AUSTRALIAN PRODUCT INFORMATION – FLUZONE HIGH-DOSE QUADRIVALENT (INFLUENZA VIRUS HAEMAGGLUTININ)

1 NAME OF THE MEDICINE

Inactivated quadrivalent influenza vaccine, split virion (Influenza virus haemagglutinin)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluzone High-Dose Quadrivalent for intramuscular injection is an inactivated influenza virus vaccine. It contains 240 micrograms (µg) influenza virus haemagglutinin (HA) per 0.7 mL dose in the recommended ratio of 60 µg HA of each of the four strains recommended for the 2019 influenza season:

- A/Michigan/45/2015 (H1N1) pdm09-like virus (A/Michigan/45/2015 X-275)
- A/Switzerland/8060/2017 (H3N2)- like virus (A/Brisbane/1/2018 X-311)
- B/Phuket/3073/2013-like virus (B/Phuket/3073/2013; Yamagata lineage)
- B/Colorado/06/2017-like virus (B/Maryland/15/2016 BX-69A; Victoria lineage)

The type and amount of viral antigens contained in Fluzone High-Dose Quadrivalent conform to the annual requirements of the Australian Influenza Vaccine Committee (AIVC) recommendations for the season.

Fluzone High-Dose Quadrivalent is prepared from influenza viruses propagated in embryonated chicken eggs and inactivated with formaldehyde. The influenza virus is concentrated and purified, and is then chemically disrupted to produce a “split virus”. The split virus is further purified by diafiltration and diluted to appropriate concentration. Antigens from the four strains included in the vaccine are produced separately and then combined to make the quadrivalent formulation.

For the full list of excipients, see Section 6.1 List of excipients.

Fluzone High-Dose Quadrivalent is presented in prefilled syringes that are not made with natural rubber latex.

3 PHARMACEUTICAL FORM

Fluzone High-Dose Quadrivalent suspension for injection is clear and slightly opalescent in colour.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Fluzone High-Dose Quadrivalent should be given in accordance with the national recommendation as per the current Immunisation Handbook.

The recommended dosage of Fluzone High-Dose Quadrivalent is 1 dose of 0.7 mL, annually, in persons 65 years of age and older.

Administration should be carried out by intramuscular route.

Injections of Fluzone High-Dose Quadrivalent should be administered intramuscularly, preferably in the deltoid muscle. The vaccine should not be injected into the gluteal region, or into areas where there may be a major nerve trunk.

For needle size and length, refer to the national recommendations as per the current Immunisation Handbook.

Do not administer this product intravenously.

Shake before use to distribute suspension uniformly before administration.

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

The syringe is for single use only and must not be reused. Discard any remaining unused contents.

4.3 CONTRAINDICATIONS

Fluzone High-Dose Quadrivalent is contraindicated in anyone with a history of severe allergic reaction

- after previous administration of any influenza vaccine ~~or~~
- to any component of the vaccine (i.e., as defined under Section 2 Qualitative and quantitative composition and Section 6.1 List of excipients.) Refer to Section 4.4 Special warnings and precautions for use for individuals with egg allergy.

- to a vaccine containing the same components.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

Hypersensitivity

Prior to any vaccine injection, all known precautions should be taken to prevent hypersensitivity reactions. This includes a review of the individual's prior vaccination history with respect to possible hypersensitivity to the vaccine or similar vaccines. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in the event of severe allergic reaction/anaphylactic reaction following administration of Fluzone High-Dose Quadrivalent.

Each dose may contain traces of formaldehyde, ovalbumin, and octoxinol-9, which are used during vaccine production. Caution should be exercised when the vaccine is administered to individuals with hypersensitivity to any components of the vaccine including manufacturing residuals.

Individuals with egg allergy of any severity may be vaccinated.

- Individuals who report having had an allergic reaction to eggs involving only symptoms of urticaria (hives) may receive the vaccine.
- Individuals who report having had a severe allergic reaction/anaphylaxis (e.g., angioedema, respiratory distress, light headedness, or recurrent emesis, or who required epinephrine or another emergency medical intervention) to egg should have the influenza vaccine administered in an inpatient or outpatient medical setting (including, but not necessarily limited to, hospitals, clinics, health departments, and physician offices). Vaccine administration should be supervised by a healthcare provider who is able to manage severe allergic reactions.

