

AUSTRALIAN PRODUCT INFORMATION - Flud[®] Quad (influenza virus haemagglutinin)

1. NAME OF THE MEDICINE

Flud[®] Quad

Inactivated quadrivalent influenza vaccine (surface antigen), adjuvanted, suspension for injection; containing Influenza virus haemagglutinin as active ingredient.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mL dose contains influenza virus surface antigens (haemagglutinin and neuraminidase) of each of four antigens representative of the influenza virus types expected to circulate in the Southern Hemisphere winter according to WHO recommendations for the [year] season:

- A/XXXX (H1N1) – like virus (reassortants used):
15 micrograms HA* per dose
 - A/XXXX (H3N2) – like virus (reassortants used):
15 micrograms HA* per dose
 - B/XXXX – like virus (reassortants used):
15 micrograms HA* per dose
 - B/XXXX – like virus (reassortants used):
15 micrograms HA* per dose
- *HA = haemagglutinin

Flud[®] Quad vaccine is prepared from virus grown in embryonated hens' eggs and inactivated with formaldehyde before purification and combination with MF59C.1, an adjuvant known to increase the immunogenicity of vaccines. MF59C.1 adjuvant is a squalene based oil-in-water emulsion. Squalene is a normal component in the human body and is easily metabolized and excreted. For a full list of excipients, see **Section 6.1 – List of Excipients**.

The type and amount of viral antigens in Flud[®] Quad conform to the requirements of the Australian Influenza Vaccine Committee for the [year] Southern Hemisphere Influenza season. The strains chosen for vaccine manufacture are endorsed by the Australian Influenza Vaccine Committee as being antigenically equivalent to the reference virus.

3. PHARMACEUTICAL FORM

Flud[®] Quad is a milky-white suspension for intramuscular injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Active immunisation against influenza in persons 65 years of age and older.

4.2. Dose and Method of Administration

Flud[®] Quad is for use in adults 65 years of age and older only. See **Section 4.1 – Therapeutic Indications**.

A single 0.5 mL dose should be administered by intramuscular injection, preferably into the deltoid muscle of the upper arm.

Gently shake before use. After shaking, the normal appearance of the vaccine is a milky-white 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.

Flud[®] Quad contains no antimicrobial preservative. Use in one patient on one occasion only. Discard any residue.

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

Persons with a history of egg allergy (non-anaphylaxis) can receive a full dose of vaccine in any immunisation setting (See also **Section 4.4 – Special Warnings and Precautions for Use**).

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 6.1 – List of Excipients**), except egg proteins (See also **Section 4.4 – Special warnings and precautions for use**) 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 an anaphylactic event occurs following the administration of the vaccine.

Persons with a history of anaphylaxis to egg should be vaccinated only in medical facilities with staff experienced in recognising and treating anaphylaxis. For full details regarding recommendations for influenza vaccination in individuals with egg allergy, please refer to the relevant national immunisation guidelines.

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

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

A protective 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 Flud[®] Quad should be based on careful consideration of the potential benefits and risks.

The syringe and all associated syringe components for Flud[®] Quad AUST R 313724 pre-filled syringe needle-free do not contain natural rubber latex. Flud[®] Quad AUST R 316323 pre-filled syringe with attached needle cannot be considered to be latex-free as the sheath covering the needle contains natural rubber latex. See **Section 6.5 – Nature and Contents of Container** for further information.

Use in the elderly

Flud[®] Quad is approved for active immunisation against influenza in persons 65 years of age and older. See **Section 4.1 – Therapeutic Indications** and also **Section 5 – Pharmacological Properties**.

Paediatric use

Paediatric data have not been evaluated.

Effects on laboratory tests

No data available.

4.5. Interactions with Other Medicines and other Forms of Interactions

No clinical data on concomitant administration of Flud[®] Quad with other vaccines are available.

Data from two studies on the concomitant administration of Flud[®] (inactivated, trivalent influenza vaccine (surface antigen), adjuvanted, suspension for injection) with an approved 13-valent pneumococcal conjugate vaccine (PCV13) and an approved 23-valent pneumococcal polysaccharide vaccine (PPSV23) in an elderly population are available. These studies indicated that coadministration of Flud[®] with either PCV-13 or PPSV23 did not show significant

interference in antibody response. Although concomitant vaccination induced more frequent local pain, most of the local adverse reactions were mild. Systemic adverse reactions were generally mild, and no serious vaccine-related adverse events occurred.

