AUSTRALIAN PRODUCT INFORMATION – FLUAD® (influenza virus haemagglutinin).

1. NAME OF THE MEDICINE

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluad® is a purified, inactivated, surface antigen influenza vaccine, adjuvanted with MF59C.1 in a milky-white suspension for injection.

Each 0.5 mL dose contains influenza virus surface antigens of each of three purified surface antigens representative of the influenza virus types expected to circulate in the Southern Hemisphere winter according to WHO recommendations for the 2019 season:

- A/Michigan/45/2015 (H1N1) pdm09 - like virus (A/Singapore/GP1908/2015 (IVR-180)):
  15 micrograms HA* per dose
- A/Switzerland/8060/2017 (H3N2) – like virus (A/Brisbane/1/2018 (X-311)):
  15 micrograms HA* per dose
- B/Phuket/3073/2013 – like virus (B/Phuket/3073/2013 (BVR-1B)):
  15 micrograms HA* per dose

  *HA = haemagglutinin

Fluad® 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 contains the oil squalene which is obtained from shark liver and is also found in humans as a metabolite of cholesterol and as a normal component of cell membranes.

The type and amount of viral antigens in Fluad® conform to the requirements of the Australian Influenza Vaccine Committee for the 2019 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.

Excipients
For full list of excipients, see Section **6.1 LIST OF EXCIPIENTS.**

3. PHARMACEUTICAL FORM

FLUAD® is a milky-white suspension for intramuscular injection.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Active immunisation against influenza in the elderly (65 years of age and older), especially for those with an increased risk of associated complications (i.e. patients affected by underlying chronic diseases including diabetes, cardiovascular and respiratory diseases).

4.2 DOSE AND METHOD OF ADMINISTRATION

A single 0.5 mL dose should be administered by intramuscular injection into the deltoid muscle.

Fluad® should not be administered sub-cutaneously or intravascularly. Gently shake before use. After shaking, the normal appearance of Fluad® is a milky-white suspension.

Visually inspect the contents of each Fluad® pre-filled syringe for particulate matter or discoloration prior to administration. If either condition is observed, do not use the contents.

Fluad® is for single use in a single patient only, discard any residue.

Annual vaccination is recommended.

4.3 CONTRAINDICATIONS

Hypersensitivity to eggs, chicken proteins, kanamycin sulfate, neomycin sulfate, formaldehyde, or cetyltrimethylammonium bromide (CTAB), any constituent of the vaccine or in anyone who has had an anaphylactoid reaction to previous influenza vaccination.

Immunisation should be postponed in patients with acute febrile illness.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluad® should not be administered intravascularly or sub-cutaneously.

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

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

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

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

The syringe is for single use only and should not be used in more than one person.

The syringe and all associated syringe components for Fluad® AUST R 306718 prefilled syringe needle-free do not contain natural rubber latex. Fluad® AUST R 90339 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

Fluad® is approved for active immunization against influenza in the elderly (see section **4.1 THERAPEUTIC INDICATIONS**). Refer also to section **5 PHARMACOLOGICAL PROPERTIES**.

Paediatric use

No data available.

Effects on laboratory tests

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, hepatitis C and, especially HTLV1 have been observed. The Western Blot technique disproves the results. The transient false positive reactions could be due to the IgM response to the vaccine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Fluad® must not be mixed with other preparations for injection.

Fluad® may be given at the same time as other vaccines although no clinical data on concomitant administration with other vaccines are available. Immunisation should be carried out on separate limbs. It should be noted that any adverse reactions might be intensified.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

Influenza vaccine can impair the metabolism of Warfarin, Theophylline, Phenytoin, Phenobarbitone and Carbamazepine by the hepatic P450 system. Results from studies have been variable in the degree of interaction and time after vaccination for the interaction to take effect. The interaction may be idiosyncratic. Patients taking Warfarin, Theophylline, Phenytoin, Phenobarbitone or Carbamazepine should be advised of the possibility of interaction and told to look out for signs of elevated levels of medication.

