

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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 It may have been superseded.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/products/australian-register-therapeutic-goods-artg/product-information-one>>

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Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

AUSTRALIAN PRODUCT INFORMATION

Flucelvax® Quad (Influenza virus haemagglutinin)

For Season 2022

1 NAME OF THE MEDICINE

Quadrivalent influenza vaccine (surface antigen, inactivated, prepared in cell cultures), suspension for injection containing Influenza virus haemagglutinin as active ingredient.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a purified, inactivated, subunit influenza vaccine. Each 0.5 mL dose contains influenza virus surface antigens (haemagglutinin and neuraminidase)*, for the 2022 influenza season representative of the following types:

A/Wisconsin/588/2019 (H1N1)pdm09-like virus (A/Washington/19/2020)	15 micrograms HA**
A/Darwin/6/2021 (H3N2)-like virus (A/Darwin/11/2021)	15 micrograms HA**
B/Austria/1359417/2021-like virus (B/Singapore/WUH4618/2021)	15 micrograms HA**
B/Phuket/3073/2013-like virus (B/Singapore/INFTT-16-0610/2016)	15 micrograms HA**

per 0.5 ml dose

* propagated in Madin Darby Canine Kidney (MDCK) cells

** haemagglutinin

Flucelvax® Quad is prepared in MDCK cells, adapted to grow freely in suspension in culture medium. The virus is inactivated with β -propiolactone, disrupted by the detergent cetyltrimethylammonium bromide and purified through several process steps. Therefore Flucelvax® Quad may contain traces of propiolactone, cetyltrimethylammonium bromide and polysorbate 80 (refer to **Section 4.3 CONTRAINDICATIONS**). Eggs are not used in the manufacturing process, therefore, Flucelvax® Quad does not contain egg proteins. For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

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Seqirus

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AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

The vaccine complies with the World Health Organization (WHO) recommendation and Australian Influenza Vaccine Committee (AIVC) for the 2022 Southern Hemisphere Influenza season. The strains chosen for vaccine manufacture are endorsed by the AIVC as being antigenically equivalent to the reference virus.

3 PHARMACEUTICAL FORM

Flucelvax® Quad is a clear to slightly opalescent suspension for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the prevention of influenza caused by Influenza Virus, Types A and B contained in the vaccine. The vaccine is indicated for use in adults and children 2 years of age and older.

For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Age Group	Dose	Schedule
Paediatrics		
2 to < 9 years	One or two ^a 0.5 mL doses	If 2 doses, administer at least 4 weeks apart
9 to < 18 years	One 0.5 mL dose	Not applicable
Adults		
≥ 18 years	One 0.5 mL dose	Not applicable

^a Children less than 9 years of age who have not been previously vaccinated against influenza, should receive a second dose.

Method of Administration

Flucelvax® Quad should be administered by intramuscular injection only. **The vaccine must not be injected intravascularly, subcutaneously or intradermally.**

The preferred site for intramuscular injection is the deltoid muscle of the upper arm.

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Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

Flucelvax® Quad must not be mixed with other vaccines in the same syringe.

Shake before use. After shaking, the vaccine should appear as a clear to slightly opalescent suspension.

Visually inspect the contents of each pre-filled syringe for particulate matter and/or variation in appearance prior to administration. If either condition is observed, do not administer the vaccine.

Flucelvax® Quad does not contain preservative or antibiotics. Each pre-filled syringe is for use in one patient on one occasion only. Discard any residue.

4.3 CONTRAINDICATIONS

The vaccine is contraindicated in individuals with known severe allergic reactions (e.g. anaphylaxis) to:

- any component of the vaccine (refer to **Section 2. QUALITATIVE AND QUANTITATIVE COMPOSITION & Section 6.1 LIST OF EXCIPIENTS**) or
- a previous dose of any influenza vaccine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Immunisation should be postponed in patients with febrile illness or acute infection.

In immunocompromised patients the antibody response may be lower.

A protective immune response may not be elicited in all vaccine recipients.

If Guillain-Barré syndrome has occurred within 6 weeks of previous influenza vaccination, the decision to give Flucelvax® Quad vaccine should be based on careful consideration of the potential benefits and risks.

The syringe and all associated syringe components for Flucelvax® Quad AUST R 319093 pre-filled syringe needle-free do not contain natural rubber latex.

Flucelvax® Quad AUST R 341450 pre-filled syringe with attached needle cannot be considered to be latex-free as the sheath covering the needle may contain natural rubber

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

Seqirus

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AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

latex. See **Section 6.5 NATURE AND CONTENTS OF CONTAINER** for further information.

Use in the elderly

Of the total number of subjects who received one dose of Flucelvax® Quad in clinical studies and included in the safety population (2493), 26.47% (660) were 65 years of age and older and 7.7% (194) were 75 years of age or older.

Antibody responses to Flucelvax® Quad were lower in the geriatric (adults 65 years and older) population than in younger subjects.

Paediatric use

Flucelvax® Quad is not indicated in children less than 2 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There are no data available on co-administration of Flucelvax® Quad with other vaccines. Based on clinical experience with cell-based trivalent influenza vaccine (TIVc), Flucelvax® Quad can be given at the same time as other vaccines. If Flucelvax® Quad is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered to separate limbs. It should be noted that adverse reactions may be intensified.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no reproductive and developmental toxicity studies with Flucelvax® Quad.

