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 2025 influenza season:

- A/Victoria/4897/2022 (H1N1)pdm09-like strain (A/Victoria/4897/2022, IVR-238)
- A/Croatia/10136RV/2023 (H3N2)-like strain (A/Croatia/10136RV/2023, X-425A)
- B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild type)
- B/Phuket/3073/2013-like strain (B/Phuket/3073/2013; wild type)

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 a colourless opalescent liquid.

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 60 years of age and older.

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

See Section 5.1 Pharmacodynamic properties, 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 60 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
- 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 recipients.

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 60 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

Co-administration of Fluzone High-Dose Quadrivalent with an investigational booster 100 mcg dose of COVID-19 mRNA vaccine (nucleoside modified/elasomeran) has been evaluated in a limited number of participants in a descriptive clinical study (see Section 4.8 and Section 5.1).

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

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.

It should be noted that the adverse reactions may be intensified by any co-administration.

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)

Summary of the safety profile

Adverse event information is based on data coming from two clinical trials with Fluzone High-Dose Quadrivalent and on the clinical and post-marketing experience with Fluzone High-Dose (inactivated trivalent influenza vaccine, TIV-HD).

The safety of Fluzone High-Dose Quadrivalent was assessed in a pooled analysis of two clinical trials (QHD00013 and QHD00011) in which 2549 adults from 60 years of age and older (378 adults from 60 to 64 years of age and 2171 adults 65 years of age and older) received Fluzone High-Dose Quadrivalent.

The most frequently reported adverse reaction after vaccination was injection site pain reported by 42.6% of study participants followed by myalgia (23.8%), headache (17.3%), and malaise (15.6%). Most of these reactions occurred and resolved within three days of vaccination. The intensity of most of these reactions was mild to moderate.

Overall, adverse reactions were generally less frequent in participants aged 65 years and older than in participants aged 60 to 64 years.

Reactogenicity of Fluzone High-Dose Quadrivalent was slightly increased as compared to the standard dose vaccine, but no major difference in intensity was observed.

The safety of Fluzone High-Dose Quadrivalent (QIV-HD) was evaluated in a descriptive study (QHD00028) in which subjects received QIV-HD together with an investigational booster 100 mcg dose of COVID-19 mRNA vaccine (nucleoside modified) (n=100), QIV-HD only (n=92) or an investigational booster 100 mcg dose of COVID-19 mRNA vaccine (nucleoside modified) only (n=104). The frequency and severity of local and systemic adverse reactions was similar in subjects who were co-administered with QIV-HD and licensed COVID-19 mRNA vaccine and subjects administered with a booster dose of licensed COVID-19 mRNA vaccine.

Tabulated list of adverse reactions

The data below summarizes the frequencies of adverse reactions that were recorded following vaccination with Fluzone High-Dose Quadrivalent and adverse reactions reported during clinical development and post-marketing experience with TIV-HD (marked with * in the table below).

Adverse events are ranked under headings of frequency using the following convention:
Very common (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);
Rare (≥1/10,000 to <1/1,000);
Very rare (<1/10,000);
Not known (cannot be estimated from available data).

Adverse Reactions	Frequency
General Disorders and Administration Site Conditions	

Adverse Reactions	Frequency
Injection site pain, injection site erythema, malaise	Very common
Injection site swelling, injection site induration, injection site bruising, fever (≥37.5° C), shivering	Common
Injection site pruritis, fatigue	Uncommon
Asthenia	Rare
Chest pain	Not known*
Musculoskeletal and Connective Tissue Disorders	
Myalgia	Very common
Muscle weakness[a]	Uncommon
Arthralgia, pain in extremities	Rare
Nervous System Disorders	
Headache	Very common
Lethargy[a]	Uncommon
Dizziness, paraesthesia	Rare
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)	Not known*
Blood and Lymphatic System Disorders	
Thrombocytopenia, lymphadenopathy	Not known*
Respiratory, Thoracic and Mediastinal Disorders	
Cough, oropharyngeal pain	Uncommon
Rhinorrhea	Rare
Dyspnea, wheezing, throat tightness	Not known*
Gastrointestinal Disorders	
Nausea, vomiting, dyspepsia[a], diarrhoea	Uncommon
Immune System Disorders	
Pruritus, urticaria, night sweats, rash	Rare
Anaphylaxis, other allergic/hypersensitivity reactions (including angioedema)	Not known*
Vascular Disorders	
Flushing	Rare
Vasculitis, vasodilatation	Not known*
Ear and Labyrinth Disorders	
Vertigo	Rare
Eye Disorders	
Ocular hyperemia	Rare

a Dyspepsia, lethargy, and muscular weakness were observed with TIV-HD in the QHD00013 trial.

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 60 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 Poison Information Centre on 131126 (Australia).

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 in adults 60 years of age and older is based on:

- The demonstration of noninferior immunogenicity between Fluzone High-Dose Quadrivalent and TIV HD in persons 65 years of age and older (QHD00013), which

allows the efficacy and effectiveness of Fluzone High-Dose Quadrivalent to be inferred from that of TIV HD.

- Similar immune responses observed in subjects 60 to 64 years of age and in subjects 65 years of age and older (QHD00011), which allows for the extension of the efficacy and effectiveness of TIV HD in adults 65 years of age and older to adults from 60 years of age and older.

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 60 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 1**.