If Flud[®] Quad needs to be used at the same time as another vaccine, immunisation should be given at separate injection sites, preferably on different limbs. It should be noted that the adverse reactions may be intensified.

4.6. Fertility, Pregnancy and Lactation

Effects on fertility

No data available.

Use in pregnancy

Category B2.

Animal reproduction studies have not been conducted with Flud[®] Quad. In a reproductive and developmental study in rabbits dosed with the trivalent vaccine Flud[®] (AUST R 90339 and AUST R 306718) twice pre-mating (21 and 7 days before mating) and during gestation (gestation day 7 and 20), there were no significant effects on the does, their fetuses or pups. The HA dose in rabbits was approximately 11-times the recommended clinical dose of a HA dose per body weight basis. Circulating anti-H1N1 antibodies were detected in the does, fetuses and pups.

There are no adequate and well-controlled studies in pregnant women. Flud[®] Quad is indicated for persons 65 years and over.

Use in lactation

No data available.

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)

The overall safety profile of Flud[®] Quad is similar to the adjuvanted trivalent influenza vaccine, Flud[®].

Clinical trials

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trial(s) of a vaccine cannot be directly compared to rates in the clinical trial(s) of another vaccine and may not reflect the rates observed in practice.

The safety of a single dose of Flud[®] Quad in subjects 65 years of age and older was evaluated in clinical study V118_20. Refer to **Section 5.1 – Pharmacodynamic Properties** for further detail.

In study V118_20, adverse events were collected as either solicited or unsolicited AEs. Solicited local and systemic events were collected for 7 days after vaccination (**Table 1**). Unsolicited AEs were collected for 21 days following vaccination, and for the full duration of study participation for serious AEs (SAEs), AEs leading to withdrawal from the study, new onset of chronic diseases (NOCDs), AEs of special interest (AESIs).

In the study, 51.8% of subjects reported any solicited AE after Flud[®] Quad vaccination, compared with 48.7%, and 48.2 % in the Flud[®] and aTIV-2 groups respectively. The most commonly reported

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Induration	7.0	0.0	5.4	0.0	5.3	0.0
Ecchymosis	2.5	0.1	1.5	0.0	1.5	0.0
Systemic Reactions						
Fatigue	16.0	0.7	15.4	0.7	11.5	1.4
Headache	12.0	0.5	10.6	0.7	11.3	0.7
Arthralgia	9.1	0.3	8.5	0.0	7.1	1.2
Myalgia	8.1	0.5	7.8	0.0	6.9	0.9
Diarrhoea	5.5	0.6	5.5	0.5	6.9	0.7
Chills	4.7	0.2	3.4	0.5	4.4	0.7
Nausea	4.0	0.2	4.1	0.0	4.6	0.9
Loss of appetite	3.2	0.2	4.8	0.0	3.7	0.5
Vomiting	0.8	0.1	0.5	0.0	2.1	0.7
Fever	0.5	0.1	0.2	0.0	0.5	0.0

Abbreviation: N=number of subjects with solicited safety data;

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

^b Solicited Safety Population: all subjects in the exposed population who provided post-vaccination solicited safety data

^c "Any" definitions: Erythema, Induration and Ecchymosis = 25 mm diameter, fever =

^d "Severe" definitions: Erythema, Induration and Ecchymosis >100 mm diameter; injection site pain, nausea, fatigue, myalgia, arthralgia, headache, and chills = prevents daily activity; loss of appetite = not eating at all; vomiting = 6 or more times in 24 hours or requires intravenous hydration; diarrhoea = 6 or more loose stools in 24 hours or requires intravenous hydration; Fever = 39°C.

Unsolicited Adverse Events (AEs) were collected for 21 days after vaccination. The frequency of unsolicited AEs was similar between the different vaccination groups, Flud[®] Quad (15.3%), Flud[®] (11.3%) and aTIV-2 (15.3%). Influenza-like-illness (2.0%), injection site bruising (1.1%)
[®] Quad.

