerbation of pre-existing cardio-respiratory conditions, hospitalisations, overall medication use, antipyretic/analgesic/non-steroidal anti-inflammatory drug (NSAID) use, and antiviral use was lower in the Fluzone High-Dose than the Fluzone Standard-Dose treated group for Years 1 and 2 combined (in patients with confirmed diagnosis of influenza) although difference was not statistically significant with wide CIs. Results of Study FIM12 have previously been evaluated by the TGA.

Supplementary analyses of data from the pivotal TIV-HD Study FIM12 has not previously been evaluated by the TGA. For the supplementary analysis, selected serious cardiorespiratory events reported in Study FIM12 were grouped into 7 pre-specified categories and represented the following endpoints: pneumonia events, asthma/chronic obstructive pulmonary disease (COPD)/bronchial events, influenza events (serious laboratory-confirmed influenza diagnosed outside study procedures by a subject's health-care provider), other respiratory events, coronary artery events, congestive heart failure events and cerebrovascular events.

A total of 3173 hospitalisation events (all-cause) (1590 in Year 1 and 1583 in Year 2) were reported during the entire surveillance period. Rates (events per 1000 subject-seasons) of all-cause hospitalisation did not differ between the Fluzone High- and Standard-Dose vaccine groups in Year 1 (109.89 (797 events among 7253 subjects) versus 109.47 (793 events among 7244 subjects) per 1000 subject-seasons (relative risk (RR) 1.00; 95% CI: 0.91, 1.10)), whereas they were significantly lower for the Fluzone High-Dose vaccine group in Year 2 (83.90 (733 events in 8737 subjects) versus 97.15 (850 events among 8749 subjects) per 1000 subject-seasons (RR, 0.86; 95% CI: 0.79, 0.95)) and for both study years combined (95.68 (1530 events among 15,990 subjects) versus 102.73 (1643 events among 15,993 subjects) per 1000 subject-seasons (RR, 0.931; 95% CI: 0.872, 0.995)).

For the 2 study years combined, the aggregate rates of any selected serious cardiorespiratory events possibly related to influenza (overall) were lower in the Fluzone High-Dose vaccine group compared to the Fluzone Standard-Dose vaccine group. For both years combined, there was a significant reduction in the total number of serious cardiorespiratory events (relative vaccine effectiveness, 17.7% (95% CI: 6.6%, 27.4%)) among Fluzone High-Dose vaccine recipients compared to Fluzone vaccine recipients, including a significant reduction in serious pneumonia events (relative vaccine effectiveness, 39.8% (95% CI: 19.3%, 55.1%)). In addition, a borderline significant reduction in all-cause hospitalisation (relative vaccine effectiveness, 6.9%; 95% CI: 0.5%, 12.8%) was observed.

Figure 1: Study FIM12 (further analyses) Effectiveness of Fluzone High-Dose vaccine relative to Fluzone (standard dose) vaccine against all-cause hospitalisation and specific serious cardiorespiratory events possibly related to influenza (Years 1 and 2 combined; full analysis set)



Note: Horizontal lines (95% CIs) that do not intersect the vertical line (null value) represent point estimates that are statistically significant.

CI: confidence interval; HD: high-dose (Fluzone High-Dose vaccine); LRR: lower bound of 95% CI; RR: rate ratio; SD: standard-dose (Fluzone vaccine); URR: upper bound of 95% CI

Gravenstein et al. (2016; 2018)

This study evaluated feasibility of comparison of TIV-HD or TIV-SD in a cluster-randomised trial in US Medicare certified nursing homes.¹⁰

Overall 39 nursing homes were randomised (19 TIV-SD and 20 TIV-HD), coordinated vaccine delivery, implemented web-based data collection, and accessed Minimum Data Set (MDS) data.¹⁵ There were 2,957 eligible residents (TIV-SD 1496; TIV-HD 1461) with similar characteristics between groups.

The adjusted RR for residents receiving TIV-HD compared to TIV-SD vaccine was 0.68 (CI: 0.54, 0.86, $p < 0.001$) for any hospitalisation during influenza season and was 0.83 (CI: 0.68, 1.03, $p = 0.087$) for mortality. Functional decline outcomes were not different, based on average Activity of Daily Living (ADL) scores before and after, or by threshold worsening of a clinically meaningful 4 points or more (13.4% TIV-HD, 13.8% TIV-SD, $p = 0.74$) (adjusted RR 0.99, CI: 0.77, 1.28, $p = 0.964$.)

¹⁵ The **Minimum Data Set (MDS)** is part of a US federally mandated process for clinical assessment of all residents in American Medicare or Medicaid certified nursing homes. This process entails a comprehensive, standardised assessment of each resident's functional capabilities and health needs. Assessments are conducted by trained nursing home clinicians on all patients at admission and discharge, in addition to other time intervals (for example, quarterly, annually, and when residents experience a significant change in status).

Study GRC75-EXT

This was a Phase IV, multi-facility, nationally representative, single-blind, 2 x 2 factorial cluster-randomised controlled study of the effect of high-dose influenza vaccine versus standard-dose vaccine in preventing influenza hospitalisation, mortality and functional decline rates of long-stay nursing home residents.

Of the 989 American nursing homes screened, 823 were recruited to the study, of which 409 facilities were randomised for residents to receive Fluzone High-Dose vaccine, and 414 facilities for residents to receive Fluzone vaccine. The facilities housed 92,269 residents, of whom 75,917 were aged ≥ 65 years and 53,008 were also long-stay residents.

Based on Medicare Fee-for-Service claims, the 6-month incidence of respiratory-related hospitalisation in the 2013–2014 influenza season was lower in the Fluzone High-Dose vaccine than Fluzone vaccine facilities but difference was not statistically significant (3.4% versus 3.9%; 0.185 versus 0.211 hospital admissions per 1000 resident days; unadjusted risk ratio = 0.888; 95% CI: 0.785, 1.005, $p = 0.061$). When adjusting for the pre-specified patient and facility characteristics related to overall hospital admission rates, a 20.9% reduction in incidence of hospitalisation due to pneumonia was observed in the Fluzone High-Dose facilities (adjusted relative risk = 0.791; 95% CI: 0.267, 0.953, $p = 0.013$); a 12.7% relative reduction was observed in the incidence of hospital admissions for respiratory illness among Fee-for-Service Medicare beneficiaries living in Fluzone High-Dose vaccine facilities (absolute risk reduction = 0.873; 95% CI: 0.776, 0.982, $p = 0.023$). The incidence of all-cause hospital admissions for the Fee-for-Service group matched to Medicare hospital claims was lower in the High-Dose vaccine group than in the Standard-Dose vaccine group (1.021 versus 1.113 per 1000 resident days, absolute risk reduction = 0.915; 95% CI: 0.863, 0.970, $p = 0.0028$).

