AUSTRALIAN PRODUCT INFORMATION – FLUBLOK QUADRIVALENT (INFLUENZA HAEMAGGLUTININ RECOMBINANT) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Quadrivalent Recombinant Influenza Vaccine, Influenza Haemagglutinin Recombinant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mL dose of vaccine contains influenza haemagglutinin recombinant* of the following strains:

- A/Victoria/2570/2019 (H1N1)pdm09 - like strain (A/Victoria/2570/2019, IVR-215) 45 microgram HA**
- A/Hong Kong/2671/2019 (H3N2) - like strain (A/Hong Kong/2671/2019, IVR-208) 45 microgram HA
- B/Washington/02/2019 - like strain (B/Washington/02/2019, wild type) 45 microgram HA
- B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, wild type) 45 microgram HA

* Produced by recombinant DNA technology using a baculovirus expression system in a continuous insect cell line (*expres*SF+®) that is derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda*.

** Haemagglutinin

The type and amount of viral antigens contained in Flublok Quadrivalent conform to the annual requirements of the Australian Influenza Vaccine Committee (AIVC) and the World Health Organization (WHO) recommendations for the 2021 season.

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

3 PHARMACEUTICAL FORM

Solution for injection.

Flublok Quadrivalent is clear and colourless without particulate matter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Flublok Quadrivalent is indicated for active immunisation for the prevention of influenza disease caused by influenza virus types A and B contained in the vaccine. Flublok Quadrivalent is approved for use in persons 18 years of age and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

Given the variation of the influenza viruses and the duration of immunity provided by the vaccine, it is recommended to vaccinate against influenza every year.

- Individuals 18 years of age and older receive a 0.5 mL single dose annually.

Method of administration

Administration should be carried out by intramuscular route, preferably in the deltoid muscle.

Do not administer this product intravenously, subcutaneously or intradermally.

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

Flublok Quadrivalent should not be administered to anyone with a known severe allergic reaction (anaphylaxis) to any component of the vaccine as defined under Section 2 Qualitative and quantitative composition and Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution should be exercised when the vaccine is administered to individuals with hypersensitivity to the vaccine itself or any of its components. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

Protection

As with any vaccine, vaccination with Flublok Quadrivalent may not protect 100% of vaccine recipients.

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated.

If GBS has occurred within 6 weeks following previous influenza vaccination, the decision to give Flublok Quadrivalent should be based on careful consideration of the potential benefits and risks.

Bleeding Disorders

Because any intramuscular injection can cause an injection site haematoma in individuals with any bleeding disorders, such as haemophilia or thrombocytopenia, or in individuals on anticoagulant therapy, intramuscular injections with Flublok 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 hematoma formation following injection.

Altered Immunocompetence

If Flublok Quadrivalent is administered to immunocompromised individuals, including persons receiving immunosuppressive treatment, the immune response may be diminished.

Intercurrent illness

Vaccination should be postponed in patients with acute febrile illness until the fever is resolved.

Syncope

Syncope (fainting) has been reported following vaccination with Flublok Quadrivalent. Procedures should be in place to prevent falling injury and to manage syncopal reactions to any intramuscular injection.

Use in the elderly

Refer to Section 4.8 Adverse Effects and Section 5.1 Pharmacodynamic Properties for safety and efficacy of Flublok Quadrivalent administration in individuals older than 50 years of age.

Paediatric use

Safety and efficacy of Flublok Quadrivalent have not been established in children less than 18 years of age and the vaccine is not indicated in that age group.

Data from a randomised, controlled trial demonstrated that children 6 months to less than 3 years of age had diminished haemagglutination inhibition (HI) responses to trivalent recombinant influenza vaccine as compared to a U.S.-licensed influenza vaccine approved for use in this population, strongly suggesting that trivalent recombinant influenza vaccine would not be effective in children younger than 3 years of age.

Effects on laboratory tests

Interference of Flublok Quadrivalent with laboratory and/or diagnostic tests has not been studied.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Flublok Quadrivalent should not be mixed with another vaccine in the same syringe or vial.

If Flublok Quadrivalent is to be given at the same time as another injectable vaccine(s), the vaccine(s) should be administered at different injection sites.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no fertility data available in humans and effects on fertility have not been investigated in animal studies with Flublok Quadrivalent.