No treatment-related SAE or death were reported in the study.

Two AESIs were reported during the study: one in the Flud[®] group, and one in the Flud[®] Quad group. Neither of the AESIs was considered to be related to study vaccine.

The frequency of unsolicited events leading to NOCD was similar across study groups: Flud[®] Quad (2.6%); Flud[®] (3.6%) and aTIV-2 (3.2%). NOCDs were heterogeneous in nature and consistent with the clinical conditions spontaneously occurring in subjects 65 years of age and older. No reported NOCDs were considered related to study vaccine.

No unsolicited AEs led to withdrawal from the study.

Post-marketing surveillance

There are currently no post-marketing data available for Flud[®] Quad.

However, the post-marketing experience with Flud[®] may be relevant to Flud[®] Quad because both vaccines are manufactured using the same process and have overlapping compositions. The following adverse reactions were reported from post marketing surveillance in subjects 65 years of age or older administered Flud[®].

As these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish, for all events, a causal relationship to vaccine exposure.

Blood and lymphatic system disorders

Thrombocytopenia (some very rare cases were severe with platelet counts less than 5,000 per mm³), lymphadenopathy.

General disorders and administration site conditions

Extensive swelling of injected limb lasting more than one week, Injection-site cellulitis-like reaction (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than 1 week).

Immune system disorders

Allergic or immediate hypersensitivity reactions, including anaphylactic shock

Musculoskeletal and connective tissue disorders

Muscular weakness

Nervous system disorders

Encephalomyelitis, Guillain-Barré Syndrome, convulsions, neuritis, neuralgia, paraesthesia,

Skin and subcutaneous tissue disorders

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

Vascular disorders

Vasculitis which may be associated with transient renal involvement.

Reporting of 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 via at <http://www.tga.gov.au/reporting-problems>

4.9. overdose

There are no data on overdose with Flud[®] Quad.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) and the New Zealand Poisons Centre on 0800 POISON or 0800 764766 (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Mechanism of action

Flud[®] Quad provides active immunisation against four influenza virus strains (two A subtypes and two B types) contained in the vaccine.

Flud[®] Quad has been shown to evoke antibody responses to the viral surface glycoproteins, haemagglutinin and neuraminidase. These antibodies provide protection against clinical illness in a high proportion of vaccine recipients.

The antibody response to Flud[®] Quad is similar to Flud[®] which is increased when compared to the response to vaccines without adjuvant, and is most pronounced for A/H3N2 influenza antigens. This increased response is even more pronounced in subjects 65 years of age and older. The inclusion of the second B strain in Flud[®] Quad also provides additional benefit compared to Flud[®].

The adjuvant MF59 broadens the overall immune response allowing the vaccine to offer greater protection against heterologous strains of the virus. This may be important when there is a mismatch between the virus strains included in the vaccine and the strains circulating in the community. The antibody response is increased when compared to the response to non-adjuvanted Inactivated Influenza Vaccine. This increased response is seen particularly in elderly subjects with low pre-immunisation titres and/or with underlying diseases (diabetes, cardiovascular and respiratory diseases) who are at increased risk of complications of influenza infection.

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 in adults, antibody titres of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects.

Antibody against a specific influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to a specific antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype.

The addition of the squalene-based MF59 oil-in-water emulsion adjuvant in Flud[®] Quad leads to enhanced antigen uptake by recruiting immune cells at the injection site and differentiating into antigen presenting cells. This results in an increased magnitude, breadth and persistence of the immune response through the duration of the influenza season compared with non-adjuvanted influenza vaccines.

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

Clinical trials

Immunogenicity

The immunogenicity of Flud[®] Quad was evaluated in clinical study V118_20, a multi-centre, randomised, double-blind, non-inferiority, comparator controlled study conducted in subjects 65 years of age and older in the 2017-18 Northern Hemisphere influenza season. In this study, 888 received Flud[®] Quad, 444 subjects received the licensed trivalent influenza vaccine (Flud[®], aTIV-1) and 444 subjects received an adjuvanted trivalent influenza vaccine containing the alternative B strain (a-TIV-2).