Young-Xu et al. (2018)

This study;¹¹ estimated the relative vaccine effectiveness of high dose versus standard dose vaccines using a retrospective cohort of Veterans Health Administration (VHA);¹⁶ patients aged ≥ 65 years in the 2015 to 2016 influenza season. The study population included all VHA patients aged ≥ 65 years with at least 1 inpatient or outpatient encounter in prior respiratory season of 2014 to 2015.

The primary outcome of the study was any hospitalisation in which the patient record indicated either pneumonia or influenza (ICD-9: 480–488);^{17,18} as a principal or secondary diagnosis. Additional outcomes were explored.

¹⁶ The **Veterans Health Administration (VHA)** is the component of the United States Department of Veterans Affairs (VA) led by the Under Secretary of Veterans Affairs for Health that implements the healthcare program of the VA through the administration and operation of numerous VA medical centres, outpatient clinics and nursing homes.

¹⁷ The **International Classification of Diseases (ICD)** is a globally used diagnostic tool published and maintained by the World Health Organization (WHO) providing a code-based index used for categorising diseases, disorders, injuries and other related health conditions. It is the international standard for defining and reporting diseases and health conditions. As well as enabling the storage and retrieval of diagnostic information for clinical, epidemiological (which deals with the study of the causes, distribution, and control of disease in populations) and quality purposes, ICD records also form the basis for compiling national mortality and morbidity statistics by WHO Member States.

¹⁸ ICD-9: 480-488 is the coding in the ninth edition of the ICD covering pneumonia and influenza and covers the following diagnoses:

ICD-9 480-488; Pneumonia and influenza (480–488): 480 Viral pneumonia; 480.31 Pneumonia, SARS associated coronavirus; 480.9 Pneumonia, viral, unspec.; 481 Pneumococcal pneumonia; 482 Other bacterial pneumonia; 482.9 Pneumonia, bacterial, unspec.; 483 Pneumonia due to other specified organism; 483.0 Mycoplasma pneumonia; 485 Bronchopneumonia, organism unspecified; 486 Pneumonia, organism unspecified; 487 Influenza; 487.0 Influenza w/ pneumonia; 487.1 Influenza w/ other respiratory manifestations; 488 Influenza due to identified Avian influenza virus; 488.1 Influenza due to identified 2009 H1N1 virus.

The study evaluated 104,965 standard-dose and 125,776 high-dose recipients. During the baseline period, a higher rate of hospitalisation was observed where influenza or pneumonia was present in the patient record for those eventually receiving high-dose than for those eventually receiving standard dose (relative risk of 1.29; 95% CI: 1.12, 1.48). However, during the observation period, rates of hospitalisation for influenza or pneumonia were nearly identical between the 2 groups, resulting in a relative risk of 0.99 (95% CI: 0.95, 1.03). The PERR-adjusted relative vaccine effectiveness estimate of high-dose against influenza- or pneumonia-associated hospitalisation in the unmatched cohort was 23% (95% CI: 9%, 35%).

After matching, the study population comprised 49,091 and 24,682 veterans for the standard-dose and high-dose cohorts, respectively, which were more similar to one another than were the unmatched cohorts for the majority of baseline characteristics. The matched, PERR-adjusted relative vaccine effectiveness was 25% (95% CI: 2%, 43%) against influenza- or pneumonia-associated hospitalisation, 7% (95% CI: -2%, 14%) against all-cause hospitalisation, 14% (95% CI: -8%, 32%) against influenza- or pneumonia-associated outpatient visit, 5% (95% CI: 2%, 8%) against all-cause outpatient visit and 38% (95% CI: -5%, 65%) against laboratory confirmed influenza.

Safety

The safety of QIV-HD was assessed in 1 pivotal clinical study (Study QHD00013) and 1 supportive clinical study (Study QHD00008). Supportive evidence of safety was provided by the 3 TIV-HD studies and post-marketing experience with TIV-HD.

Study QHD00013

In the pivotal Study QHD00013, all 2,670 enrolled subjects were vaccinated and they were therefore included in the safety analysis set. All subjects received the correct vaccine according to the group to which they were randomised: 1,777 subjects received QIV-HD and 893 subjects received one of the TIV-HD vaccines.

Table 6 (shown below) presents a safety overview of Study QHD00013.

Table 6: Study QHD00013 Safety overview after vaccine injection (safety analysis set)