Table 1: 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 Nc=1679-1680	TIV-HD1[d] (B1 Victoria) Nc=423	TIV-HD2[e] (B2 Yamagata) Nc=430	QIV-HD over TIV-HD (95% CI)	QIV-HD Nc=1668-1669	TIV-HD1[d] (B1 Victoria) Nc=420-421	TIV-HD2[e] (B2 Yamagata) Nc=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

Influenza Strain	GMT			GMT Ratio	Seroconversion Rate (Percentage)[b]			Difference of Seroconversion Rates	Met Pre-defined Noninferiority Criteria[f]
	QIV-HD Nc=1679-1680	TIV-HD1[d] (B1 Victoria) Nc=423	TIV-HD2[e] (B2 Yamagata) Nc=430	QIV-HD over TIV-HD (95% CI)	QIV-HD Nc=1668-1669	TIV-HD1[d] (B1 Victoria) Nc=420-421	TIV-HD2[e] (B2 Yamagata) Nc=428	QIV-HD minus TIV-HD (95% CI)	
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.

QHD00011

QHD00011 was a randomised, active-controlled, modified double-blind, Phase III, clinical trial conducted in Europe in adults 60 years and older to demonstrate the superiority of Fluzone High-Dose Quadrivalent over QIV-SD for all strains, as assessed by HAI (hemagglutinin inhibition) geometric mean antibody titers (GMTs) at Day 28 in adults 60 to 64 years of age and in adults 65 years of age and older.

A total of 1539 adults (760 adults 60 to 64 years of age and 779 adults 65 years of age and older) were randomised to receive either one dose of Fluzone High-Dose Quadrivalent or one dose of QIV-SD.

Table 2: Study 2[a]: Analyses of Superiority of Fluzone High-Dose Quadrivalent Relative to QIV-SD by Post-Vaccination HAI Antibody GMTs in Adults 60-64 Years of Age and 65 Years of Age and Older, Full Analysis Set

Influenza Strain	Adults 60 to 64 Years of Age				Adults 65 years of Age and Older			
	GMT		GMT Ratio	Met Pre-defined Superiority Criteria[c]	GMT		GMT Ratio	Met Pre-defined Superiority Criteria[c]
	QIV-HD N[b]=376-377 (95% CI)	QIV-SD N[b]=377 (95% CI)	QIV-HD over QIV-SD (95% CI)		QIV-HD N[b]=392 (95% CI)	QIV-SD N[b]=381 (95% CI)	QIV-HD over QIV-SD (95% CI)	
A (H1N1)	471 (416 ; 533)	248 (217 ; 283)	1.90 (1.58 ; 2.28)	Yes	286 (250 ; 326)	162 (139 ; 190)	1.76 (1.44 ; 2.15)	Yes
A (H3N2)	303 (262 ; 350)	178 (154 ; 206)	1.70 (1.38 ; 2.08)	Yes	324 (281 ; 374)	151 (129 ; 176)	2.15 (1.74 ; 2.65)	Yes
B1 (Victoria)	497 (450 ; 548)	330 (297 ; 367)	1.51 (1.30 ; 1.74)	Yes	405 (366 ; 447)	262 (236 ; 291)	1.55 (1.34 ; 1.79)	Yes
B2 (Yamagata)	766 (690 ; 849)	433 (391 ; 480)	1.77 (1.53 ; 2.04)	Yes	536 (485 ; 592)	305 (274 ; 340)	1.76 (1.52 ; 2.03)	Yes

[a] NCT04024228
[b] N is the number of participants with available data for the considered endpoint
[c] Superiority was concluded if the lower limit of the two-sided 95% CI of the ratio of GMTs between groups (QIV-HD/QIV-SD) was > 1 for each strain and in each age group

The efficacy and effectiveness results of TIV-HD are thus inferred to Fluzone High-Dose Quadrivalent, given the demonstration of statistically comparable immunogenicity between TIV-HD and Fluzone High-Dose Quadrivalent in adults 65 years of age and older (QHD00013) and similar immune responses observed in adults 60 to 64 years of age and in adults 65 years of age and older (QHD00011).

In addition, Fluzone High-Dose Quadrivalent induced an immune response that was superior to the responses induced by QIV-SD for all 4 virus strains 28 days post-vaccination in adults 60 to 64 years of age and in adults 65 years of age and older.

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 strain (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 3**.

Table 3: 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)**	**GMTR3 TIV-HD/TIV-SD (95% CI)**	
H1N1:	2543	115.79 (111.41; 120.34)	1252	67.29 (63.65; 71.13)	1.72 (1.61; 1.84)	Superior[6]
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]

	TIV-HD N=2576	Standard dose Trivalent inactivated influenza vaccine N=1275	Superiority

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 post-vaccination 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 4: 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 healthcare 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.

Concomitant Administration with COVID-19 mRNA vaccine (nucleoside modified)

In a descriptive open-label clinical study (NCT04969276), healthy adults aged 65 years and older were divided in three groups: Group 1 received Fluzone High-Dose Quadrivalent alone (N=92), Group 2 (N=100) received Fluzone High-Dose Quadrivalent concomitantly with an investigational booster 100 mcg dose of COVID-19 mRNA vaccine (nucleoside modified) at least 5 months after the second dose of the primary series, Group 3 (N=104) received only the investigational booster 100 mcg dose of COVID-19 mRNA vaccine (nucleoside modified).

Co-administration resulted in no change to influenza vaccine immune responses as measured by hemagglutination inhibition (HAI) assay. Co-administration resulted in similar responses to COVID-19 mRNA vaccine, as assessed by an anti-spike IgG assay (see Section 4.5 and Section 4.8).

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

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Macquarie Park NSW 2113
Australia

Tel: 1800 818 806

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

31 July 2020

10 DATE OF REVISION

15 November 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Annual strain update