The per protocol immunogenicity set included a total of 1741 subjects: Flud[®] Quad (N=872), Flud[®] (N=436) and aTIV-2 (N=433). In the per protocol set, the mean age of subjects at enrolment who received Flud[®] Quad was 72.4 years.

Non-inferiority of the immune response of Flud[®] Quad to that of Flud[®] (aTIV-1) and TIV-2 among adults 65 years of age or older was assessed as a co-primary endpoint. Adjusted HI Geometric Mean Titre (GMT) ratios and the difference in seroconversion rates for each vaccine

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strain were assessed 21 days after vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio ($GMT_{aTIV}/GMT_{Flud^{®} Quad}$) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference ($SCR_{aTIV} - SCR_{Flud^{®} Quad}$) did not exceed 10% for each strain.

Flud[®] Quad was non-inferior for all 4 influenza strains for both HI antibody titres and seroconversion rates (**Table 2**).

Table 2: Comparison of Immune Responses to Each Antigen 21 days After Vaccination with Flud[®] Quad and Adjuvanted Trivalent Comparator Vaccines in Subjects 65 years of Age and Older (per protocol set)

Strain	GMT (95% CI)			GMT Ratio	Met predefined non-inferiority criteria? ^a
	Flud [®] Quad N=872	Flud [®] (B-Victoria) N=436	aTIV-2 (B-Yamagata) N=433	aTIV ^d /Flud [®] Quad (95% CI)	
A/H1N1	65.01 (57.79; 73.13)	75.16 (66.68; 84.72)		1.16 (1.05; 1.27)	Yes
A/H3N2	294.91 (261.88; 332.09)	293.31 (259.91; 330.99)		0.99 (0.90; 1.09)	Yes
B/Yamagata	24.67 (22.67; 26.84)	NA	24.30 (22.0; 26.84)	0.99 (0.90; 1.08)	Yes
B/Victoria	30.78 (28.27; 33.51)	30.13 (27.31; 33.24)	NA	0.98 (0.89; 1.08)	Yes
	Seroconversion % ^c			Seroconversion Difference	Met predefined non-inferiority

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Strain	(95% CI)			aTIV ^d - Flud [®] Quad (95% CI) (95% CI) aTIV	criteria? ^b
	Flud [®] Quad N=872	aTIV-1 (B-Victoria) N=436	aTIV-2 (B-Yamagata) N=433		
A/H1N1	35.21 (32; 38.5)	39.45 (34.8; 44.2)	37.41 (32.8; 4.2)	3.23 (-1.30, 7.76)	Yes
A/H3N2	39.33 (36.1; 42.7)	39.70 (36.4; 43.0)	37.18 (32.6; 41.9)	0.37 (-4.23, 4.96)	Yes
B/Yamagata	16.4 (14.0; 19.0)	NA	15.47 (12.2;19.2)	-0.93 (-5.13; 3.27)	Yes
B/Victoria	13.42 (11.2; 15.9)	12.16 (9.24; 15.6)	NA	-1.26 (-5.07; 2.55)	Yes

Abbreviations: GMT= Geometric Mean antibody Titre; CI= Confidence Interval; NA= Not Applicable.

N=the number of vaccinated subjects with available data from the immunogenicity endpoint listed (Per Protocol Set).

^a Non-inferiority for the GMT ratio was defined as: the upper bound of the two-sided 95% CI for the ratio of the GMTs did not exceed 1.5.

^b Non-inferiority for the seroconversion difference was defined as: the upper bound of the two-sided 95% CI for the difference between the seroconversions did not exceed 10%.

^c Seroconversion was defined as pre-vaccination HI titre <1:10 and post-vaccination at least a 4-fold increase in HI from pre-

^d aTIV-1 and aTIV-2 vaccine groups are pooled for the analysis of A/H1N1 and A/H3N2 strains. For B/Victoria aTIV=aTIV-1, for B/Yamagata aTIV=aTIV-2.