Subjects experiencing at least one:	QIV-HD (N=1777)			TIV-HD1 (N=443)			TIV-HD2 (N=450)			TIV-HD Pooled (N=893)		
	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Within 28 days after injection												
Immediate unsolicited AE	5/1777	0.3	(0.1 ; 0.7)	0/443	0	(0 ; 0.8)	2/450	0.4	(0.1 ; 1.6)	2/893	0.2	(0 ; 0.8)
Immediate unsolicited AR	4/1777	0.2	(0.1 ; 0.6)	0/443	0	(0 ; 0.8)	1/450	0.2	(0 ; 1.2)	1/893	0.1	(0 ; 0.6)
Solicited reaction	938/1768	53.1	(50.7 ; 55.4)	235/440	53.4	(48.6 ; 58.1)	207/449	46.1	(41.4 ; 50.8)	442/889	49.7	(46.4 ; 53.1)
Solicited injection site reaction	779/1768	44.1	(41.7 ; 46.4)	189/440	43.0	(38.3 ; 47.7)	165/449	36.7	(32.3 ; 41.4)	354/889	39.8	(36.6 ; 43.1)
Solicited systemic reaction	548/1768	31.0	(28.8 ; 33.2)	132/440	30.0	(25.8 ; 34.5)	132/449	29.4	(25.2 ; 33.9)	264/889	29.7	(26.7 ; 32.8)
Unsolicited AE	292/1777	16.4	(14.7 ; 18.2)	79/443	17.8	(14.4 ; 21.7)	68/450	15.1	(11.9 ; 18.8)	147/893	16.5	(14.1 ; 19.1)
Unsolicited non-serious AE	279/1777	15.7	(14.0 ; 17.5)	74/443	16.7	(13.4 ; 20.5)	66/450	14.7	(11.5 ; 18.3)	140/893	15.7	(13.4 ; 18.2)
Unsolicited non-serious systemic AE	269/1777	15.1	(13.5 ; 16.9)	70/443	15.8	(12.5 ; 19.5)	65/450	14.4	(11.3 ; 18.0)	135/893	15.1	(12.8 ; 17.6)
Unsolicited AR	35/1777	2.0	(1.4 ; 2.7)	8/443	1.8	(0.8 ; 3.5)	9/450	2.0	(0.9 ; 3.8)	17/893	1.9	(1.1 ; 3.0)
Unsolicited non-serious AR	35/1777	2.0	(1.4 ; 2.7)	8/443	1.8	(0.8 ; 3.5)	9/450	2.0	(0.9 ; 3.8)	17/893	1.9	(1.1 ; 3.0)
Unsolicited non-serious injection site AR	13/1777	0.7	(0.4 ; 1.2)	4/443	0.9	(0.2 ; 2.3)	3/450	0.7	(0.1 ; 1.9)	7/893	0.8	(0.3 ; 1.6)
Unsolicited non-serious systemic AR	22/1777	1.2	(0.8 ; 1.9)	4/443	0.9	(0.2 ; 2.3)	6/450	1.3	(0.5 ; 2.9)	10/893	1.1	(0.5 ; 2.0)
AE leading to study discontinuation	1/1777	<0.1	(0 ; 0.3)	2/443	0.5	(0.1 ; 1.6)	0/450	0	(0 ; 0.8)	2/893	0.2	(0 ; 0.8)
SAE within 28 days	19/1777	1.1	(0.6 ; 1.7)	7/443	1.6	(0.6 ; 3.2)	5/450	1.1	(0.4 ; 2.6)	12/893	1.3	(0.7 ; 2.3)
Fatal*	1/1777	<0.1	(0 ; 0.3)	1/443	0.2	(0 ; 1.3)	0/450	0	(0 ; 0.8)	1/893	0.1	(0 ; 0.6)
AE of special interest (AESI)	0/1777	0	(0 ; 0.2)	0/443	0	(0 ; 0.8)	0/450	0	(0 ; 0.8)	0/893	0	(0 ; 0.4)
D29 until end of trial												
SAE	65/1777	3.7	(2.8 ; 4.6)	23/443	5.2	(3.3 ; 7.7)	16/450	3.6	(2.0 ; 5.7)	39/893	4.4	(3.1 ; 5.9)
Fatal	2/1777	0.1	(0 ; 0.4)	1/443	0.2	(0 ; 1.3)	0/450	0	(0 ; 0.8)	1/893	0.1	(0 ; 0.6)
AE of special interest (AESI)	1/1777	<0.1	(0 ; 0.3)	0/443	0	(0 ; 0.8)	2/450	0.4	(0.1 ; 1.6)	2/893	0.2	(0 ; 0.8)
During the entire trial												
SAE	80/1777	4.5	(3.6 ; 5.6)	29/443	6.5	(4.4 ; 9.3)	19/450	4.2	(2.6 ; 6.5)	48/893	5.4	(4.0 ; 7.1)
Fatal	3/1777	0.2	(0 ; 0.5)	2/443	0.5	(0.1 ; 1.6)	0/450	0	(0 ; 0.8)	2/893	0.2	(0 ; 0.8)
AE of special interest (AESI)	1/1777	<0.1	(0 ; 0.3)	0/443	0	(0 ; 0.8)	2/450	0.4	(0.1 ; 1.6)	2/893	0.2	(0 ; 0.8)

Abbreviations: AE, adverse event; AESI, adverse event of special interest; AR, adverse reaction; CI, confidence interval; QIV-HD, high-dose quadrivalent influenza vaccine, SAE, serious adverse event; TIV-HD, high-dose trivalent influenza vaccine

n: number of subjects experiencing the endpoint listed in the first column

M: number of subjects with available data for the relevant endpoint

AE leading to study discontinuation includes those subjects with at least one of the following 2 situations:

1. Termination form marked 'not completed' due to 'adverse event'
2. Any AE with at least Grade 1 within the time period (missing intensity is included) marked 'caused study termination/discontinuation'.

*SAE Fatal: Those SAEs with the onset time within 28 days and outcome 'fatal'. This line does not count the death date.

Unsolicited non-serious systemic AEs (including SAEs) within 30 minutes are considered immediate.

Missing relationship (for the definition of AR) will be considered at the time of analysis as related to the vaccine.

The percentages of subjects who reported at least 1 solicited injection site reaction within 7 days of vaccination was slightly higher in the QIV-HD group (44.1%) compared to the pooled TIV-HD groups (39.8%). For QIV-HD and pooled TIV-HD groups, pain at the injection site was the most frequently reported injection site reaction, followed by erythema, swelling, induration and bruising with similar incidence in both groups. The majority of solicited injection site reactions in all groups were of Grade 1 intensity, started within the first 3 days after vaccination, and resolved spontaneously within 7 days of onset. The incidence of Grade 3 solicited injection site reactions was low but numerically higher in the QIV-HD compared to the pooled TIV-HD group (1.5% versus 0.4%).

The percentages of subjects who reported at least 1 solicited systemic reaction were similar in the QIV-HD and the pooled TIV high dose groups (31% versus 29.7%). The most frequently reported systemic reactions were myalgia (22.7% versus 18.9%), headache (14.4% versus 13.6%), malaise (13.2% versus 13.4%), shivering (5.4% versus 4.7%) and fever (0.4% versus 0.9%).

The percentages of subjects reporting at least 1 unsolicited adverse event (AE) were comparable across the study groups.

A total of 7 subjects reported 10 unsolicited AEs within 30 minutes after vaccination. 5 of these subjects were in the QIV high dose group and reported 7 immediate unsolicited AEs. The immediate unsolicited AEs that were considered related to vaccination by the study investigator were vertigo, blurry vision, joint pain, fatigue and dizziness.

During the 6-month follow-up period, a total of 3 adverse events of special interest (AESI) were reported, 1 in the QIV-HD group and 2 in the TIV-HD (TIV-HD2) group. None of these AESIs were assessed as related to the study vaccination by the Investigators.

A total of 128 subjects experienced 162 serious adverse events (SAE) during the study. In the QIV-HD group, 1 SAE was considered as related to the vaccine by the study investigator (small fibre inflammatory neuropathy 40 days after vaccination) and 1 SAE led to termination from the study (suffered from post cardiectomy syndrome 39 days after vaccination, was hospitalised and recovered within 4 days).