A reproductive and developmental toxicity study in which female rabbits were administered cell-based TIVc, 45 mcg HA/dose, 3 times prior to mating and twice during

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Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

gestation, showed no adverse effects on the mating performance or female fertility. Male fertility has not been assessed in animals.

Use in pregnancy – Pregnancy Category B1

The safety of Flucelvax® Quad in pregnancy has not been assessed in clinical trials.

There are no reproductive and developmental toxicity studies with Flucelvax® Quad. Reproductive and developmental toxicity data from TIVc do not predict an increased risk of developmental abnormalities. In a reproductive and developmental toxicity study with TIVc, the effect of cell culture-derived antigens on embryo-foetal development was evaluated in pregnant rabbits. Anti-influenza antibodies were detected in treated rabbits and their offspring. No adverse effects on pregnancy or embryo-foetal development were observed.

Healthcare providers should assess the benefit and potential risks of administering the vaccine to pregnant women taking into consideration official recommendations. Refer to the current recommendations in the Australian Immunisation Handbook (Australia) or relevant national immunisation recommendations (New Zealand) for use in pregnancy. In general, data from influenza vaccinations in pregnant women do not indicate adverse foetal and maternal outcomes attributable to the vaccine.

Use in lactation

Flucelvax® Quad has not been evaluated in nursing mothers. No data are available on the use of Flucelvax® Quad during lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

Because clinical trials are conducted under very specific conditions, the adverse event rates observed in the clinical trials may not reflect the rates observed in the clinical

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

studies of another vaccine and may not reflect the rates of events observed in clinical practice.

Adults 18 years of age and older

The safety of Flucelvax® Quad in adults 18 years and older was evaluated in a randomised, double-blind, controlled study conducted in the US (NCT01992094, see <http://clinicaltrials.gov>) (Study V130_01). The safety population included a total of 2680 adults 18 years of age and older; 1340 adults 18 to < 65 years of age and 1340 adults 65 years of age and older. In this study, subjects received Flucelvax® Quad or one of the two formulations of comparator trivalent influenza vaccine (TIVc) (Flucelvax® Quad N=1334, TIV1c N=677 or TIV2c N= 669).

In this study, solicited local injection site and systemic adverse events were collected from subjects who completed a symptom diary card for 7 days following vaccination.

Unsolicited adverse events were collected for 21 days after vaccination. Serious adverse events (SAEs) were collected throughout the study duration (until 6 months after vaccination). All adverse events are presented regardless of any treatment causality assigned by study investigators.

Solicited adverse events in the safety population of adults 18 to < 65 years of age and 65 years of age and older are shown in Table 1.

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

Table 1: Incidence of Solicited Adverse Events¹ in the Adult and Elderly Safety Population² Reported Within 7 Days of Vaccination (Study V130_01)

	Percentages of Subjects with Any (Severe) Solicited Events ³					
	18 to < 65 years of age			≥ 65 years of age		
	Flucelvax® Quad N=663	Trivalent Influenza Vaccine		Flucelvax® Quad N=656	Trivalent Influenza Vaccine	
TIV1c N=330		TIV2c N=327	TIV1c N=340		TIV2c N=336	
Local Adverse Events						
Injection site pain	45 (< 1)	37 (< 1)	41 (0)	22 (0)	19 (0)	19 (0)
Injection site erythema	13 (0)	13 (0)	10 (0)	12 (0)	11 (0)	10 (0)
Injection site induration	12 (0)	10 (< 1)	10 (0)	9 (0)	7 (0)	8 (0)
Injection site ecchymosis	4 (0)	3 (< 1)	5 (0)	5 (0)	4 (0)	5 (0)
Systemic Adverse Events						
Headache	19 (< 1)	19 (< 1)	19 (< 1)	9 (< 1)	9 (< 1)	8 (< 1)
Fatigue	18 (< 1)	22 (< 1)	16 (2)	9 (< 1)	11 (< 1)	9 (< 1)
Myalgia	15 (< 1)	15 (< 1)	15 (1)	8 (< 1)	9 (< 1)	8 (< 1)
Nausea	10 (< 1)	7 (< 1)	9 (1)	4 (< 1)	4 (0)	4 (< 1)
Arthralgia	8 (< 1)	8 (0)	10 (< 1)	6 (< 1)	5 (< 1)	7 (< 1)
Loss of appetite	8 (< 1)	9 (< 1)	8 (< 1)	4 (< 1)	5 (0)	4 (< 1)
Diarrhoea	7 (< 1)	8 (0)	8 (< 1)	4 (< 1)	5 (< 1)	5 (< 1)
Chills	6 (< 1)	6 (< 1)	6 (0)	4 (< 1)	4 (< 1)	5 (< 1)
Vomiting	3 (0)	2 (< 1)	< 1(0)	< 1 (< 1)	< 1 (0)	< 1(0)
Fever: ≥ 38.0°C (≥ 40.0°C)	< 1 (0)	< 1 (0)	< 1 (0)	< 1 (0)	< 1 (0)	< 1 (0)

¹ All solicited local and systemic adverse events reported within 7 days of vaccination are included.

² Safety population: all subjects in the exposed population who provided post-vaccination safety data.