Refer to the current Immunisation Handbook for more information.

Neurological Disorders

Recurrence of Guillain-Barré syndrome (GBS) has been temporally associated with the administration of influenza vaccine. If GBS has occurred within 6 weeks of any previous influenza vaccination, the decision to give Fluzone High-Dose Quadrivalent should be based on careful consideration of the potential benefits and risks. Refer to the current Immunisation Handbook for more information.

Immunosuppressive Treatments or Conditions

The immunogenicity of Fluzone High-Dose Quadrivalent may be reduced by immunosuppressive treatment or in individuals with immune deficiency syndromes. In such cases it is recommended to postpone the vaccination until after the immunosuppressive treatment or resolution of the immunosuppressive condition, if feasible. Vaccination of individuals with chronic immunodeficiencies is recommended even though the antibody response may be limited.

Protection

As with any vaccine, vaccination with Fluzone High-Dose Quadrivalent may not protect 100% of recepients.

Influenza virus is remarkably unpredictable in that significant antigenic changes may occur from time to time. At this time, current influenza virus vaccines are not effective against all possible influenza strains.

Bleeding disorder

Because any intramuscular injection can cause an injection-site haematoma in individuals with any bleeding disorder, such as haemophilia or thrombocytopaenia, or in individuals on anticoagulant therapy, intramuscular injections with Fluzone High-Dose Quadrivalent should not be administered to such individuals unless the potential benefits outweigh the risk of administration. If the decision is made to administer any product by intramuscular injection to such individuals, it should be given with caution, with steps taken to avoid the risk of haematoma formation following injection.

Febrile or Acute Disease

Vaccination should be postponed in case of a moderate or severe acute disease with or without fever; however, a mild disease should not usually be a reason to postpone vaccination.

Syncope

Syncope can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury and to manage syncope.

Use in the elderly

Fluzone High-Dose Quadrivalent is intended for adults 65 years of age and over (see Section 5.1 Pharmacodynamic properties, Clinical trials).

Paediatric use

Safety and effectiveness of Fluzone High-Dose Quadrivalent in children less than 18 years of age have not been established.

Effects on laboratory tests

Interference of Fluzone High-Dose Quadrivalent with laboratory and/or diagnostic tests has not been studied.

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, hepatitis C, and especially HTLV1 have been observed. An appropriate Western Blot test should be used to confirm or disprove the results of the ELISA test. The transient false-positive reactions could be due to a non-specific IgM response induced by the vaccine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Fluzone High-Dose Quadrivalent should not be mixed with any other vaccine in the same syringe or vial.

There are no data to assess the concomitant administration of Fluzone High-Dose Quadrivalent with other vaccines. Refer to the current Immunisation Handbook for more information.

If Fluzone High-Dose Quadrivalent is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

If the vaccine is used in individuals deficient in producing antibodies due to immunosuppressive therapy, the expected immune response may not be obtained.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fluzone High-Dose Quadrivalent has not been evaluated for possible effects on human fertility.

Use in pregnancy (Category B2)

Animal reproduction studies have not been conducted with Fluzone High-Dose Quadrivalent. It is also not known whether Fluzone High-Dose Quadrivalent can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Data on the use of influenza high dose vaccine in pregnant women are limited. Fluzone High-Dose Quadrivalent should be given to pregnant women only if clearly needed and following an assessment of the risks and benefits.

Use in lactation

It is not known whether Fluzone High-Dose Quadrivalent is excreted in human milk hence, caution should be used when administering the vaccine to breastfeeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive or use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse event information is derived from one clinical trial with Fluzone High-Dose Quadrivalent and from worldwide postmarketing experience with Fluzone High-Dose (inactivated trivalent influenza vaccine, TIV-HD).

Within each system organ class, the adverse reactions are ranked under headings of frequencies, using the following convention:

Very common ≥10%; Common ≥1 and < 10%; Uncommon ≥ 0.1 and < 1%; Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

Clinical Trials Experience

The safety of Fluzone High-Dose Quadrivalent was assessed in one randomised, active-controlled, modified double-blind Phase III clinical trial conducted in the US (NCT 03282240) in which 2670 adults over 65 years of age received one dose (0.7 mL) of Fluzone High-Dose Quadrivalent. The study compared the safety and immunogenicity of Fluzone High-Dose Quadrivalent to those of TIV-HD. The safety analysis set included 1777 Fluzone High-Dose Quadrivalent recipients, 443 TIV-HD recipients, and 450 TIV-HD containing the alternate B influenza strain recipients. Safety results for the TIV-HD and investigational TIV-HD containing the alternate B influenza strain recipients were pooled for the analysis. For all subjects, safety evaluations were performed during the first 28 days following vaccination. Serious adverse reactions were collected during six months of follow-up.