There were no effects on the mating performance or fertility of female rats intramuscularly injected with the full clinical dose of Flublok (trivalent formulation), which was manufactured using the same process as Flublok Quadrivalent, 31 and 12 days prior to mating and Day 6 after mating. The effect on male fertility has not been determined.

Use in pregnancy (Category B1)

There were no developmental studies of Flublok Quadrivalent performed in animals.

The developmental effects of Flublok (trivalent formulation) are relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions. A reproductive study was conducted in female rats with Flublok (trivalent formulation). Animals were administered 0.5 mL doses of Flublok (trivalent formulation) 31 and 12 days prior to mating and on Day 6 of gestation. No vaccine-related effects on fetal development, fetal malformations or variations or pre-weaning development were observed.

The safety of Flublok Quadrivalent in pregnancy has not been assessed in clinical trials. Pregnant women are at high risk of influenza complications, including premature labour and delivery, hospitalisation, and death. Available data on Flublok Quadrivalent in pregnant women are limited. An assessment of the risks and benefits should be performed by a health care professional before administering Flublok Quadrivalent to pregnant women.

Refer to the current recommendations in the Immunisation Handbook for use in pregnancy.

Use in lactation

It is not known whether Flublok Quadrivalent is excreted in human milk. Data are not available to assess the effects of on Flublok Quadrivalent on the breast-fed infant or on milk production/excretion. An assessment of the risks and benefits should be performed by a health care professional before administering on Flublok Quadrivalent to a nursing woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse event information is derived from clinical trials and post-marketing experience.

Clinical Trials

As clinical trials are conducted under widely varying conditions, and because the strain composition of influenza vaccines is subject to annual changes, adverse reaction rates observed in the clinical trial(s) of one vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

Flublok Quadrivalent has been administered to and safety data collected from 998 adults 18-49 years of age (PSC16) and 4328 adults 50 years of age and older (PSC12). Both studies were Phase 3, multi-centre, randomised, active-controlled, double-blind trials conducted in the US.

The most common reactions occurring after vaccine administration were injection-site reactions (tenderness and pain) reported overall by 48% and 37% of study participants 18-49 years of age receiving Flublok Quadrivalent, respectively and 47% and 36% respectively of those receiving the active comparator vaccine (Table 1).

Table 1: Frequency of Solicited Injection Site and Systemic Adverse Reactions within 7 Days of Administration of Flublok Quadrivalent or Comparator in Adults 18-49 Years of Age in PSC16 (Reactogenicity Populations)[1,2]

Reactogenicity Term	Flublok Quadrivalent N=996 %			Comparator N=332 %		
	Any Grade[6]	Grade 3	Grade 4	Any Grade[6]	Grade 3	Grade 4
Subjects with ≥1 injection site reaction[3, 4]	51	1	0	52	2	0
Local Tenderness	48	1	0	47	1	0
Local Pain	37	1	0	36	1	0
Firmness / Swelling	5	0	0	3	0	0
Redness	4	0	0	1	0	0
Subjects with ≥1 systemic reaction[3,5]	34	2	<1	36	3	<1
Headache	20	1	0	21	2	<1
Fatigue	17	1	0	17	1	0
Muscle Pain	13	1	0	12	1	0
Joint Pain	10	1	0	10	1	0
Nausea	9	1	<1	9	1	0
Shivering / Chills	7	1	0	6	1	0
Fever[6, 7]	2	<1	0	1	<1	0

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results > 0 but < 1% reported as < 1%.

[1] Comparator: Quadrivalent inactivated influenza vaccine, Fluarix Tetra, manufactured by GlaxoSmithKline.

[2] PSC16 is registered as NCT02290509 under the National Clinical Trials registry.

[3] Reactogenicity Populations were defined as all randomised subjects who received study vaccine according to the treatment actually received and who had at least one non-missing data point for injection site, systemic or body temperature reactogenicity categories. For local pain, tenderness and systemic reactions: Grade 1 = No interference with activities. Grade 2 = Prevented some activities, and headache may have required non-narcotic pain reliever. Grade 3 = Prevented most or all normal activities or required prescription medications. Grade 4 = Required visit to ER or hospitalisation. For injection site redness and firmness/swelling: Grade 1=25 to ≤ 50 mm (small). Grade 2=51 to ≤ 100 mm (medium). Grade 3=> 100 mm (large). Grade 4=necrosis or exfoliative dermatitis.

[4] Denominators for injection site reactions: Flublok Quadrivalent n = 996, Comparator n =332.