³ Percentage of severe adverse events are presented in parenthesis.

Definition of severe events: Erythema, Induration and Ecchymosis: Severe= > 100 mm; Pain and systemic adverse events: Severe = unable to perform daily activity.

The most commonly reported unsolicited adverse events (reported by ≥ 3% of subjects administered Flucelvax® Quad) in adults 18 to < 65 years, and with a similar frequency to the trivalent influenza vaccine comparators, were upper respiratory tract infection (3.5%; TIV1c 2.7%; TIV2c 4.6%) and nasopharyngitis (3.0%; TIV1c 2.4%; TIV2c 2.7%). In adults ≥ 65 years, the most commonly reported unsolicited adverse events (reported by ≥

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Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

3% of subjects administered Flucelvax® Quad) were nasopharyngitis (4.4%; TIV1c 4.1%; TIV2c 3.3%) and upper respiratory tract infection (3.3%; TIV1c 3.5%; TIV2c 3.3%).

There were no serious adverse events assessed as being related to study vaccines.

Children and Adolescents 2 to less than 18 years of age

Flucelvax® Quad is indicated for use in adults and children 2 years of age and older (See **Section 4.1 THERAPEUTIC INDICATIONS**).

The safety of Flucelvax® Quad in children 2 to less than 18 years of age has been evaluated in studies V130_03 and V130_12.

Study V130_03 was a randomised, double-blind, controlled study in children 4 to less than 18 years of age conducted in the US (NCT01992107, see <http://clinicaltrials.gov>). The safety population included a total of 2332 children 4 to less than 18 years of age; 1161 children 4 to less than 9 years of age and 1171 children 9 to less than 18 years of age. In this study, subjects received Flucelvax® Quad or one of the two formulations of comparator trivalent influenza vaccine (Flucelvax® Quad N=1159, TIV1c N=593 or TIV2c N= 580).

Study V130_12 was a multinational, randomised, observer-blind study in children 2 to less than 18 years of age (NCT03165617, see <http://clinicaltrials.gov>). The safety population included a total of 4509 children 2 to less than 18 years of age who received Flucelvax® Quad (N=2255) or a non-influenza comparator vaccine (N=2254).

In both studies, children 9 to less than 18 years of age received a single dose of Flucelvax® Quad or comparator vaccine. Children less than 9 years of age received one or two doses (separated by 4 weeks) of Flucelvax® Quad or comparator vaccine depending on the subject's prior influenza vaccination history. In Study V130_12, children in the 2-dose comparator group received a non-influenza comparator vaccine as the first dose and saline placebo as the second dose.

In both paediatric studies, solicited local injection site and systemic adverse events were collected from subjects who completed a symptom diary card for 7 days following vaccination. Unsolicited adverse events were collected for 21 days after each vaccination. Serious adverse events (SAEs) were collected throughout the study duration (until 6 months after last vaccination or end of the influenza season, whichever was longer). All

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

adverse events are presented regardless of any treatment causality assigned by study investigators.

Solicited adverse events in the safety population of children 4 years to less than 18 years of age in Study V130_03 are shown in Table 2 (4 to less than 6 years of age) and Table 3 (6 to less than 18 years).

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

Table 2: Incidence of Solicited Adverse Events¹ in the Safety Population² (4 to less than 6 years of age) Reported After Any Dose Within 7 Days After Vaccination (Study V130_03)

	Children 4 to < 6 years		
	Percentages of Subjects with Any (Severe) Solicited Events ³		
	Flucelvax® Quad N=182	Trivalent Influenza Vaccine	
TIV1c N=91		TIV2c N=94	
Local Adverse Events			
Injection site tenderness	54 (2)	51 (1)	48 (2)
Injection site erythema	23 (2)	24 (1)	20 (0)
Injection site induration	15 (1)	22 (2)	14 (0)
Injection site ecchymosis	11 (1)	12 (0)	9 (0)
Systemic Adverse Events			
Sleepiness	21 (1)	13 (3)	14 (1)
Irritability	19 (2)	14 (2)	15 (1)
Change in eating habits	14 (1)	8 (4)	7 (0)
Chills	7 (1)	3 (0)	2 (0)
Vomiting	5 (0)	2 (0)	2 (0)
Diarrhoea	5 (0)	3 (0)	4 (0)
Fever: ≥ 38.0°C (≥ 40.0°C)	5 (0)	5 (0)	3 (0)

¹ All solicited local and systemic adverse events reported within 7 days of vaccination are included

² Safety population: all subjects in the exposed population who provided post-vaccination safety data

³ Percentage of subjects with severe adverse reactions are presented in parenthesis.

Definition of severe events: Erythema, Induration and Ecchymosis: Severe = >50 mm; Pain and systemic adverse events: Severe = unable to perform daily activity.