The overall safety profile of Fluzone High-Dose Quadrivalent was comparable to TIV-HD.

The most common reactions occurring after Fluzone High-Dose Quadrivalent administration were injection site pain (41.3%), myalgia (22.7%), headache (14.4%) and malaise (13.2%). Onset usually occurred within the first 3 days after vaccination. The majority of solicited reactions resolved within three days of vaccination.

Table 1 displays solicited adverse reactions for Fluzone High-Dose Quadrivalent compared to TIV-HD reported within 7 days after vaccination and collected using standardized diary cards.

Table 1 - Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events Within 7 Days After Vaccination with Fluzone High-Dose Quadrivalent compared to TIV-HD, in Adults 65 Years of Age and Older

	Fluzone High-dose Quadrivalent (N=1777)			TIV-HD (N=893)		
Subjects experiencing at least one:	**n/M**	**%**	**Frequency**	**n/M**	**%**	**Frequency**
General disorders and administration site conditions						
♠ **Overall local reactions**	779/1768	44.1	Very common	354/889	39.8	Very common
Injection Site Pain	731/1768	41.3	Very common	324/889	36.4	Very common
Injection Site Erythema	110/1768	6.2	Common	51/889	5.7	Common
Injection Site Swelling	86/1766	4.9	Common	42/887	4.7	Common
Injection Site Induration	66/1766	3.7	Common	31/887	3.5	Common
Injection Site Bruising	23/1765	1.3	Common	10/887	1.1	Common
♠ **Overall systemic reactions**	548/1768	31.0	Very common	264/889	29.7	Very common
Malaise	233/1768	13.2	Very common	119/889	13.4	Very common
Shivering	95/1768	5.4	Common	42/889	4.7	Common
Fever	7/1761	0.4	Uncommon	8/885	0.9	Uncommon

Nervous system disorders						
Headache	254/1768	14.4	Very common	121/889	13.6	Very common
Musculoskeletal and connective tissue disorders						
Myalgia	402/1768	22.7	Very common	168/889	18.9	Very common

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

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

Table 2 displays unsolicited adverse reactions for Fluzone High-Dose Quadrivalent compared to TIV-HD reported within 28 days after vaccination.

Table 2: Frequency of Unsolicited Adverse Reactions Within 28 Days After Vaccination with Fluzone High-Dose Quadrivalent compared to TIV-HD, in Adults 65 Years of Age and Older

	Fluzone High-dose Quadrivalent (N=1777)			**TIV-HD (N=893)**		
Subjects experiencing at least one:	**n**	**%**	**Frequency**	**n**	**%**	**Frequency**
General disorders and administration site conditions						
• ***Local reactions***						
Injection Site Pruritus	8	0.5	Uncommon	1	0.1	Uncommon
• ***Systemic reactions***						
Fatigue	1	<0.1	Rare	1	<0.1	Rare
Asthenia	0	0.0	-	1	0.1	Uncommon
Gastrointestinal disorders						
Diarrhea	2	0.1	Uncommon	2	0.2	Uncommon
Nausea	2	0.1	Uncommon	3	0.3	Uncommon
Vomiting	1	<0.1	Rare	0	0.0	-
Dyspepsia	0	0.0	-	1	0.1	Uncommon
Nervous system disorders						
Dizziness	1	<0.1	Rare	0	0.0	-
Lethargy	0	0.0	-	1	0.1	Uncommon
Vascular disorders						
Flushing	1	<0.1	Rare	0	0.0	-
Immune system disorders						
Pruritus	1	<0.1	Rare	1	0.1	Uncommon
Urticaria	1	<0.1	Rare	0	0.0	-
Night sweats	0	0.0	-	1	0.1	Uncommon
Rash	0	0.0	-	1	0.1	Uncommon
Musculoskeletal and connective tissue disorders						
Arthralgia	1	<0.1	Rare	0	0.0	-
Pain in extremity	1	<0.1	Rare	0	0.0	-
Muscular weakness	0	0.0	-	1	0.1	Uncommon

Respiratory, thoracic and mediastinal disorders						
Cough	3	0.2	Uncommon	1	0.1	Uncommon
Ear and labyrinth disorders						
Vertigo	2	0.1	Uncommon	0	0.0	-

n: number of subjects experiencing the endpoint.