[5] Denominators for systemic reactions: Flublok Quadrivalent n = 994, Comparator n = 332.

[6] Denominators for fever: Flublok Quadrivalent n = 990, Comparator n = 327.

[7] Fever defined as body temperature ≥ 38.00°C. Grade 1 (≥ 38.00ºC to ≤ 38.39ºC); Grade 2 (38.44ºC to ≤ 38.89ºC); Grade 3 (38.94ºC to ≤ 40.00°C). Grade 4 > 40.00°C.

In study participants 50 years of age and older, injection site tenderness was reported by 34% and 37% of those receiving Flublok Quadrivalent or active comparator, respectively (Table 2). Onset usually occurred within the first 3 days after vaccination. All resolved without sequelae.

Table 2: Frequency of Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok Quadrivalent or Comparator[1] in Adults 50 Years of Age and Older in PSC12 (Reactogenicity Populations)[2, 3]

Reactogenicity Term	Flublok Quadrivalent N=4312 %			Comparator N=4327 %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Subjects with ≥1 injection site reaction[3, 4]	38	<1	<1	40	<1	<1
Local Tenderness	34	<1	<1	37	<1	<1
Local Pain	19	<1	0	22	<1	<1
Firmness / Swelling	3	<1	0	3	<1	0
Redness	3	<1	0	2	<1	0
Subjects with ≥1 systemic reactogenicity event[3,5]	25	1	<1	26	1	<1
Headache	13	<1	<1	14	1	<1
Fatigue	12	<1	0	12	<1	<1
Muscle Pain	9	<1	<1	9	<1	<1
Joint Pain	8	<1	0	8	<1	<1
Nausea	5	<1	0	5	<1	<1
Shivering / Chills	5	<1	0	4	<1	<1
Fever[6,7]	<1	<1	0	1	<1	0

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results >0 but <1% reported as <1%.

[1]Comparator: Quadrivalent inactivated influenza vaccine, Fluarix Tetra, manufactured by GlaxoSmithKline.

[2] PSC12 is registered as NCT02285998 under the National Clinical Trials registry.

[3] Reactogenicity Populations were defined as all randomized subjects who received study vaccine according to the treatment actually received and who had at least one non-missing data point for injection site, systemic or body temperature reactogenicity categories. For local pain, tenderness, and systemic reactions: Grade 1=No interference with activity. Grade 2=Some interference with activity. Grade 3=Prevents daily activity. Grade 4=Required ER visit or hospitalisation. For injection site redness and firmness/swelling: Grade 1=25 to ≤50 mm (small). Grade 2=51 to ≤100 mm (medium). Grade 3=>100 mm (large). Grade 4=necrosis or exfoliative dermatitis.

[4] Denominators for injection site reactions: Flublok Quadrivalent n = 4307, Comparator n = 4319.

[5] Denominators for systemic reactions: Flublok Quadrivalent n = 4306, Comparator n = 4318.

[6] Denominators for fever: Flublok Quadrivalent n = 4262, Comparator n = 4282.

[7] Fever defined as body temperature ≥38.00°C. Grade 1 (≥ 38.00ºC to ≤ 38.39ºC); Grade 2 (38.44ºC to ≤ 38.89ºC); Grade 3 (38.94ºC to ≤ 40.00°C). Grade 4 > 40.00°C.

Table 3 - Frequency of Unsolicited Adverse Reactions Following Administration of Flublok Quadrivalent in PSC12 and PSC16

	PSC16 Adults aged 18-49 years		PSC12 Adults aged ≥ 50 years	
	Flublok Quadrivalent	**Comparator**	**Flublok** Quadrivalent	**Comparator**
	N=998	N=332	N=4328	N=4344
	%	%	%	%
Gastrointestinal disorders				
Diarrhoea	0.2	0	0.1	0
General disorders and administration site conditions				
Flu-like symptoms	0	0	0.2	0.2
Injection site pruritus	0.1	0	0.1	0.1
Skin and subcutaneous tissue disorders				
Pruritus	0.2	0	0.02	0.1
Dermatitis	0.1	0	0	0
Rash	0.1	0	0	0
Urticaria	0	0	0.02	0
Nervous system disorders				
Dizziness	0	0	0.05	0.1
Respiratory, thoracic and mediastinal disorders				
Cough	0.1	0	0.2	0.3
Oropharyngeal pain	0.1	0	0.2	0.3

In the 28 days following vaccination, one or more unsolicited adverse events occurred in 10.3% of Flublok Quadrivalent and 10.5% of Comparator recipients in PSC16 (adults 18-49 years of age) and in 13.9% of Flublok Quadrivalent and 14.1% of Comparator recipients in PSC12 (adults ≥ 50 years of age). In both studies, rates of individual events were similar between treatment groups, and most events were mild to moderate in severity.