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

Table 3: Incidence of Solicited Adverse Events¹ in the Safety Population² (Children 6 to less than 18 years of age) Reported After Any Dose Within 7 Days of Vaccination (Study V130_03)

	Percentage of Subjects with Any (Severe) Solicited Events					
	Children 6 to ≤ 9 years			Children 9 to < 18 years ³		
	Flucelvax® Quad N=373- 374 ⁵	Trivalent Influenza Vaccine		Flucelvax® Quad N=579	Trivalent Influenza Vaccine	
TIV1c N=185		TIV2c N=187	TIV1c N=294		TIV2c N=281- 282 ⁴	
Local Adverse Events						
Injection site pain	61 (1)	69 (1)	68 (3)	58 (1)	51 (< 1)	50 (0)
Injection site erythema	25 (< 1)	26 (1)	25 (0)	19 (< 1)	17(0)	15 (< 1)
Injection site induration	19 (0)	22 (1)	16 (0)	15 (0)	15 (0)	13 (< 1)
Injection site ecchymosis	11 (0)	11 (0)	11 (0)	4 (0)	5 (0)	5 (0)
Systemic Adverse Events						
Headache	16 (1)	16 (0)	14 (1)	22 (1)	23 (2)	18 (1)
Fatigue	16 (2)	18 (1)	19 (0)	18 (< 1)	16 (1)	16 (< 1)
Myalgia	15 (1)	18 (1)	13 (0)	16 (< 1)	17 (< 1)	15 (< 1)
Loss of appetite	10 (< 1)	9 (0)	10 (1)	9 (0)	9 (< 1)	9 (0)
Nausea	9 (1)	7 (0)	7 (1)	9 (< 1)	8 (1)	7 (1)
Fever: ≥ 38.0°C (≥ 40.0°C)	6 (0)	4 (0)	3 (0)	1 (< 1)	3 (0)	1 (0)
Arthralgia	5 (0)	7 (1)	5 (0)	6 (0)	6 (0)	8 (< 1)
Vomiting	5 (1)	4 (0)	4 (0)	2 (0)	1 (0)	2 (0)
Diarrhoea	4 (< 1)	8 (1)	5 (0)	4 (0)	4 (0)	3 (< 1)
Chills	4 (1)	5 (1)	4 (0)	7 (0)	6 (1)	4 (1)

¹ All solicited local and systemic adverse events reported within 7 days of vaccination are included.

² Safety population: all subjects in the exposed population who provided post-vaccination safety data.

³ Percentage of severe adverse events are presented in parenthesis.

⁴ 281 subjects provided data for Injection site ecchymosis.

⁵ 373 subjects provided data for Injection site pain.

Definition of severe events: Erythema, Induration and Ecchymosis: Severe= > 100 mm; Pain and systemic adverse events: Severe = unable to perform daily activity.

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

Seqirus

Flucelvax[®] Quad

AusPAR Attachment 1: Product Information for Flucelvax Quad AUST R 319093 & AUST R 341450

The incidence of local and systemic solicited adverse events in children 2 to less than 18 years of age who received Flucelvax[®] Quad or the non-influenza comparator vaccine in Study V130_12 are presented in Table 4.

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

Table 4: Incidence of Solicited Adverse Events¹ in the Safety Population² (Children 2 to less than 18 years of age) Reported After Any Dose Within 7 Days of Vaccination (Study V130_12)

	Children 2 to < 6 years		Children 6 to < 9 years		Children 9 to < 18 years	
	Percentages of Subjects with Any (Severe) Solicited Events ³					
	FLUCELVAX® QUAD N=580	Comparator ⁴ N=565	FLUCELVAX® QUAD N=564	Comparator ⁴ N=578	FLUCELVAX® QUAD N=1111	Comparator ⁴ N=1111
Local Adverse Events						
Injection site pain/Tenderness	28.7 (1.0)	25.4 (1.4)	27.9 (1.2)	20.3 (1.6)	21.7 (0.5)	18.3 (1.0)
Injection site erythema	20.2 (0.3)	24.5 (1.8)	22.4 (0.4)	22.8 (0.3)	17.2 (0)	18.7 (0.5)
Injection site induration	13.5 (0.2)	13.9 (0.7)	16.3 (0.2)	16.5 (0.2)	10.5 (0.1)	11 (0.2)
Injection site ecchymosis	9.2 (0)	6.9 (0)	10.9 (0)	8.0 (0.2)	5.0 (0)	5.2 (0)
Systemic Adverse Events						
Sleepiness	14.9 (0.9)	17.6 (1.8)	-	-	-	-
Irritability	13.8 (0.2)	10.8 (0.5)	-	-	-	-
Fatigue	-	-	13.8 (0.9)	12.7 (0.7)	17 (1.1)	18.2 (1.2)
Headache	-	-	13.8 (0.4)	11.8 (0.5)	18.1 (1.4)	17.4 (0.6)
Loss of appetite	-	-	10.6 (0.5)	8.0 (0.5)	8.5 (0.5)	7.5 (0.5)
Change of eating habits	9.9 (1.0)	10.1 (0.7)	-	-	-	-
Fever: ≥ 38.0°C (≥ 40.0°C)	8.8 (0.5)	7.7 (0.4)	6.4 (0.5)	4.5 (0)	2.8 (0.1)	3.0 (0.3)
Diarrhoea	8.3 (0.5)	8.5 (0.9)	4.6 (0.4)	5.2 (0.3)	7.4 (0.5)	8.1 (0.3)
Arthralgia	-	-	5.2 (0.4)	6.2 (0.3)	7.1 (0.4)	8.4 (0.5)
Nausea	-	-	5.2 (0)	4.5 (0.7)	6.0 (0.2)	6.1 (0.6)
Vomiting	4.8 (0.5)	4.1 (0.7)	5.0 (0.7)	4.2 (0.5)	3.0 (0.3)	3.0 (0.4)
Chills/Shivering	4.7 (0.7)	3.9 (0.4)	6.1 (0.5)	3.8 (0.3)	7.6 (0.4)	7.6 (0.3)
Myalgia	-	-	2.9 (0.2)	4.0 (0.3)	6.1 (0.5)	5.5 (0.5)

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Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

¹ All solicited local and systemic adverse events reported from 6 hours post-vaccination to 7 days after vaccination are included.