Within 28 days after vaccination, there were a total of 3 AEs leading to withdrawal from the study. 1 subject in the QIV-HD group died suddenly of natural causes, 1 subject in the TIV-HD1 group experienced myocardial infarction, and 1 subject in the TIV-HD1 group experienced a rib fracture. All AEs leading to withdrawal from the study were considered SAEs and were assessed as not related to the study vaccination.

Age, sex, medical history and history of previous influenza vaccination in prior year did not affect the safety profile of QIV-HD. In Study QHD00013 a total of 5 deaths were reported during the study: 3 subjects in the QIV-HD group and 2 subjects in the TIV-HD1 group. None were assessed as related to vaccination.

Study QHD00008

In Study QHD00008, 175 subjects were randomised with 60 subjects receiving QIV-HD (IM), 60 subjects receiving QIV-HD (SC) and 55 subjects receiving a QIV-SD licensed in Japan by SC route of administration. The percentages of subjects who reported at least one solicited reaction were similar between the QIV-HD IM and QIV-SD SC groups, 43.3% (26 out of 60 subjects) and 45.5% (25 out of 55 subjects), respectively, and were lower than the percentage of subjects who reported at least one solicited reaction in the QIV-HD SC group (70.0%; 42 out of 60 subjects).

The percentages of subjects who reported at least one solicited injection site reaction was highest in the in the QIV-HD SC group (66.7%; 40 out of 60 subjects) and it was similar in the QIV-HD IM (41.7%; 25 out of 60 subjects) and QIV-SD SC (41.8%; 23 out of 55 subjects) groups.

The percentage of subjects who reported at least one solicited systemic reaction was also highest in the QIV-HD SC group (18.3% (11 out of 60), 33.3% (20 out of 60) and 16.4% (9 out of 55) in the QIV-HD IM, QIV-HD SC and QIV-SD SC groups, respectively). The most frequent solicited systemic reaction was myalgia followed by headache.

In Study QHD00008, there were no deaths during the study. There was one SAE reported by one subject in the QIV-SD SC group (subject experienced sudden hearing loss 3 days after vaccination, and was hospitalised; the event was recovering or resolving at the third visit and assessed as not related to vaccination by the investigator). There were no AEs leading to study discontinuation within 28 days after vaccination in any of the groups.

Post-marketing experience

Fluzone High Dose Quadrivalent (QIV-HD) has not yet received marketing approval in any country.¹⁹

¹⁹ At the time of the issuing of the Delegate's Overview.

Fluzone High Dose as a trivalent vaccine (TIV-HD) has had a total of more than 100 million doses distributed since 2009. A number of spontaneously reported events were listed which may occur in people who receive the proposed QIV-HD. Taken from the clinical evaluation report, the following events have been spontaneously reported during the post-marketing use of TIV-HD. These AEs may occur in people receiving the proposed QIV-HD:

- Blood and Lymphatic System Disorders: Thrombocytopenia, lymphadenopathy
- Immune System Disorders: Anaphylaxis, other allergic/hypersensitivity reactions (including angioedema)
- Eye Disorders: Ocular hyperaemia
- Nervous System Disorders: Guillan-Barré syndrome, convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), paraesthesia
- Vascular Disorders: Vasculitis, vasodilatation
- Respiratory, Thoracic and Mediastinal Disorders: Dyspnoea, wheezing, throat tightness oropharyngeal pain and rhinorrhoea
- General Disorders and Administration Site Conditions: asthenia, chest pain
- Gastrointestinal Disorders: vomiting.

Clinical evaluator's conclusions on clinical safety

Safety of the QIV-HD was evaluated in an adequate number of patients representative of the target patient population. Safety results of the proposed QIV-HD from the pivotal Study QHD00013 showed that vaccination with QIV-HD in adults aged ≥ 65 years was found to be safe and well tolerated. There were no fatal SAEs or AESIs which were considered related to the vaccine.

The safety profile of QIV-HD was found to be comparable to that of TIV-HD with similar rates of occurrence of unsolicited AEs, AEs leading to study discontinuation, SAEs, fatal SAEs and AESIs between both vaccine groups. The overall reactogenicity profile of QIV-HD, in terms of the percentage of subjects who reported a solicited reaction was comparable to that of the TIV-HD as demonstrated by similar rates of solicited injection site and systemic reactions between both vaccine groups.

Clinical evaluator's recommendation

Clinical evaluator's benefit-risk assessment (at the first round of evaluation)

The main evidence to support efficacy of proposed QIV-HD was provided by the Phase III immunogenicity and safety study, Study QHD00013, in 2670 healthy adults aged ≥ 65 years. The proposed Fluzone High-Dose Quadrivalent achieved the primary endpoint of non-inferior immunogenicity compared to two trivalent formulations of Fluzone High-Dose, each containing one of the two influenza B strains recommended for inclusion in the vaccine for the 2017 to 2018 influenza season. In a secondary endpoint of the trial, each B strain in Fluzone High-Dose Quadrivalent induced a superior immune response compared to the trivalent formulation not containing the corresponding B strain. Furthermore, addition of the additional B virus strain did not affect the immunogenicity or safety of other strains.

Fluzone Quadrivalent High-Dose (QIV-HD) was as immunogenic as TIV-HD for GMTs and seroconversion rates for the common influenza strains and also induced a superior immune response with respect to the additional B strain than the immune response

induced by TIV-HD that does not contain the corresponding B. Whether the increased immune response (especially with additional B virus strain) translated into superior efficacy in terms of prevention of influenza disease and pneumonia/ hospitalisations was not evaluated in any of the QIV-HD studies.

Results of this study met the criteria provided by the European Medicines Evaluation Agency (EMA).^{20,21}

The supporting Study QHD00008 was considered to be limited relevance for Australian patients due to study being conducted only in Japanese subjects and because comparator vaccines were administered by the SC route. In Australia, the approved route of administration for the QIV-SD vaccine is IM.

Evidence for prevention of influenza illness was provided by the pivotal TIV-HD Study FIM12 which showed 25% reduction in incidence of laboratory confirmed influenza caused by any viral strain and a 35% reduction for viral strains similar to those contained in the vaccine. The initial study report showed a trend towards lower incidence of pneumonia, hospitalisations and other serious cardiorespiratory illness in the TIV-HD group (compared to TIV-SD) although differences were not significant (with wide 95% CIs).