Data from post-marketing experience

The following adverse events have been reported during the post-marketing use of Flublok Quadrivalent. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

- *Immune system disorders*: anaphylaxis, anaphylactoid reactions, allergic reactions, and other forms of hypersensitivity.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: influenza vaccine, ATC code: J07BB04

Mechanism of action

Flublok Quadrivalent contains recombinant HA proteins of the four strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine.

Using the recombinant production technology, the HA in Flublok Quadrivalent has an identical primary structure to the HA in the wild type virus strains selected for seasonal vaccines without the mutations that may occur when the virus is adapted to grow in a culture matrix that is foreign to the wild-type strain. This assures the vaccine viral strains represent antigens that are an exact match to the WHO selected strains which induce the desired humoral immune response (as measured by HI antibody that is known to protect against influenza 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 virologic basis for seasonal epidemics and the reason for the usual replacement of one or more influenza virus strains in each year's influenza vaccine. Therefore, influenza vaccines are standardised to contain the hemagglutinins of influenza virus strains (i.e., typically two type A and two type B), 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.

Clinical trials

Immunogenicity

Immunogenicity of Flublok Quadrivalent was evaluated in healthy adults of 18-49 years of age in a randomised, observer-blind, active controlled, multi-centre trial conducted during the 2014-2015 influenza season (PSC16).

In PSC16, subjects received Flublok Quadrivalent (N=998) or the comparator quadrivalent inactivated influenza vaccine (IIV4) (N=332) licensed in US and Australia. Immunogenicity was assessed before and 28 days after administration of a single dose of study vaccine.

HI geometric mean titres (GMTs) were determined for the two vaccine groups for each vaccine antigen. Immunogenicity was compared by calculating the difference in seroconversion rates (SCR) and the ratios of GMTs of Comparator to Flublok Quadrivalent. Seroconversion was defined as either a pre-vaccination HI titre of < 1:10 and a post-vaccination HI titre of ≥ 1:40, or a pre-vaccination HI titre of ≥ 1:10 and a minimum 4- fold rise in post vaccination HI titre, at Day 28.

PSC16 had eight co-primary endpoints: GMTs and Day 28 HI seroconversion rates for each of the four antigens contained in the study vaccines.

Success in meeting the GMTs endpoint was pre-defined as an upper bound (UB) of the two-sided 95% CI of $GMT_{Comparator} / GMT_{Flublok\ Quadrivalent} \leq 1.5$. Flublok Quadrivalent met the success criterion for GMTs for three of the four antigens. The very low titres in both vaccine groups yielded a ratio that did not meet the success criteria for the B/Victoria lineage antigen (Table 4).

Table 4 - Comparison of Day 28 Post-Vaccination GMT for Flublok Quadrivalent and Comparator in Adults 18-49 Years of Age, PSC16 (Immunogenicity Population)[1,2]

Antigen	Post-vaccination GMT Flublok Quadrivalent N=969	Post-vaccination GMT Comparator N=323	GMT Ratio Comparator/ Flublok Quadrivalent (95% CI)
A/H1N1	493	397	0.81 (0.71, 0.92)
A/H3N2	748	377	0.50 (0.44, 0.57)
B/Yamagata	156	134	0.86 (0.74, 0.99)
B/Victoria	43	64	1.49 (1.29, 1.71)

Abbreviations: CI, confidence interval; GMT, geometric mean titre.
[1] HI titres were assayed using egg-derived antigens.
[2] Comparator: Quadrivalent inactivated influenza vaccine, Fluarix Tetra, manufactured by GlaxoSmithKline.

Success in meeting the SCR endpoint was pre-defined as an upper bound (UB) of the two-sided 95% CI of SCR Comparator – SCR Flublok Quadrivalent ≤ 10%. Flublok Quadrivalent met the success criterion for SCRs for three of the four antigens (Table 5). The HI response to the B/Victoria lineage antigen in both vaccine groups was low and did not meet the success criterion.