² Solicited Safety Population: subjects who were vaccinated and provided any solicited local or systemic adverse event safety data, from 6 hours through 7 days after vaccination

³ Percentage of subjects with severe adverse events are presented in parenthesis

⁴ Meningococcal (Group ACWY) Conjugate Vaccine

Definitions of severe adverse events (subjects 2 to < 6 years of age): Erythema, Induration and Ecchymosis: > 50 mm; Tenderness and Shivering: prevents daily activity; Change of eating habits: Missed more than 2 feeds/meals; Sleepiness: Sleeps most of the time and is hard to arouse him/her; Vomiting: 6 or more times in 24 hours or requires intravenous hydration; Diarrhea: 6 or more loose stools in 24 hours or requires intravenous hydration; Irritability: unable to console.

Definitions of severe adverse events (subjects 6 to < 18 years of age): Erythema, Induration and Ecchymosis: > 100 mm; Loss of appetite: Not eating at all; Vomiting: 6 or more times in 24 hours or requires intravenous hydration; Diarrhea: 6 or more loose stools in 24 hours or requires intravenous hydration; Pain, Nausea, Fatigue, Myalgia, Arthralgia, Headache and Chills: prevents daily activity.

“-“ denotes adverse events was not solicited in this age group.

In Study V130_03, the most commonly reported unsolicited adverse event (reported by ≥ 3% of subjects administered Flucelvax® Quad) in children 4 to less than 18 years of age (regardless of treatment causality), was cough (3.0%), with a similar frequency reported for the trivalent influenza vaccine comparators (TIV1c 4.0%; TIV2c 3.0%).

In Study V130_12, the most commonly reported unsolicited adverse events (reported by ≥ 3% of subjects administered Flucelvax® Quad) in children 2 to less than 18 years of age (regardless of causality), and with a similar frequency to the non-influenza comparator vaccine were influenza-like illness (9.4%; Comparator 8.9%), upper respiratory tract infection (4.5%; Comparator 4.1%), cough (3.4%; Comparator 3.2%) and rhinitis (3.4%; Comparator 3.8%).

In children 2 to less than 18 years of age, there were no serious adverse events assessed as being related to the study vaccines in either Study V130_03 or Study V130_12.

Post-marketing adverse reactions

The following events have been identified during post-approval use of Flucelvax® Quad:

General disorders and administration site conditions

Extensive swelling of injected limb.

Immune system disorders

Allergic or immediate hypersensitivity reactions, including anaphylactic shock.

Nervous system disorders

Paraesthesia.

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Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

Skin and subcutaneous tissue disorders

Generalised skin reactions including pruritus, urticaria, or non-specific rash.

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 (Australia) or <https://nzphvc.otago.ac.nz/consumer-reporting/> (New Zealand).

4.9 OVERDOSE

There is no experience of overdose with Flucelvax® Quad.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or the New Zealand Poisons Centre on 0800 POISON or 0800 767 4766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance and analysis of influenza virus isolates permits identification of yearly antigenic variants. Specific levels of haemagglutination inhibition (HI) antibody titres post-vaccination with inactivated influenza vaccine have not been correlated with protection from influenza virus. In some human studies, antibody titres of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects. Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype.

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

Clinical trials

Immunogenicity of Flucelvax® Quad

Adult Studies

Immunogenicity of Flucelvax® Quad was evaluated in adults 18 years of age and older in a randomised, double-blind, controlled study conducted in the US (NCT01992094, see <http://clinicaltrials.gov>) (Study V130_01). In this study, subjects received Flucelvax® Quad or one of the two formulations of comparator trivalent influenza vaccine (Flucelvax® Quad N= 1334, TIV1c N= 677 or TIV2c N= 669). In the per protocol set, the mean age of subjects who received Flucelvax® Quad was 57.5 years; 55.1% of subjects were female and 76.1% of subjects were Caucasian, 13% were Black and 9% were Hispanic. The immune response to each of the vaccine antigens was assessed, 21 days after vaccination.

The immune response of Flucelvax® Quad was non-inferior to TIVc for all 4 influenza strains (GMT ratio and differences in vaccine group seroconversion rates). The antibody response to influenza B strains contained in Flucelvax® Quad was superior to the antibody response after vaccination with TIVc containing an influenza B strain from the alternate lineage. There was no evidence that the addition of the second influenza B strain resulted in immune interference to other strains included in the vaccine.

Non-inferiority criteria were also met for all 4 influenza strains in age subgroup analyses for subjects 18 to less than 65 years of age and 65 years of age and above.

The non-inferiority data observed are summarised in Table 5.