Based on data from TIV-HD, solicited injection site reactions and systemic adverse reactions were slightly more frequent after vaccination with TIV-HD compared to a standard dose vaccine.

Adverse Reactions from Post-Marketing Surveillance

The following events have been spontaneously reported during the post-approval use of TIV-HD, and may occur in people receiving Fluzone High-Dose Quadrivalent.

- *Blood and Lymphatic System Disorders*: Thrombocytopaenia, lymphadenopathy
- *Immune System Disorders:* Anaphylaxis, other allergic/hypersensitivity reactions (including angioedema)
- *Eye Disorders*: Ocular hyperaemia
- *Nervous System Disorders:* Guillain-Barré syndrome (GBS), 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
- *Gastrointestinal Disorders*: Vomiting
- *Respiratory, Thoracic and Mediastinal Disorders:* Dyspnoea, wheezing, throat tightness, oropharyngeal pain, and rhinorrhoea
- *Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson syndrome
- *General Disorders and Administration Site Conditions:* Asthenia, chest pain

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Cases of administration of more than the recommended dose have been reported with TIV-HD associated with inadvertent use in the population below 65 years of age due to medication error. When adverse reactions were reported, the information was consistent with the known safety profile of TIV-HD.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB

Mechanism of action

Influenza illness and its complications like primary viral or secondary bacterial pneumonia, serious cardiac events, and neurologic complications as well as exacerbation of underlying conditions like congestive heart failure, chronic obstructive pulmonary disease (COPD), asthma, and diabetes follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HAI) antibody titre post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza virus infection.

Antibodies against one influenza virus type or subtype confer limited or no protection against another. Furthermore, antibodies to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual change of one or more strains in each year's influenza vaccine. Therefore, influenza vaccines are standardized to contain the hemagglutinins of influenza virus strains representing the influenza viruses likely to be circulating in the upcoming season.

Annual influenza vaccination is recommended because immunity during the year after vaccination declines and because circulating strains of influenza virus change from year to year.

The indication of Fluzone High-Dose Quadrivalent is based on the demonstration of noninferior immunogenicity between Fluzone High-Dose Quadrivalent and TIV-HD which allows the efficacy of Fluzone High-Dose Quadrivalent to be inferred from that for TIV-HD. Similarly, the effectiveness for Fluzone High-Dose Quadrivalent can also be inferred from the data generated for TIV-HD.

Thus, Fluzone High-Dose Quadrivalent is inferred to be more effective in preventing influenza and its complications, compared to standard dose inactivated influenza vaccine (15 micrograms of each of the strains) in adults 65 years of age and older.

Clinical trials

Immunogenicity

QHD00013

QHD00013 was a randomised, active-controlled, modified double-blind Phase III clinical trial conducted in the US (NCT 03282240) in adults 65 years and older.

The objective was to demonstrate the noninferiority of Fluzone High-Dose Quadrivalent over TIV-HD, as assessed by HAI (hemagglutinin inhibition) Geometric mean antibody titres (GMTs) at Day 28 and seroconversion rates.

A total of 2670 adults from 65 years of age were randomised to receive either one dose of Fluzone High-Dose Quadrivalent or one dose of TIV-HD (one of two formulations of comparator vaccine [TIV-HD1 or TIV-HD2]); each TIV-HD formulation contained a B strain that corresponds to one of the two B strains in Fluzone High-Dose Quadrivalent (either a B strain of the Yamagata lineage or a B strain of the Victoria lineage). The mean age was 72.9 years in the Fluzone High-Dose Quadrivalent group (ranged from 65 through 100 years) and the mean age was 73.0 in the TIV-HD group (ranged from 65 through 95 years). 35.4% of participants in the Fluzone High-Dose Quadrivalent group and 35.8% of participants in the TIV-HD group were 75 years of age or older.

The immunogenicity results of Fluzone High-Dose Quadrivalent in the QHD00013 study are summarised below in **Table 3**.