Table 5 - Comparison of Day 28 Seroconversion Rates for Flublok Quadrivalent and Comparator in Adults 18-49 Years of Age, PSC16 (Immunogenicity Population)[1,2]

Antigen	SCR (%, 95% CI) Flublok Quadrivalent N=969	SCR (%, 95% CI) Comparator N=323	SCR Difference (%) Comparator – Flublok Quadrivalent [95% CI]
A/H1N1	66.7 (63.6, 69.6)	63.5 (58.0, 68.7)	-3.2 (-9.2, 2.8)
A/H3N2	72.1 (69.2, 74.9)	57.0 (51.4, 62.4)	-15.2 (-21.3, -9.1)
B/Yamagata	59.6 (56.5, 62.8)	60.4 (54.8, 65.7)	0.7 (-5.4, 6.9)
B/Victoria	40.6 (37.4, 43.7)	58.2 (52.6, 63.6)	17.6 (11.4, 23.9)

Abbreviations: CI, confidence interval; SCR, seroconversion rate
[1] HI titres were assayed using egg-derived antigens.
[2] Comparator: Quadrivalent inactivated influenza vaccine, Fluarix Tetra, manufactured by GlaxoSmithKline.

PSC16 in adults 18-49 years was conducted in parallel to PSC12 in adults of 50 years of age and older. These adults 18-49 years were vaccinated during the same influenza season (2014-2015 Northern Hemisphere influenza season) and received the same Flublok Quadrivalent formulation (same vaccine strain composition) as adults of 50 years of age and older in PSC12. The immune response induced by Flublok Quadrivalent was assessed by the same HI assay and performed by the same laboratory for both studies. The immunogenicity results in adults 18-49 years of age (PSC16) and adults 50 years of age and older (PSC12) are presented in Table 6.

The HA immune response induced by Flublok Quadrivalent in Adults 18-49 years is similar to that observed in adults ≥ 50 years.

Therefore, based on these immunogenicity data, the relative efficacy of Flublok Quadrivalent in adults 18-49 years is expected to be at least similar to the relative efficacy observed in adults ≥ 50 years. However relative efficacy was not studied in PSC16.

Table 6 - Summary of HI Antibody Response to Flublok Quadrivalent for Each Strain in Adults 18-49 years (PSC16) and Adults ≥ 50 years (PSC12) - Immunogenicity Analysis Set

	Adults 18-49 years N=969	Adults ≥ 50 years N=314
GMT pre-vaccination (95% CI)		
A/California/7/2009 (H1N1)	59 (54; 65)	44 (38; 51)
A/Texas/50/2012 (H3N2)	74 (68; 82)	87 (73; 103)
B/Massachusetts/02/2012 (Yamagata lineage)	26 (24; 29)	17 (15; 20)
B/Brisbane/60/2008 (Victoria lineage)	12 (11; 13)	14 (12; 15)
GMT **post-vaccination (95% CI)**		
A/California/7/2009 (H1N1)	493 (460; 527)	190 (164; 221)
A/Texas/50/2012 (H3N2)	748 (700; 800)	522(462; 589)
B/Massachusetts/02/2012 (Yamagata lineage)	156 (145; 168)	55 (48; 64)

	Adults 18-49 years N=969	Adults ≥ 50 years N=314
B/Brisbane/60/2008 (Victoria lineage)	43 (40; 46)	29 (26; 33)
SCR % (95% CI)		
A/California/7/2009 (H1N1)	66.7 (63.6; 69.6)	44.9 (39.3; 50.6)
A/Texas/50/2012 (H3N2)	72.1 (69.2; 74.9)	54.5 (48.8; 60.1)
B/Massachusetts/02/2012 (Yamagata lineage)	59.6 (56.5; 62.8)	38.9 (33.4; 44.5)
B/Brisbane/60/2008 (Victoria lineage)	40.6 (37.4; 43.7)	21.0 (16.6; 25.9)

N=number of subjects with available data for the considered endpoint
GMT: Geometric Mean Titre; CI: Confidence Interval; SCR: Seroconversion rate

Efficacy

PSC12 evaluated the efficacy of Flublok Quadrivalent in a randomised, observer-blind, active controlled, multi-centre trial conducted during the 2014-2015 influenza season in the Unites States in adults 50 years of age and older.