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

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Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

Table 5: Non-inferiority of Flucelvax® Quad relative to TIVc in adults 18 years of age and above – Per protocol analysis set (Study V130_01)

		Flucelvax® Quad N = 1250	TIV1c/TIV2c^a N = 635/N =639	Vaccine group Ratio (95% CI)	Vaccine Group Difference (95% CI)
A/H1N1	GMT at Day 1 (95% CI)	60.7 (56.0-65.9)	59.6 (53.0-67.0)	-	-
	GMT at Day 22 (95% CI)	302.8 (281.8-325.5)	298.9 (270.3-330.5)	1.0 (0.9- 1.1)	-
	Seroconversion Rate ^b (95% CI)	49.2% (46.4-52.0)	48.7% (44.7-52.6)	-	-0.5% (-5.3- 4.2)
	Seroprotection Rate ^c (95% CI)	96.3% (95.1-97.3)	96.7% (95.0-97.9)	-	-
A/H3N2	GMT at Day 1 (95% CI)	122.5 (112.7-133.1)	128.1 (113.6-144.6)	-	-
	GMT at Day 22 (95% CI)	372.3 (349.2-396.9)	378.4 (345.1-414.8)	1.0 (0.9- 1.1)	-
	Seroconversion Rate ^b (95% CI)	38.3% (35.6-41.1)	35.6% (31.9-39.5)	-	-2.7% (-7.2- 1.9)
	Seroprotection Rate ^c (95% CI)	98.4% (97.5-99.0)	98.6% (97.3-99.3)	-	-
B1	GMT at Day 1 (95% CI)	45.3 (42.6-48.1)	43.8 (40.2-47.7)	-	-
	GMT at Day 22 (95% CI)	133.2 (125.3-141.7)	115.6 (106.4-125.6)	0.9 (0.8- 1.0)	-
	Seroconversion Rate ^b (95% CI)	36.6% (33.9-39.3)	34.8% (31.1-38.7)	-	-1.8% (-6.2- 2.8)
	Seroprotection Rate ^c (95% CI)	93.6% (92.1-94.9)	91.8% (89.4-93.8)	-	-
B2	GMT at Day 1 (95% CI)	59.2 (56.0-62.7)	58.0 (53.4-63.0)	-	-
	GMT at Day 22 (95% CI)	177.2 (167.6-187.5)	164.0 (151.4-177.7)	0.9 (0.9- 1.0)	-
	Seroconversion Rate ^b (95% CI)	39.8% (37.0-42.5)	35.4% (31.7-39.2)	-	-4.4% (-8.9- 0.2)
	Seroprotection Rate ^c (95% CI)	97.7% (96.7-98.4)	96.9% (95.2-98.1)	-	-

Abbreviations: GMT = geometric mean titer. CI = confidence interval.

^a The comparator vaccine for non-inferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 it is TIV2c.

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Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

^b Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and postvaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a minimum 4-fold increase in post-vaccination HI antibody titer

^c Seroprotection rate = percentage of subjects with HI titre ≥1:40. Seroprotection was not used for non-inferiority evaluation.

Bold = Non-inferiority criterion met

Paediatric Studies

Immunogenicity of Flucelvax® Quad was evaluated in children 4 to less than 18 years of age in a randomised, double-blind, controlled study conducted in the US (NCT01992107, see <http://clinicaltrials.gov>) (Study V130_03). In this study, subjects received Flucelvax® Quad or one of the two formulations of comparator trivalent influenza vaccine (Flucelvax® Quad N= 1159, TIV1c N= 593 or TIV2c N= 580). In the per protocol set, the mean age of subjects who received Flucelvax® Quad was 9.8 years; 47% of subjects were female and 54% of subjects were Caucasian, 22% were Black and 19% were Hispanic. The immune response to each of the vaccine antigens was assessed, 21 days after vaccination.

The immune response of Flucelvax® Quad was non-inferior to TIVc for all 4 influenza strains (GMT ratio and differences in vaccine group seroconversion rates). The antibody response to influenza B strains contained in Flucelvax® Quad was superior to the antibody response after vaccination with TIVc containing an influenza B strain from the alternate lineage. There was no evidence that the addition of the second influenza B strain resulted in immune interference to other strains included in the vaccine.

The non-inferiority data observed are summarised in Table 6 in children and adolescents aged 4 to less than 18 years.

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

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Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

Table 6: Non-inferiority^a of Flucelvax® Quad relative to TIVc in children and adolescents 4 to less than 18 years of age – Per-protocol analysis set (Study V130_03)