Immunogenicity based on CBER (Center for Biologics Evaluation and Research) criteria as measured by the percentage of subjects achieving seroconversion for HI antibodies and percentage of subjects achieving an HI antibody titre at 21 days post-vaccination was assessed as a second co-primary endpoint. Success criteria was met if the lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody met

or exceeded 30% and the lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titre

The second co-primary objective was met for A strains (H1N1 and H3N2), but not for B strains (B-Yamagata and B-Victoria). Results for B strains in the Flud[®] and aTIV-2 groups were similar to those obtained for Flud[®] Quad.

Immunological superiority of Flud[®] Quad compared to Flud[®] and aTIV-2 for the B strain that was not included in each aTIV vaccine was assessed by the GMT ratio and difference in seroconversion at 21 days post-vaccination. Superiority was met if the upper limit of the two-sided 95% CI for the GMT ratio ($\text{GMT}_{\text{aTIV}}/\text{GMT}_{\text{Flud}^{\text{®}} \text{Quad}}$) was <1 , and the upper limit of the two-sided 95% CI for the difference in SCRs ($\text{SCR}_{\text{aTIV}} - \text{SCR}_{\text{Flud}^{\text{®}} \text{Quad}}$) was <0 , for both B strains.

The pre-specified criteria for immunological superiority for the alternate B strain of Flud[®] Quad relative to each aTIV vaccine were met.

5.2. Pharmacokinetic Properties

Not applicable.

5.3. Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity (60 mcg HA/dose), local tolerance and sensitization (45 mcg HA/dose). For the reproductive and development toxicity refer to **Section 4.6 – Fertility, Pregnancy and Lactation**.

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACOLOGICAL PARTICULARS

6.1. List of Excipients

Each 0.5 mL dose of Flud[®] Quad contains MF59C.1 (a proprietary adjuvant): containing squalene 9.75 mg, polysorbate 80 1.175 mg, sorbitan trioleate 1.175 mg, sodium citrate dihydrate 0.66 mg, citric acid monohydrate 0.04 mg and water for injections and the following excipients.

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Sodium chloride	4.00 mg
Potassium chloride	0.10 mg
Monobasic potassium phosphate	0.10 mg
Dibasic sodium phosphate dihydrate	0.67 mg
Magnesium chloride hexahydrate	0.05 mg
Calcium chloride dihydrate	0.06 mg
Water for injections	up to 0.5 mL

Flud[®] Quad is manufactured in eggs and trace amounts of kanamycin sulfate, neomycin sulfate, ovalbumin (1 microgram/0.5 mL dose), formaldehyde 1 microgram/0.5 mL dose), cetrimonium bromide (12 microgram/0.5 mL dose), sucrose and hydrocortisone may be present as residues of the manufacturing process.

6.2. Incompatibilities

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

6.3. Shelf Life

12 months

6.4. Special Precautions for Storage

Store at 2 °C to 8 °C. Do not freeze. Protect from light.

6.5. Nature and Contents of Container

Not all pack sizes may be marketed.

AUST R 313724

Flud[®] Quad, inactivated, quadrivalent influenza vaccine (surface antigen), adjuvanted, suspension for injection, 0.5 mL pre-filled syringe, needle-free (AUST R 313724) is a 0.5 mL suspension for injection in a needle-free pre-filled syringe (type I glass).

The syringe barrel, plunger and rubber stopper are not manufactured with natural rubber latex.

Pack sizes: 1's; 10's.

AUST R 316323

Flud[®] Quad, inactivated, quadrivalent influenza vaccine (surface antigen), adjuvanted, suspension for injection, 0.5 mL pre-filled syringe, with attached needle (AUST R 316323) is a 0.5 mL suspension for injection in a pre-filled syringe (type I glass) with attached needle.

The sheath covering the needle contains natural rubber latex (see **Section 4.4 – Special Warnings and Precautions for Use**).

The syringe barrel, plunger and rubber stopper are not manufactured with natural rubber latex.

Pack sizes: 1's; 10's.

6.6. Special Precautions for Disposal

In Australia, 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)

Schedule 4 (Prescription Only Medicine)

8. SPONSOR

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

9. DATE OF FIRST APPROVAL

01 October 2019

10. DATE OF REVISION

Not applicable.

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

Flud[®] is a registered trademark of Seqirus UK Limited or its affiliates.