Table 3: Study 1[a]: Analyses of Noninferiority of Fluzone High-Dose Quadrivalent Relative to TIV-HD by Post-Vaccination HAI Antibody GMTs and Seroconversion Rates in Adults 65 Years of Age and Older, Per-Protocol Analysis Set

Influenza Strain	GMT			GMT Ratio	Seroconversion Rate (Percentage)[b]			Difference of Seroconversion Rates	Met Pre-defined Noninferiority Criteria[f]
	QIV-HD N[c]=1679-1680	TIV-HD1[d] (B1 Victoria) N[c]=423	TIV-HD2[e] (B2 Yamagata) N[c]=430	QIV-HD over TIV-HD (95% CI)	QIV-HD N[c]=1668-1669	TIV-HD1[d] (B1 Victoria) N[c]=420-421	TIV-HD2[e] (B2 Yamagata) N[c]=428	QIV-HD minus TIV-HD (95% CI)	
A (H1N1) [g]	312	374		0.83 (0.744; 0.932)	50.4	53.7		-3.27 (-7.37; 0.86)	Yes
A (H3N2) [g]	563	594		0.95 (0.842; 1.066)	49.8	50.5		-0.71 (-4.83; 3.42)	Yes
B1 (Victoria)	516	476	--	1.08 (0.958; 1.224)	36.5	39.0	--	-2.41 (-7.66; 2.70)	Yes
B2 (Yamagata)	578	--	580	1.00 (0.881; 1.129)	46.6	--	48.4	-1.75 (-7.04; 3.53)	Yes

[a] NCT03282240

[b] Seroconversion Rates: For subjects with a pre-vaccination titre <10 (1/dil), proportion of subjects with a post-vaccination titre ≥40 (1/dil) and for subjects with a pre-vaccination titre ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titre.

[c] N is the number of vaccinated participants with available data for the immunologic endpoint listed

[d] TIV-HD1 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008 (B1, Victoria lineage).

[e] TIV-HD2 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Phuket/3073/2013 (B2, Yamagata lineage).

[f] Predefined noninferiority criterion for seroconversion rates: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (Fluzone High-Dose Quadrivalent minus TIV-HD) is >-10%. Predefined noninferiority criterion for the GMT ratio: the lower limit of the 95% CI of the GMT ratio (Fluzone High-Dose Quadrivalent divided by TIV-HD) is >0.667.

[g] For the A strain comparison, TIV-HD1 and TIV-HD2 were pooled into a TIV-HD group for comparison with Fluzone High-Dose Quadrivalent.

Fluzone High-Dose Quadrivalent was as immunogenic as TIV-HD for GMTs and seroconversion rates for the common influenza strains. Moreover, Fluzone High-Dose Quadrivalent 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.

The efficacy and effectiveness results of TIV-HD are thus inferred Fluzone High-Dose Quadrivalent given the demonstration of statistically comparable immunogenicity between TIV-HD and Fluzone High-Dose Quadrivalent in the QHD00013 study.

FIM05 (data from TIV-HD)

FIM05 was a multi-center, randomised, double-blind controlled trial conducted in the US in adults 65 years and older. The objective was to demonstrate the superiority of TIV-HD over a standard dose inactivated influenza vaccine containing 15 micrograms of each strains (2 A strains and 1 B strain), as assessed by seroconversion rates and GMTs.

The immunogenicity results of the FIM05 Phase 3 study on TIV-HD are summarised below in **Table 4**.

Table 4: Superiority of TIV-HD by Seroconversion Rates and GMT 28 Days Post-Vaccination - Immunogenicity Analysis

	TIV-HD N=2576		**Standard dose Trivalent inactivated influenza vaccine N=1275**			**Superiority**
Seroconversion rates						
Influenza Strain	**n/M**	**SC rate % (95% CI)**	**n/M**	**SC rate[1] % (95% CI)**	**% Difference[2] TIV-HD minus TIV-SD (95% CI)**	
H1N1	1229/2531	48.56 (46.59; 50.53)	289/1249	23.14 (20.83; 25.58)	25.42 (22.38; 28.46)	Superior[4]
H3N2	1749/2531	69.10 (67.26; 70.90)	633/1248	50.72 (47.91; 53.53)	18.38 (15.08; 21.69)	Superior[4]
B	1056/2529	41.76 (39.82; 43.71)	374/1249	29.94 (27.41; 32.57)	11.81 (8.63; 15.00)	Higher[5]
GMT ratios						
Influenza Strain	**M**	**GMT (95% CI)**	**M**	**GMT (95% CI)**	**GMTR[3] TIV-HD/TIV-SD (95% CI)**	
H1N1:	2543	115.79	1252	67.29	1.72	Superior[6]