A total of 8963 healthy, medically stable adults were randomised in a 1:1 ratio to receive a single dose of Flublok Quadrivalent k (n=4474) or a Quadrivalent inactivated influenza vaccine licensed in the US and Australia (n=4489). A total of 5186 (60%) subjects were 50-64 years of age and 3486 (40%) were ≥ 65 years of age.

Real-time polymerase chain reaction (rtPCR)-confirmed influenza was assessed by active and passive surveillance for influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 6 months post- vaccination. ILI was defined as having at least one symptom (no specified duration) in each of two categories of respiratory and systemic symptoms. Respiratory symptoms included sore throat, cough, sputum production, wheezing and difficulty breathing. Systemic symptoms included fever > 37°C oral, chills, fatigue, headache and myalgia. A nasopharyngeal swab sample was collected for rtPCR testing from subjects with an episode of ILI. Reflex viral culture was performed on rtPCR-positive samples.

The primary efficacy endpoint of PSC12 was rtPCR-positive, protocol-defined ILI due to any strain of influenza. Antigenic and phylogenetic evaluations of the similarity ("matching") of clinical isolates to vaccine antigens were not performed. US epidemiological data for the 2014-2015 influenza season indicated that Influenza A (H3N2) viruses predominated and that most influenza A/H3N2 viruses were antigenically dissimilar while A/H1N1 and B viruses were antigenically similar to vaccine antigens. PCR assay distinguished influenza A H1, A H3 and B viruses. The relative vaccine efficacy (rVE) for rtPCR-positive protocol-defined ILI due to any influenza strain was +30% (95% CI: 10-47%) meeting the pre-specified non-inferiority criterion (defined as a lower bound of the two sided 95% CI >-20%) (Table 7). Flublok Quadrivalent also met the pre-specified exploratory criterion for superiority (defined as a lower bound of the two sided 95% CI >+9%). However, neither the non-inferiority nor superiority criterion was met when B strains were analysed separately to A strains due to too small number of B cases. The overall superior vaccine performance was driven by the

predominance of influenza A strains, and there are no clinical trials data with true efficacy endpoints from other seasons available for Flublok Quadrivalent.

Of the 4328 participants exposed to Flublok Quadrivalent in a phase 3 active-controlled study (PSC12), a total of 1759 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger participants, the number of patients aged 65 and over in this study was not sufficient to determine statistically whether this age group will respond differently from younger individuals.

Table 7 - Relative Vaccine Efficacy (rVE) of Flublok Quadrivalent versus Comparator against Laboratory-Confirmed Influenza, Regardless of Antigenic Similarity to Vaccine Antigens, Adults 50 Years of Age and Older, PSC12 (Efficacy Population)[1]

	Flublok Quadrivalent (N=4303)		Comparator (N=4301)		RR	rVE % (95% CI)
	n	Attack Rate % (n/N)	n	Attack Rate % (n/N)		
All rtPCR-positive Influenza[2]	96	2.2	138	3.2	0.70	30 (10, 47)
All rtPCR-positive Influenza A[3]	73	1.7	114	2.7	0.64	36 (14, 53)
All rtPCR-positive Influenza B[3]	23	0.5	24	0.6	0.96	4 (-72, 46)
All Culture-confirmed Protocol-defined ILI[3,4]	58	1.3	101	2.3	0.57	43 (21, 59)

Abbreviations: rtPCR=reverse transcriptase polymerase chain reaction;
Comparator: Quadrivalent inactivated influenza vaccine, Fluarix Tetra, manufactured by GlaxoSmithKline;
n=number of influenza cases;
N=number of subjects in treatment group;
RR=relative risk (Attack Rate Flublok Quadrivalent/Attack Rate Comparator); rVE = [(1-RR) x 100].
[1] Excluded subjects with protocol deviations that could adversely affect efficacy.
[2] Primary Analysis. All cases of rtPCR-confirmed influenza are included.
[3] *Post hoc* analyses. All cases of influenza A were A/H3N2. Cases of influenza B were not distinguished by lineage.
[4] Culture of rtPCR-positive samples was performed in MDCK cells.

Efficacy of trivalent recombinant influenza vaccine (RIV3)

The efficacy of trivalent recombinant influenza vaccine (RIV3) is relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions.

The efficacy of trivalent recombinant influenza vaccine in protecting against influenza illness was evaluated in a randomized, observer-blind, placebo-controlled multi-centre trial conducted in the US during the 2007-2008 influenza season in adults 18-49 years of age (PSC04).