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

Use in lactation

No data available.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE OF 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

The following information is based on clinical trials conducted with an earlier formulation of Fluad® that contained thiomersal (an organomercuric compound) 0.05 mg per dose as a preservative which may have contributed to the nature and incidence of post-immunisation reactions observed in these studies.

A higher incidence of mild post-immunisation reactions have been reported with Fluad® compared to non-adjuvanted vaccines.

Most commonly reported reactions after treatment are:
Local reactions, including redness, swelling, induration, pain at the injection site and ecchymosis.

Systemic reactions including fever, malaise, shivering, fatigue, headache, sweating, myalgia, arthralgia.
These reactions usually disappear within 1-2 days without treatment.

Clinical trial data

The table below shows the post-immunisation reactions (onset 0 to 6 days) reported in elderly subjects in Fluad® Phase II/III studies. These reactions were self-limited, mild in nature and of short duration.

	Fluad® (n=1982)	Comparator (n=1438)
Injection Site Reactions		
Erythema	357 (18.0%)	194 (13.5%)
Induration	296 (14.9%)	141 (9.8%)
Pain	654 (40.0%)	205 (14.3%)
Warmth	373 (18.8%)	160 (11.1%)
Systemic Reactions		
Body as a Whole		
Chills	67 (3.4%)	25 (1.7%)

Fever	14 (0.7%)	9 (0.6%)
Malaise	138 (7.0%)	65 (4.5%)
Gastrointestinal		
Nausea	48 (2.4%)	33 (2.3%)
Musculo/Skeletal		
Arthralgia	63 (3.2%)	27 (1.9%)
Myalgia	172 (8.7%)	40 (2.8%)
Neurological		
Headache	141 (7.1%)	71 (4.9%)
Skin		
Rash	9 (0.5%)	6 (0.4%)

Studies providing data following second and third annual vaccinations of Fluad® confirmed that revaccination gave a similar adverse effect profile.

Post-marketing study data

In a large post-marketing study including approximately 10,000 Fluad®-treated patients and approximately 5,000 patients vaccinated with a non-adjuvanted vaccine, no difference in the incidence of adverse effects requiring a physician visit with Fluad® treated patients (0.3%) compared to patients treated with a non-adjuvanted vaccine (0.4%) was seen.

Hospitalisation during the influenza season occurred in 5.4% of subjects given Fluad® and in 5.7% of subjects given a non-adjuvanted vaccine. Death during the influenza season was reported for 0.91% of patients given Fluad® and for 0.83% of patients given a non-adjuvanted vaccine. These differences were not statistically significant.

Adverse events considered at least possibly related to Fluad® vaccination and requiring a physician visit occurred uncommonly (0.1% to <1%) to rarely (0.01% to <0.1%) as follows:

Reported uncommonly:
Body as a whole: fever

Reported rarely:
Body as a whole: injection site reaction; asthenia; injection site pain; malaise; allergic reaction; chills; pain; rheumatoid arthritis
Cardiovascular: tachycardia
Digestive system: cholangitis; diarrhoea; enteritis; pancreatitis
Musculo/Skeletal: arthralgia; arthrosis; myalgia
Nervous system: vertigo
Respiratory system: asthma; bronchitis
Skin and Appendages: rash; urticarial

Adverse reactions from post-marketing spontaneous reports

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.

In addition to the adverse reactions observed during clinical trials, the following adverse reactions were reported from post marketing surveillance in subjects older than 65 years of age:

Blood and lymphatic system disorders

Thrombocytopenia (some very rare cases were severe with platelet counts less than 5,000 per mm^3), 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, pruritis or non-specific rash.

Vascular disorders

Vasculitis with transient renal involvement.

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/reporting-problems.

4.9 OVERDOSE

Overdosage is unlikely to have any untoward effect.

For information on the management of overdose, contact the POISONS Information Centre on 131126 (Australia) or the New Zealand Poisons Centre on 0800 POISON or 0800764766 (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Fluad® 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 vaccinees.

Seroprotection from Fluad® is generally obtained within 2 to 3 weeks. The duration of post vaccination immunity varies, but it is usually 6-12 months.