		(111.41; 120.34)		(63.65; 71.13)	(1.61; 1.84)	
H3N2	2544	608.87 (583.54; 635.30)	1252	332.46 (310.44; 356.05)	1.83 (1.70; 1.98)	Superior[6]
B	2542	69.06 (66.60; 71.60)	1252	52.34 (49.48; 55.35)	1.32 (1.24; 1.41)	Higher[7]

N is the number of subjects in the Immunogenicity Analysis Set
n is the number of subjects who achieved seroconversion for each strain
M is the number of subjects with both pre- and post-vaccination serology results for the strain, including results reported as <LLOQ (lower limit of quantification)
[1]Seroconversion: For subjects with a Day 0 pre-vaccination titre <10 (1/dil): Titre ≥40 (1/dil) on Day 28.
For subjects with a Day 0 pre-vaccination titre ≥10 (1/dil): ≥4-fold increase in titre on Day 28.
[2]As defined in the study protocol: Superiority for a virus strain: the lower limit of the 95% CI of the difference of the seroconversion rates (HD minus Standard dose inactivated influenza vaccine) is >10%.
[3]Superiority of TIV-HD: At least 2 of the 3 virus strains must demonstrate superiority. If one strain fails, then it must demonstrate noninferiority with the lower limit of the 95% CI ≥-10%.
As defined in the study protocol: Superiority for a virus strain: the lower limit of the 95% CI for GMT ratio TIV-HD over a standard dose inactivated influenza vaccine is >1.5.
Superiority of High Dose, Trivalent Influenza Vaccine (Split Virion, Inactivated): At least 2 of the 3 virus strains must demonstrate superiority. If one strain fails, then it must demonstrate noninferiority with the lower limit of the 95% CI >0.67.
[4]As per the study's primary objective, superiority was demonstrated if the lower limit of the Confidence Interval (CI) was greater than 10% for at least two of the three virus strains, a more stringent statistical criteria.
[5]A post hoc analysis was performed using the generally accepted superiority criteria of the lower limit of the CI greater than 0%.
[6]As per the study's primary objective, superiority was demonstrated if the lower limit of the Confidence Interval (CI) was greater than 1.5 for at least two of the three virus strains, a more stringent statistical criteria.
[7]A post hoc analysis was performed using the generally accepted superiority criteria of the lower limit of the CI greater than 1.

According to the criteria set in the protocol, TIV-HD elicited a superior immune response compared to a standard dose trivalent inactivated influenza vaccine for both seroconversion rates and GMTs.

Efficacy of TIV-HD in Adults 65 Years of age and Older (FIM12 Study)

FIM12 was a multi-center, double-blind efficacy trial conducted in the US and Canada in which adults 65 years of age and older were randomised (1:1) to receive either TIV-HD or a standard dose influenza vaccine. The study was conducted over two influenza seasons (2011-2012 and 2012-2013) to assess the occurrence of laboratory-confirmed influenza caused by any influenza viral type/subtype in association with influenza-like illness (ILI) as the primary endpoint.

Participants were monitored for the occurrence of a respiratory illness by both active and passive surveillance, starting 2 weeks postvaccination for approximately 7 months. After an episode of respiratory illness, nasopharyngeal swab samples were collected for analysis; attack rates and vaccine efficacy were calculated.