In this submission, support for efficacy of TIV-HD (compared to TIV-SD) in preventing '*associated complication of pneumonia-related hospitalisation*' was provided by the following 3 studies:

- Supplementary analyses of data from pivotal TIV-HD Study FIM12, which showed a 39% reduction in risk of serious pneumonia events; however, the analysis did not evaluate reduction in pneumonia-related hospitalisation and overall rate of all-cause hospitalisations was only reduced by 8% with TIV-HD compared to TIV-SD.
- The cluster-RCT by Gravenstein et al., (2018);¹⁰ including approximately 53,000 nursing homes residents demonstrated a 20.9% reduction in hospital admissions for pneumonia in residents living in TIV-HD vaccine facilities compared to facilities where residents received TIV-SD vaccine (absolute risk reduction: 0.791; 95% CI 0.267, 0.953, p = 0.013).
- Study GRC75-EXT was the first randomised, prospective study to show the comparative effectiveness of influenza vaccine in reducing respiratory-related hospital admissions as a primary endpoint in an elderly, frail, long-stay nursing home population. However, interpretation was limited by low event rates, greater than expected variability and lack of laboratory data from the study population to confirm influenza activity.
- The retrospective cohort study by Young-Xu et al., (2018);¹¹ showed a matched, PERR-adjusted relative vaccine effectiveness (for TIV-HD versus TIV-SD) of 25% (95% CI: 2%, 43%) against influenza- or pneumonia-associated hospitalisation.

The clinical evaluator, in their report, considered that although above studies do provide some evidence to demonstrate efficacy of TIV-HD over TIV-SD in preventing pneumonia-related hospitalisation, interpretation was confounded by various limitations discussed above and do not justify inclusion of '*preventing pneumonia-related hospitalisation*' in wording of proposed indications for QIV-HD.

Vaccination with QIV-HD among adults 65 years of age and older was found to be safe, with no new safety concerns identified. The safety profiles of QIV-HD and TIV-HD were

²⁰ EMA (European Medicines Evaluation Agency) Note for Guidance CPMP/BWP/214/96 for the immunological evaluation of influenza vaccines for adult and elderly populations.

²¹ Prior to 2004, the **European Medicines Agency (EMA)** was known as the **European Medicines Evaluation Agency (EMA)**.

found to be similar. Rates of local and systemic reactions that occurred following immunisation with Fluzone High-Dose Quadrivalent were similar to those induced by trivalent formulations of Fluzone High-Dose.

The first round clinical evaluation report recommended registration with the modified indication:

'Fluzone Quadrivalent High-Dose is indicated for active immunisation for the prevention of influenza disease caused by influenza virus types A and B contained in the vaccine in persons 65 years of age and older.'

In response to Question 1 (of the report) the sponsor identified a total of 17 subjects reported being a resident of an assisted-living facility or nursing home within the last 6 months in Study QHD00013.

In response to Question 2, the sponsor identified that Study QHD0008's main purpose was to support the safety and immunogenicity of the QIV-HD Japan Clinical Development Program. In Japan, influenza vaccines are administered subcutaneously as the standard of care.

In response to Question 3, the sponsor commented that the most recent periodic benefit-risk evaluation report (PBRER);²² as part of the pre-Advisory Committee on Vaccines (ACV) response package.

In a response to the indications recommended in by the clinical evaluator (in their report), the sponsor states the added wording '*associated complication of pneumonia-related hospitalisation*' to the proposed indication is based on the large body of evidence generated with TIV-HD in RCT and post-licensure effectiveness studies. To date, these data have not been generated by any other influenza vaccines in a consistent manner and over many influenza seasons as TIV-HD has done. This additional data generated includes TIV-HD's improved benefit over TIV-SD influenza vaccines for a variety of important clinical endpoints such as hospitalisations due to ILI, pneumonia, cardio-respiratory events, all-cause deaths. Most of them were not available at the time of the TIV-HD submission in Australia. The sponsor has commented that the Australian Technical Advisory Group on Immunisation (ATAGI);²³ has evaluated the same data and ATAGI state that there is evidence to support efficacy of TIV-HD against pneumonia.

The sponsor also comments that the Fluvad Quad PI contains a broad clinical efficacy statement.

²² A **periodic benefit risk evaluation report (PBRER)** is a post-approval analysis of the safety and efficacy of an authorised drug or medication. PBRERs are to be submitted periodically, that is, every 6 months until the product is placed on the market, every 6 months for the first 2 years after the product is placed on the market and once a year for the following 2 years. Each PBRER is required to provide a clear, concise and accurate assessment of new and emerging identified risks or concerns identified with further use of newly approved drug.

²³ The **Australian Technical Advisory Group on Immunisation (ATAGI)** are a Working Group providing advice to the Government on the effective and equitable use of vaccines available in Australia, as directed by the Department of Health. The Working Group is made up of medical and scientific experts meeting throughout the year to advise the Minister for Health to advise on the medical administration of vaccines available in Australia including the those available through the National Immunisation Program NIP and to carry out the following roles: to provide advice to research organisations on current immunisation research and areas that need more research; to provide industry sponsors with Pre-submission Advice for potential submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) on vaccine effectiveness and use in Australia. ATAGI advice must be sought prior to a sponsor making a submission to the PBAC (see parallel processing requirements for PBAC vaccine submissions and pre-submission advice for industry sponsors wishing to make a PBAC submission); to consult with relevant organisations to produce the Australian Immunisation Handbook; and to consult with relevant organisations in implementing immunisation policies, procedures and vaccine safety.

In addition, the sponsor does not agree with the wording '*caused by influenza virus types A and B contained in the vaccine*'. Study FIM12 demonstrated superior efficacy of Fluzone High-Dose (TIV-HD) versus standard-dose (TIV-SD) Fluzone against laboratory-confirmed influenza caused by any influenza viral types/subtypes associated with ILI. In addition, it is evident from the data presented that there is a differential clinical efficacy in the two influenza seasons. It is known that the season where the efficacy was lower, although still superior to QIV-SD, was a mismatch year. This demonstrates that the vaccine is not only effective against other strains of influenza but remains clearly superior to QIV-SD even in the face of a mismatch.

Clinical evaluator's benefit-risk assessment (at the second round of evaluation)

The clinical evaluator concludes the second benefit-risk balance is unchanged from that in first round evaluation. Registration is recommended with indications:

'Fluzone High-Dose Quadrivalent is indicated for active immunisation for the prevention of influenza disease in persons 65 years of age and older. The use of Fluzone High-Dose Quadrivalent should be based on official recommendations.'