		Flucelvax® Quad	TIV1c/TIV2c ^b	Vaccine Group Ratio (95% CI)	Vaccine Group Difference (95% CI)
A/H1N1		N = 1014	N = 510		
	GMT at Day 1 (95% CI)	96 (86-107)	100 (86-116)	-	-
	GMT at Day 22 or 50 (95% CI)	1090 (1027-1157)	1125 (1034-1224)	1.03 (0.93-1.14)	-
	Seroconversion Rate ^c (95% CI)	72% (69-75)	75% (70-78)	-	2% (-2.5- 6.9)
	Seroprotection Rate ^d (95% CI)	99% (98%-100%)	100% (99%-100%)	-	-
A/H3N2		N = 1013	N = 510		
	GMT at Day 1 (95% CI)	206 (188-225)	196 (172-222)	-	-
	GMT at Day 22 or 50 (95% CI)	738 (703-774)	776 (725-831)	1.05 (0.97-1.14)	-
	Seroconversion Rate ^c (95% CI)	47% (44-50)	51% (46-55)	-	4% (-1.4- 9.2)
	Seroprotection Rate ^d (95% CI)	100% (99%-100%)	100% (99%-100%)		
B1		N = 1013	N = 510		
	GMT at Day 1 (95% CI)	26 (24-28)	23 (21-26)	-	-
	GMT at Day 22 or 50 (95% CI)	155 (146-165)	154 (141-168)	0.99 (0.89-1.1)	-
	Seroconversion Rate ^c (95% CI)	66% (63-69)	66% (62-70)	-	0% (-5.5- 4.5)
	Seroprotection Rate ^d (95% CI)	93% (91%-94%)	93% (90%-95%)	-	-
B2		N = 1009	N = 501		
	GMT at Day 1 (95% CI)	23 (21-25)	23 (21-26)	-	-
	GMT at Day 22 or 50 (95% CI)	185 (171-200)	185 (166-207)	1 (0.87-1.14)	-
	Seroconversion Rate ^c (95% CI)	73% (70-76)	71% (67-75)	-	-2% (-6.5- 3.2)
	Seroprotection Rate ^d (95% CI)	92% (90%-93%)	90% (87%-93%)	-	-

Abbreviations: GMT = geometric mean titer. CI = confidence interval.

^a Analyses are performed on data for day 22 for previously vaccinated subjects and day 50 for not previously vaccinated subjects

^b The comparator vaccine for non-inferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for the B2 strain the comparator vaccine is TIV2c

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Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

^c Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and post-vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a minimum 4-fold increase in post-vaccination HI antibody titer

^d Seroprotection rate = percentage of subjects with HI titre ≥ 1:40. Seroprotection was not used for non-inferiority evaluation.

Bold = Non-inferiority criterion met

Efficacy of Flucelvax® Quad in Children (2 to less than 18 years of age)

Efficacy of Flucelvax® Quad was evaluated in children 2 to less than 18 years of age in Study V130_12 (NCT03165617, see <http://clinicaltrials.gov>). This was a multinational, randomised, non-influenza vaccine comparator-controlled efficacy study conducted in 8 countries. The study enrolled 4513 subjects who received either Flucelvax® Quad (N=2258) or a non-influenza vaccine comparator, Menveo® Meningococcal ACWY Conjugate Vaccine (N=2255). The full analysis set (FAS) for efficacy consisted of 4509 subjects.

Children 2 to less than 9 years of age received one or two doses (separated by 4 weeks) of Flucelvax® Quad or comparator vaccine depending on the subject's prior influenza vaccination history. Children 9 to less than 18 years of age received a single dose of Flucelvax® Quad or comparator vaccine. Children in the 2-dose comparator group received non-influenza comparator vaccine as the first dose and saline placebo as the second dose. Among all enrolled subjects, the mean age was 8.8 years, 49% were female, 51% were 2 to less than 9 years of age, 50% were Caucasian and 49% were Asian. There were no notable differences in the distribution of demographic and baseline characteristics between the two treatment groups.

Flucelvax® Quad efficacy was assessed by the number of confirmed influenza illness caused by any influenza Type A or B strain in the vaccine groups. Influenza cases were identified by active and passive surveillance of influenza-like illness (ILI) and confirmed by cell culture or real-time polymerase chain reaction (RT-PCR). ILI was defined as a fever (oral temperature ≥ 100.0°F / 37.8°C) along with any of the following: cough, sore throat, nasal congestion, or rhinorrhea. Overall vaccine efficacy was determined for influenza caused by any Type A or B strain (Table 7).

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Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

Table 7: Number of Subjects with First-Occurrence RT-PCR Confirmed or Culture Confirmed Influenza and Absolute Vaccine Efficacy (95% CI), in Subjects 2 to less than 18 Years of Age– FAS Efficacy¹ (Study V130_12)

	Number of subjects per protocol ¹	Number of cases of influenza	Attack Rate (%)	Vaccine Efficacy (VE) ²	
				%	95% CI of VE ³
All RT-PCR or Culture Confirmed Influenza					
Flucelvax® Quad	2257	175	7.8	54.6	45.7, 62.1
Non-Influenza Comparator ⁴	2252	364	16.2	-	-
All Culture Confirmed Influenza					
Flucelvax® Quad	2257	115	5.1	60.8	51.3, 68.5
Non-Influenza Comparator ⁴	2252	279	12.4	-	-
All Antigenically Matched Culture-Confirmed Influenza					
Flucelvax® Quad	2257	90	4.0	63.6	53.6, 71.5
Non-Influenza Comparator ⁴	2252	236	10.5	-	-

¹ Number of subjects in the Full-Analysis Set (FAS)– Efficacy, which included all subjects randomised, received a study vaccination and provided efficacy data.

² Efficacy against influenza was evaluated over three influenza seasons, SH 2017, NH 2017-18 and NH 2018-19

³ Flucelvax® Quad met the pre-defined success criterion defined as the lower limit of the two-sided 95% CI of absolute vaccine efficacy greater than 20%

⁴ Meningococcal (Group ACWY) Conjugate Vaccine. Children assigned to 2 doses received saline placebo as second dose

Efficacy of Trivalent Influenza Vaccine

The efficacy experience with trivalent influenza vaccine (TIVc) is relevant to Flucelvax® Quad because both vaccines are manufactured using the same process and have overlapping compositions.