PSC04 enrolled and vaccinated 4648 healthy adults randomised in a 1:1 ratio to receive a single dose of RIV3 (n=2344) or saline placebo (n=2304).

Culture-confirmed influenza was assessed by active and passive surveillance for ILI beginning 2 weeks post-vaccination until the end of the influenza season, approximately 7 months post- vaccination.

The primary efficacy endpoint of PSC04 was defined as an ILI with a positive culture for an influenza virus strain antigenically resembling a strain represented in RIV3. ILI is defined as fever of ≥ 37.8°C oral accompanied by cough, sore throat, or both, on the same or consecutive days. Attack rates and vaccine efficacy (VE), defined as the reduction in the influenza rate for RIV3 relative to placebo, were calculated for the total vaccinated cohort (n=4648).

The pre-defined success criterion for the primary efficacy analysis was that the lower bound of the 95% confidence interval (CI) of VE should be at least 40%.

Due to very small number of cultured confirmed influenza cases with matched strains, an exploratory analysis of VE of RIV3 against all strains, regardless of antigenic match, isolated from any subject with an ILI, not necessarily meeting ILI criteria was done, demonstrated an efficacy estimate of 44.8% (95% CI 24.4, 60.0). See Table 8 or VE by case definition.

Table 8 - Vaccine Efficacy Against Culture-Confirmed Influenza in Healthy Adults 18-49 Years of Age, PSC04*

Case definition	RIV3 (N=2344)		Saline Placebo (N=2304)		RIV3 Vaccine Efficacy[2] %	95% Confidence Interval
	Cases, n	Rate, %	Cases, n	Rate, %		
Positive culture with a strain represented in the vaccine						
CDC-ILI1, all matched strains[3]	1	0.04	4	0.2	75.4	(-148.0, 99.5)
Any ILI, all matched strains[4,5]	2	0.1	6	0.3	67.2	(-83.2, 96.8)
Positive culture with any strain, regardless of match to the vaccine						
CDC-ILI[1], all strains[6]	44	1.9	78	3.4	44.6	(18.8, 62.6)
Sub-Type A	26	1.1	56	2.4	54.4	(26.1, 72.5)
Type B	18	0.8	23	1.0	23.1	(-49.0, 60.9)
Any ILI, all strains[4]	64	2.7	114	4.9	44.8	(24.4, 60.0)
Sub-Type A	41	1.7	79	3.4	49.0	(24.7, 65.9)
Type B	23	1.0	36	1.6	37.2	(-8.9, 64.5)

* Vaccine efficacy (VE) = 1 minus the ratio of RIV3 /placebo infection rates (10).
[1] Centers for Disease Control and Prevention - defined influenza-like illness (CDC-ILI) defined as fever of ≥ (37.8°C oral accompanied by cough and/or sore throat, on the same day or on consecutive days.
[2] Determined under the assumption of Poisson event rates, according to Breslow and Day, 1987.
[3] Primary endpoint of trial.
[4] All culture-confirmed cases are considered, regardless of whether they qualified as CDC-ILI.
[5] Secondary endpoint of trial.
[6] Exploratory (prespecified) endpoint of trial.

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Flublok Quadrivalent has not been evaluated for genotoxic potential.

Carcinogenicity

Flublok Quadrivalent has not been evaluated for carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, polysorbate 20 and water for injections.

Each 0.5 mL dose of Flublok Quadrivalent may also contain residual amounts of baculovirus and *Spodoptera frugiperda* cell proteins (≤ 19 microgram), baculovirus and cellular DNA (≤ 10 ng), and octoxinol 9 (≤ 100 microgram).

Flublok Quadrivalent does not contain egg proteins, antibiotics, or preservatives.

There is no gelatin added in Flublok Quadrivalent as a stabiliser.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

12 months when stored at 2°C to 8°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Keep the syringe in the outer carton in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Pack of 1 or 10 single dose (0.5 mL) syringes.

The single-dose, pre-filled syringes contain no natural rubber latex.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Not applicable to vaccines.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Only Medicine

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Australia

Tel: 1800 818 806

9 DATE OF FIRST APPROVAL

13 May 2021

10 DATE OF REVISION

Attachment 1: AusPAR - Flublok Quadrivalent – influenza haemagglutinin recombinant – Sanofi-Aventis Australia Pty Ltd – PM-2019-04824-1-2 Final 8 July 2021 This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information