Risk management plan

The sponsor has submitted EU risk management plan (RMP) version 1.0 (dated 20 March 2019; data lock point (DLP) 15 September 2018) and Australian-specific Annex (ASA) version 1.0 (dated 31 July 2019) in support of this application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 8.²⁴

²⁴ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 7: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Nil				
Important potential risks	Anaphylactic reactions	Ü	-	Ü	-
	Guillain-Barre Syndrome	Ü	-	Ü	-
	Neuritis (Bell's palsy, optic neuritis)	Ü	-	Ü	-
	Convulsions	Ü	-	Ü	-
	Encephalomyelitis / Transverse myelitis	Ü	-	Ü	-
	Thrombocytopenia	Ü	-	Ü	-
	Vasculitis	Ü	-	Ü	-
Missing information	Nil				

- The summary of safety concerns has differences to that of the Fluzone trivalent high dose vaccine, including the level of concern for anaphylactic reactions and omission of gastrointestinal disorders. The summary above is adequate.
- Routine pharmacovigilance activities have been proposed to monitor all safety concerns. Enhanced pharmacovigilance (targeted questionnaires) is in place for risks not included in the summary of safety concerns (use in pregnancy; use in patients with chronic diseases). No additional pharmacovigilance activity has been proposed. The sponsor has undertaken to discuss with the TGA an alternative approach for enhanced safety surveillance if and when required (if the vaccine is not included in the AusVaxSafety program).
- Routine risk minimisation activities are proposed. No additional risk minimisation activity is proposed. This approach is consistent with other inactivated influenza vaccines.
- There are no new or outstanding recommendations at the second round.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Fluzone High-Dose Quadrivalent EU-Risk Management Plan (RMP) (version 1.0, dated 20 March 2019, data lock point 15 September 2018), with Australian Specific Annex (version 1.0, dated 31 July 2019), included with submission PM-2019-03202-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the PSUR requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

The following wording is recommended for the pharmacovigilance requirement in the absence of inclusion in the AusVaxSafety program:²⁵

The sponsor must 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 sponsor has undertaken to discuss with the TGA an alternative approach for enhanced safety surveillance if and when required (if the vaccine is not included in the AusVaxSafety program).

²⁵ **AusVaxSafety** is a national system for monitoring vaccine safety in Australia. The purpose of AusVaxSafety is to optimise community and healthcare provider confidence in the safety of the National Immunisation Program vaccines by complementing existing post-marketing vaccine pharmacovigilance for the detection of adverse events following immunisation.

Risk-benefit analysis

Delegate's considerations

The Phase III immunogenicity and safety-based Study QHD00013 in 2670 healthy adults aged > 65 years provides adequate support for the registration of Fluzone High-Dose Quadrivalent.

The sponsor proposes the added wording '*associated complication of pneumonia-related hospitalisation*' to the proposed indications, which has not been accepted in the second round clinical evaluation report.

Effectiveness analyses were based on TIV-HD rather than QIV-HD. Supplementary analyses of data from the pivotal TIV-HD Study FIM12 showed a 39% reduction in risk of serious pneumonia events. The clinical evaluator commented (in their report) that the analysis did not evaluate reduction in pneumonia-related hospitalisation and overall rate of all-cause hospitalisations was only reduced by 8% with TIV-HD compared to TIV-SD. Interpretation is also limited as although study evaluated multiple associated outcomes, there was lack of correction for multiplicity; the initial study was not powered for this supplementary analysis; and outcomes evaluated in the supplementary analysis were not influenza-specific.

The cluster-RCT by Gravenstein et al., (2016, 2018);¹⁰ including approximately 53,000 nursing homes residents and confirmed improved prevention of hospitalisations related to respiratory diseases or pneumonia when compared with TIV-SD where hospital admission related to and including pneumonia on the basis of ICD-9-coded US Medicare claims;¹⁸ was a secondary endpoint: there was a 20.9% reduction in hospital admissions for pneumonia in residents living in TIV-HD vaccine facilities compared to facilities where residents received TIV-SD vaccine (absolute risk reduction = 0.791; 95% CI 0.267, 0.953, p = 0.013).

Study GRC75-EXT was the first randomised, prospective study to show the comparative effectiveness of influenza vaccine in reducing respiratory-related hospital admissions as a primary endpoint in an elderly, frail, long-stay nursing home population. The clinical evaluator comments that interpretation was limited by low event rates, greater than expected variability and lack of laboratory data from the study population to confirm influenza activity.

The retrospective cohort study by Young-Xu et al., (2018);¹¹ matched PERR-adjusted relative vaccine effectiveness (for TIV-HD versus TIV-SD) was 25% (95% CI: 2%, 43%) against influenza- or pneumonia-associated hospitalisation. The clinical evaluator comments interpretation was limited by wide 95% CIs. Other limitations of this study were: analyses was not restricted to periods of peak influenza activities (use of the broader period may have biased results due to misclassification of study outcomes); despite matching, the potential for confounding by indication and by unmeasured variables cannot be entirely eliminated due to observational study design; and, the generalisability of results was limited as data was only obtained from patients treated at VHA facilities and these patients may also use healthcare services outside the VHA.

The sponsor has responded stating the indications statement is based on the large body of evidence generated with TIV-HD in the RCT and post-licensure effectiveness studies. To date, these data have not been generated by any other influenza vaccines in a consistent manner and over many influenza seasons as TIV-HD has done. This additional data generated includes TIV-HD's improved benefit over TIV-SD influenza vaccines for a variety of important clinical endpoints such as hospitalisations due to ILI, pneumonia, cardio-respiratory events, all-cause deaths. Most of them were not available at the time of the TIV-HD submission in Australia. The sponsor has commented that ATAGI has evaluated

the same data and in pre-PBAC;²⁶ advice to the sponsor, ATAGI stated that there is evidence to support efficacy of TIV-HD against pneumonia. The sponsor also comments that the Fluvad Quad PI contains a broad clinical efficacy statement.

The sponsor did not agree with the indications wording recommended in first round clinical evaluation report, which contained following '*caused by influenza virus types A and B contained in the vaccine*'. The second round clinical evaluation recommends the indications:

'Fluzone High-Dose Quadrivalent is indicated for active immunisation for the prevention of influenza disease in persons 65 years of age and older. The use of Fluzone High-Dose Quadrivalent should be based on official recommendations.'

Summary of issues

The sponsor proposes the added wording: '*associated complication of pneumonia-related hospitalisation*' to the proposed indications, which has not been accepted in the second round clinical evaluation report.