Efficacy against Culture-Confirmed Influenza

A multinational (US, Finland and Poland), randomised, observer-blinded, placebo-controlled trial was performed to assess clinical efficacy and safety of TIVc during the

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Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

2007-2008 influenza season in adults aged 18 to 49 years (NCT00630331, see <http://clinicaltrials.gov>) (Study V58P13). A total of 11,404 subjects were enrolled to receive TIVc (N=3828), Agrippal (N=3676) or placebo (N=3900) in a 1:1:1 ratio. Among the overall study population enrolled, the mean age was 33 years, 55% were female, 84% were Caucasian, 7% were Black, 7% were Hispanic, and 2% were of other ethnic origin.

TIVc efficacy was defined as the prevention of culture-confirmed symptomatic influenza illness caused by viruses antigenically matched to those in the vaccine compared to placebo. Influenza cases were identified by active and passive surveillance of influenza-like illness (ILI). ILI was defined according to Centers for Disease Control and Prevention (CDC) case definition, i.e., a fever (oral temperature $\geq 100.0^{\circ}\text{F}$ / 38°C) and cough or sore throat. After an episode of ILI, nose and throat swab samples were collected for analysis. Vaccine efficacies against vaccine-matched influenza viral strains, against all influenza viral strains, and against individual influenza viral subtypes were calculated (Table 8).

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Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

Table 8: Efficacy of TIVc against culture confirmed influenza by influenza viral subtype (Study V58P13)

		TIVc (N=3776)		Placebo (N=3843)		Vaccine Efficacy*	
		Attack Rate (%)	Number of Subjects with Influenza	Attack Rate (%)	Number of Subjects with Influenza	%	Lower Limit of One- Sided 97.5% CI
Antigenically Matched Strains							
Overall		0.19	7	1.14	44	83.8	61.0
Individual strains	A/H3N2**	0.05	2	0	0	--	--
	A/H1N1	0.13	5	1.12	43	88.2	67.4
	B**	0	0	0.03	1	--	--
All Culture-Confirmed Influenza							
Overall		1.11	42	3.64	140	69.5	55.0
Individual strains	A/H3N2	0.16	6	0.65	25	75.6	35.1
	A/H1N1	0.16	6	1.48	57	89.3	73.0
	B	0.79	30	1.59	61	49.9	18.2

* Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks.

Vaccine Efficacy = (1 - Relative Risk) x 100%;

** There were too few cases of influenza due to vaccine-matched influenza A/H3N2 or B to adequately assess vaccine efficacy.

5.2 PHARMACOKINETIC PROPERTIES

Not applicable.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Flucelvax® Quad has not been evaluated for genotoxic potential.

Carcinogenicity

Flucelvax® Quad has not been evaluated for carcinogenic potential.

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

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Flucelvax[®] Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 0.5ml dose of Flucelvax[®] Quad contains the following excipients:

Table 9: List of excipients

Sodium chloride	4 mg
Potassium chloride	0.1 mg
Magnesium chloride hexahydrate	0.05 mg
Dibasic sodium phosphate dihydrate	0.646 mg
Monobasic potassium phosphate	0.1865 mg
Water for injections	Up to 0.5 mL

Flucelvax[®] Quad does not contain preservative or antibiotics.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at +2°C to +8°C. (Refrigerate. Do not freeze.) Discard if the vaccine has been frozen. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Not all presentations or pack sizes may be marketed.

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax Quad AUST R 319093 & AUST R 341450

AUST R 319093

Flucelvax® Quad (Influenza virus haemagglutinin) Suspension for Injection needle-free (AUST R 319093) is a 0.5 mL suspension for injection in a needle-free pre-filled Type 1 glass syringe. The syringe and all associated syringe components do not contain natural rubber latex.

Pack sizes: 1's, 10's

AUST R 341450

Flucelvax® Quad (Influenza virus haemagglutinin) Suspension for Injection (AUST R 341450) is a 0.5 mL suspension for injection pre-filled Type 1 glass syringe with attached needle. The sheath covering the needle may contain natural rubber latex (See **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.**)

Pack sizes: 1's, 10's

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Not applicable.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Seqirus Pty Ltd
ABN 26 160 735 035
63 Poplar Road
Parkville, VIC 3052
Australia

Attachment 1: Product information for AusPAR - Flucelvax Quad - quadrivalent influenza vaccine - Seqirus Pty Ltd - PM-2020-05368-1-2 Final 18 November 2022. 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/products/australian-register-therapeutic-goods-artg/product-information-one>>

Seqirus

Flucelvax® Quad

AusPAR Attachment 1: Product Information for Flucelvax QuadAUST R 319093 & AUST R 341450

9 DATE OF FIRST APPROVAL

14 August 2020

10 DATE OF REVISION

10 November 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Strain information added for SH2022 season.
4.1, 4.2, 4.4, 4.8, 5.1	Information updated for change in indication of the vaccine for use in adults and children from '9 years of age' to '2 years of age'.

Flucelvax® Quad is a trademark of Seqirus UK Limited or its affiliates.