Table 5: FIM12: Relative Efficacy to the Vaccine Components, Associated with Influenza-Like Illness[a], Adults 65 Years of Age and Older

	TIV-HD N[b]=15,892 n[c] (%)	Standard dose inactivated influenza vaccine N[b]=15,911 n[c] (%)	Relative Efficacy % (95% CI)
Laboratory-Confirmed Influenza[d] caused by:			
- **Any type/subtype[e]**	227 (1.43)	300 (1.89)	24.2 (9.7; 36.5)[f]
- **Viral strains similar to those contained in the vaccine**	73 (0.46)	113 (0.71)	35.3 (12.4; 52.5)

[a] Occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrent with at least one of the following systemic signs or symptoms: temperature >37.2°C, chills, tiredness, headaches or myalgia.
[b] N is the number of vaccinated participants in the per-protocol analysis set for efficacy assessments.
[c] n is the number of participants with protocol-defined influenza-like illness with laboratory confirmation.
[d] Laboratory-confirmed: culture- or polymerase-chain-reaction-confirmed.
[e] Primary endpoint.
[f] The pre-specified statistical superiority criterion for the primary endpoint (lower limit of the 2-sided 95% CI of the vaccine efficacy of TIV-HD relative to Standard dose inactivated influenza vaccine >9.1%) was met.

For the supplementary analysis, selected serious cardiorespiratory events reported in 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.

For both years combined, there was a significant reduction in the total number of serious cardiorespiratory events (relative Vaccine Efficacy (rVE), 17.7% [95% CI: 6.6%–27.4%]) among TIV-HD recipients compared to standard dose influenza vaccine recipients, including a significant reduction in serious pneumonia events (rVE, 39.8% [95% CI: 19.3%–55.1%]). In addition, a borderline significant reduction in all-cause hospitalisation (rVE, 6.9%; 95% CI: 0.5%–12.8%) was observed. It is noted that most of the reductions in the TIV-HD group were observed in Year 2 with no significant differences observed in Year 1.

Effectiveness of TIV-HD in Adults 65 Years of Age and Older

Randomised Clinical Trials

A cluster-randomised, controlled clinical trial in United States nursing homes assessed the relative effect of TIV-HD versus a standard dose of influenza vaccine in hospitalisations among 53,008 individuals during the 2013-2014 influenza season.

During the 2013-2014 season, when adjusting for the pre-specified patient and facility characteristics, the incidence of respiratory-related hospital admissions (primary objective) was significantly reduced in facilities where residents received TIV-HD compared with those that received standard-dose influenza vaccines by 12.7% (adjusted risk ratio [ARR] 0.873, 95% CI 0.776 to 0.982, p=0.023). Moreover, with respect to secondary endpoints, TIV-HD reduced hospital admissions for pneumonia by 20.9% (ARR 0.791, 95% CI: 0.267 to 0.953,

p=0.013) and all-cause hospital admissions by 8% (ARR 0.915, 95% CI: 0.863 to 0.970, p=0.0028).

Observational Studies

Several retrospective studies, over 8 influenza seasons and in more than 24 million individuals 65 years of age and older, confirmed the superior protection offered by TIV-HD compared to standard-dose influenza vaccines against complications of influenza such as pneumonia hospitalisation (13.4% (95%CI: 7.3% to 19.2%, p<0.001)), cardio-respiratory hospitalisations 17.9% (95%CI :14.9% to 20.9%, p<0.001) and all –cause hospitalisation 8.1% (95%CI: 5.9% to 10.3%, p<0.001); although the impact may vary per season.

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fluzone High-Dose Quadrivalent has not been tested for genotoxic potential.

Carcinogenicity

Fluzone High-Dose Quadrivalent has not been tested for carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Fluzone High-Dose Quadrivalent contains sodium chloride, dibasic sodium phosphate, monobasic sodium phosphate, octoxinol-9 and water for injections as excipients.

Fluzone High-Dose Quadrivalent may also contain traces of formaldehyde (≤ 140 µg) and ovalbumin (≤ 1 µg). Neither antibiotics nor preservative are used during manufacture.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this vaccine must not be mixed with other vaccine or medicinal products.

6.3 SHELF LIFE

12 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate, Do not freeze). Discard if vaccine has been frozen.

6.5 NATURE AND CONTENTS OF CONTAINER

Fluzone High-Dose Quadrivalent is available as a 0.7 mL single-dose, pre-filled syringe without needle. Packs of 5 or 10 syringes*.

*Not all pack sizes are marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

After use, any remaining vaccine and container must be disposed of safely, according to locally acceptable procedures.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Only Medicine

8 SPONSOR

sanofi-aventis australia pty ltd
Talavera Corporate Centre – Building D
12-24 Talavera Road
Macquarie Park NSW 2113
Australia

Tel: 1800 818 806

9 DATE OF FIRST APPROVAL

31 July 2020

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information