Effectiveness analyses were based on the TIV-HD rather than the QIV-HD. Supplementary analyses of data from pivotal TIV-HD based Study FIM12 reported a 39% reduction in risk of serious pneumonia events. The clinical evaluation report comments the analysis did not evaluate reduction in pneumonia-related hospitalisation and overall rate of all-cause hospitalisations was only reduced by 8% with TIV-HD compared to TIV-SD. Interpretation is also limited as although study evaluated multiple associated outcomes, there was lack of correction for multiplicity; the initial study was not powered for this supplementary analysis; and outcomes evaluated in the supplementary analysis were not influenza-specific.

The cluster-RCT by Gravenstein et al., (2016, 2018);¹⁰ including approximately 53,000 nursing homes residents and confirmed improved prevention of hospitalisations related to respiratory diseases or pneumonia when compared with TIV-SD where hospital admission related to and including pneumonia on the basis of ICD-9-coded Medicare claims was a secondary endpoint: a 20.9% reduction in hospital admissions for pneumonia in residents living in TIV-HD vaccine facilities compared to facilities where residents received TIV-SD vaccine (absolute risk reduction = 0.791; 95% CI 0.267, 0.953, p = 0.013).

Study GRC75-EXT was the first randomised, prospective study to show the comparative effectiveness of influenza vaccine in reducing respiratory-related hospital admissions as a primary endpoint in an elderly, frail, long-stay nursing home population. The clinical evaluation report comments that interpretation was limited by low event rates, greater than expected variability and lack of laboratory data from the study population to confirm influenza activity.

The retrospective cohort study by Young-Xu et al., (2018);¹¹ matched PERR-adjusted relative vaccine effectiveness (for HD versus SD) was 25% (95% CI: 2%, 43%) against influenza- or pneumonia-associated hospitalisation. The clinical evaluator comments interpretation was limited by wide 95% CIs. Other limitations of this study were that analyses was not restricted to periods of peak influenza activities (use of the broader

²⁶ The **Pharmaceutical Benefits Advisory Committee (PBAC)** was established under the National Health Act (1953). Its primary role is to recommend to the Minister for Health which medicines should be subsidised under the **Pharmaceutical Benefits Scheme (PBS)**.

The PBAC is required, under the Act, to consider the effectiveness and cost of the proposed medicine compared with existing therapies. The functions of the PBAC are outlined in s101 of the Act. In particular, the PBAC is required to consider the effectiveness and cost of the proposed medicine compared with alternative therapies. It cannot make a positive recommendation for a medicine that is substantially more costly than an alternative medicine unless it is satisfied that the proposed medicine also provides a significant improvement in health.

period may have biased results due to misclassification of study outcomes); despite matching, the potential for confounding by indication and by unmeasured variables cannot be entirely eliminated due to observational study design; and the generalisability of results was limited as data was only obtained from patients treated at VHA facilities and these patients may also use healthcare services outside the VHA.

The clinical evaluator considered that although above studies do provide some evidence to demonstrate efficacy of TIV-HD over TIV-SD in preventing pneumonia-related hospitalisation, interpretation was confounded by various limitations discussed above and do not justify inclusion of 'preventing pneumonia-related hospitalisation' in wording of proposed indications for QIV-HD.

The sponsor has responded stating the indications statement is based on the large body of evidence generated with TIV-HD in RCT and post-licensure effectiveness studies. To date, these data have not been generated by any other influenza vaccines in a consistent manner and over many influenza seasons as TIV-HD has done. This additional data generated includes TIV-HD's improved benefit over TIV-SD influenza vaccines for a variety of important clinical endpoints such as hospitalisations due to ILI, pneumonia, cardio-respiratory events, all-cause deaths. Most of them were not available at the time of the TIV-HD submission in Australia. The sponsor has commented that ATAGI has evaluated the same data and in pre-PBAC advice to the sponsor ATAGI stated that there is evidence to support efficacy of TIV-HD against pneumonia. The sponsor also comments that the Flud Quad PI contains a broad clinical efficacy statement.

Proposed action

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

Request for Advisory Committee on Vaccines advice

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

1. Indications have not been resolved between the clinical evaluation report and sponsor.

The sponsor proposes the added wording '*associated complication of pneumonia-related hospitalisation*' to the proposed indication based on the large body of evidence generated with TIV-HD in RCT and post-licensure effectiveness studies.

Does the ACV consider the (following) proposed indications are adequately supported:

'Fluzone High-Dose Quadrivalent is indicated for active immunisation for the prevention of influenza disease and the associated complication of pneumonia-related hospitalisation. Fluzone Quadrivalent High-Dose is indicated for use in persons 65 years of age and older. The use of Fluzone Quadrivalent High-Dose should be based on official recommendations'

2. Does the ACV support inclusion of evidence for prevention of complications associated with influenza for TIV-HD in section 5.1 (Clinical trials) of the draft PI?

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.

Advisory Committee considerations²⁷

The Advisory Committee on Vaccines (ACV), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACV considered the vaccine to have an overall positive benefit-risk profile for the indication:

'Fluzone High-Dose Quadrivalent is indicated for active immunisation for the prevention of influenza disease. Fluzone High-Dose Quadrivalent is indicated for use in persons 65 years of age and older. The use of Fluzone High-Dose Quadrivalent should be based on official recommendations.'

In providing this advice the ACV:

- was of the view that vaccine efficacy was acceptable for persons 65 years and over
- considered the safety profile was adequate

Specific advice

The ACV advised the following in response to the Delegate's specific questions.

1. Does the ACV consider the (following) proposed indications are adequately supported?

Fluzone High-Dose Quadrivalent is indicated for active immunisation for the prevention of influenza disease and the associated complication of pneumonia-related hospitalisation. Fluzone Quadrivalent High-Dose is indicated for use in persons 65 years of age and older. The use of Fluzone Quadrivalent High-Dose should be based on official recommendations

The ACV advised that prevention of pneumonia-related hospitalisation should not be included in the indication.

The ACV noted the sponsor's argument that the overall weight of evidence from randomised clinical trials, the Gravenstein et al. (2018) study in aged care facilities;¹⁰ and the Lee meta-analysis;²⁸ showed an incremental reduction in pneumonia-related hospitalisations in TIV-HD recipients compared to persons receiving standard dose vaccines. Other important clinical endpoints such as hospitalisations due to ILI, pneumonia, cardiorespiratory events, and all-cause deaths were also considered in some studies. The protective effect appeared greater in A/H3N2-dominant seasons.

The committee acknowledged that comparable data have not been generated for other influenza vaccines in a consistent manner and over multiple influenza seasons as has been

²⁷ The **Advisory Committee on Vaccines (ACV)** provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of vaccines supplied in Australia including issues relating to pre-market assessment, post-market monitoring and safe use in national immunisation programs.

The Committee is established under Regulation 39F of the Therapeutic Goods Regulations 1990 and the members are appointed by the Minister for Health.

The ACV was established in January 2017, following consolidation of previous functions of the Advisory Committee on the Safety of Vaccines (ACSOV) and the pre-market functions for vaccines of the Advisory Committee on Prescription Medicines (ACPM).

Membership comprises professionals with expertise in specific scientific, medical or clinical fields, or consumer health issues.

²⁸ Lee J, Lam G, Shin T, Kim J, Krishnan A, Greenberg D and Chit A; Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis (2018). Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis, *Expert Review of Vaccines*, 17:5, 435-443.

done for TIV-HD. However, the committee also noted the following points, which did not allow it to support the indication of prevention of pneumonia-related hospitalisation:

- Effectiveness analyses were based on studies using TIV-HD and not QIV-HD
- The approved indication in Australia for TIV-HD does not include prevention of pneumonia related hospitalisation
- There was uncertainty in the measured outcomes in the clinical studies and analysis:
 - from Study FIM12 (supplementary evaluation):
 - § the supplementary analysis reviewed serious pneumonia events but not pneumonia-related hospitalisation
 - § the initial study was not powered to support the supplementary analysis
 - § while the number of cases of pneumonia and hospitalisations (all cause) were lower in the QIV-HD group, the differences were not statistically significant and the confidence intervals were wide
 - § outcomes evaluated in the supplementary analysis were not influenza-specific
 - § most of the reductions in the TIV-HD group were observed in Year 2 with no significant differences observed in Year 1.
 - Gravenstein et al., reviewed hospital admissions related to and including pneumonia based on ICD-9-coded medical insurance claims; such data may not be precise.
 - In Study GRC75-EXT interpretation was limited by low event rates, greater than expected variability, and lack of laboratory data from the study population to confirm influenza activity.
 - In Young-Xu et al., the prior event rate ratio-adjusted relative vaccine effectiveness (for high dose versus standard dose) was 25% (95% CI 2%, 43%) against influenza- or pneumonia-associated hospitalisation. As well as the wide 95% CI, the study was not restricted to periods of peak influenza activity.

The ACV viewed the similarity of relative efficacy of the vaccine in the prevention of influenza (35.3%; 95% CI 12.4%-52.5%) to the reduction in serious pneumonia events (relative vaccine effectiveness 39.8%; 95% CI 19.3%, 55.1%) as implausible, as pneumonia events were unlikely to have all been caused by influenza.

The committee did not agree with the sponsor's analogy between the proposed indication for QIV-HD and the approved indication for Zostavax. The protocol for the pivotal study;²⁹ for Zostavax included the incidence of postherpetic neuralgia as a secondary end point, rather than as a post-hoc analysis of an initial study not powered to support such an analysis. In addition, the postherpetic neuralgia complication can relate only to herpes zoster disease, whereas 'pneumonia-related hospitalisation' encompasses a range of conditions including non-viral causes.

2. Does the ACV support inclusion of evidence for prevention of complications associated with influenza for TIV-HD in section 5.1 (Clinical trials) of the draft PI?

The ACV supported the inclusion of evidence for prevention of complications associated with influenza for TIV-HD in section 5.1 (Clinical trials) of the PI for Fluzone High-Dose Quadrivalent. Limitations of the study data should be presented. The lack of data on

²⁹ Oxman MN, Levin MJ, Johnson GR, et al. A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults. *N Engl J Med* 2005. 352(22):2271-84. doi: 10.1056/NEJMoa051016.

clinical efficacy on the prevention of complications associated with influenza for QIV-HD should be acknowledged.

The ACV advised that the related wording in the CMI, if any, should be suitable to the consumer group.

The committee noted the sponsor's view that the PI for a competitor product, Flud Quad, contains a broad clinical efficacy statement.³⁰

3. Any other issues relevant to a decision on whether to approve the application?

The ACV advised that the vaccine's labelling should clearly identify the age group of patients, to avoid errors in administration. This applies to all influenza vaccines.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Fluzone High-Dose Quadrivalent inactivated high-dose quadrivalent influenza vaccine (split virion) 0.7 mL pre-filled syringe containing 240 µg inactivated (split virion) influenza virus haemagglutinin via intramuscular injection, indicated for:

Fluzone High-Dose Quadrivalent is indicated for active immunisation for the prevention of influenza disease. Fluzone High-Dose Quadrivalent is indicated for use in persons 65 years of age and older.

The use of Fluzone High-Dose Quadrivalent should be based on official recommendations.

See Section 5.1 Clinical Trials for information on the effects on influenza associated complications.

Specific conditions of registration applying to these goods

- The additional requested quality data should be provided prior to the lodgement of the Annual strain Update for the Southern Hemisphere (SH) 2021 Influenza season.
- The Fluzone High-Dose QIV EU-Risk Management Plan (RMP) (version 1.0, dated 20 March 2019, data lock point 15 September 2018), with Australian Specific Annex (version 1.0, dated 31 July 2019), included with submission PM-2019-03202-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The sponsor must conduct an enhanced safety surveillance study in Australia, if requested by the 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.
- Batch release testing and compliance with the Certified Product Details conditions of registration for Fluzone Quadrivalent

It is a condition of registration that all independent batches of Fluzone Quad imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and the sponsor has received notification acknowledging release from the Laboratories Branch, TGA.

³⁰ Flud Quad (inactivated quadrivalent influenza vaccine (surface antigen), adjuvanted) is indicated for active immunisation against influenza in persons 65 years of age and older. Sponsor Seqirus Pty Ltd. Approved October 2019.

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@health.gov.au.
 - Complete summary protocols for manufacture and QC, including all steps in production.
 - At least 20 (twenty) doses of the first consignment of each batch of Fluzone Quadrivalent with the Australian approved labels, PI and packaging
 - At least 10 (ten) doses of any further consignment of each batch of Fluzone Quadrivalent with the Australian approved labels, PI and packaging
 - Certificate of Release from 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.
- 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) <https://www.tga.gov.au/guidance-7-certified-product-details> 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 <https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescriptionmedicines>. The CPD should be sent as a single bookmarked PDF document to Vaccines@health.gov.au as soon as possible after registration/approval of the product or any subsequent changes as indicated above.
 - For all injectable products the Product Information (PI) must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Fluzone High Dose Quadrivalent 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>>.

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<https://www.tga.gov.au>