The antibody response to Fluad® is increased when compared to the response to vaccines without adjuvant, and is most pronounced for B and A/H3N2 influenza antigens. This increased response is even more pronounced in elderly persons with low pre-immunisation titres and/or with underlying diseases (diabetes, cardiovascular and respiratory diseases). A similar immunogenicity profile has been noted after a second and third immunisation with Fluad®.

Significant antibody rises after immunisation with Fluad® has also been shown against heterovariant strains, antigenically different from those included in the vaccine.

Influenza viral strains undergo antigenic changes from year to year. Therefore the antigen component of Fluad® is revised for every flu season and annual vaccination is recommended.

Clinical Trials

The following information is based on clinical trials conducted with an earlier formulation of Fluad® that contained thiomersal (an organomercuric compound) 0.05 mg per dose as a preservative.

A pooled analysis of 12 Phase II/III studies and 1 post-marketing study included data from 2102 subjects given a first vaccination with Fluad® and 1498 subjects vaccinated with a comparator vaccine. Fluad® resulted in higher GMR's to each of the influenza antigens, a higher percentage of subjects with seroconversion and a higher percentage of subjects with HI titres ≥ 40 compared with the combined influenza vaccine comparators for the B, A/H3N2 and A/H1N1 antigens. Increased efficacy in the prevention of influenza in comparison with non-adjuvanted influenza vaccines has not been demonstrated.

Table 1: Immunogenic Response in Elderly Subjects with a Pre-immunisation titre of ≤ 20

	Absolute titres 28 days post immunisation		**GMR** Day 28: Day 0 (95% CI)	**Sero-Conversion** n (%)
	≥ 40	**≥ 160**		
B antigen				
Fluad (n=573)	484 (84%)	178 (31%)	7.7 (6.9%, 8.6%)*	440 (77%)*
Comparator (n=427)	304 (71%)	100 (23%)	5.8 (5.1%, 6.5%)	275 (64%)

A/H3N2				
Fluad (n=377)	321 (85%)#	181 (48%)*	11 (9.7%, 13%)*	327 (87%)*
Comparator (n=340)	252 (74%)	115 (34%)	7.3 (6.1%, 8.6%)	252 (74%)
A/H1N1				
Fluad (n=368)	314 (85%)	181 (48%)	11 (9.1%, 13%)*	287 (78%)
Comparator (n=257)	252 (74%)	115 (34%)	9.6 (8%, 12%)	184 (72%)

*Significant difference between the Fluad and comparator group at the p ≤ 0.001 level.
#Significant difference between the Fluad and comparator group at the p ≤ 0.01 level.

Similarly patients with a history of cardiovascular, respiratory or diabetes disease given Fluad® also achieved better immunogenic responses than those subjects given the comparator non-adjuvanted vaccine.

Table 2: Immunogenic Response in Elderly Subjects with a History of Diabetes, Cardiovascular or Respiratory Disease

	Absolute titres 28 days post immunisation		**GMT ratio** Day 28: Day 0 Fluad:Comparator
	≥ 40	**≥ 160**	
B antigen			
Fluad (n=1245)	1187 (95%)	726 (58%)	1.37*
Comparator (n=921)	814 (88%)	470 (51%)	(n=1239:911)
A/H3N2			
Fluad (n=1101)	1055 (96%)	820 (74%)	1.43*
Comparator (n=771)	703 (91%)	466 (60%)	(n=1095:761)
A/H1N1			
Fluad (n=1245)	1218 (98%)	886 (71%)	1.17*
Comparator (n=921)	894 (97%)	623 (68%)	(n=1239:911)

*Significant difference between the Fluad and comparator group at the p ≤ 0.001 level.

A comparison of immunogenicity data from elderly subjects immunised with the thiomersal-containing formulation and the thiomersal-free formulation indicates that there is no difference in the immunogenicity profile measured at days 0 and 21 post immunisation between the two treatment groups.

Although it is generally recognised that vaccine-induced haemagglutination inhibition antibody titres measured against influenza antigens from strains causing disease in the community are a surrogate marker of efficacy, a precise threshold for protection or an absolute correlation between magnitude of antibody titre and reduction in clinical symptoms has not been established.

5.2 PHARMACOKINETIC PROPERTIES

Not applicable.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

Other excipients:

Sodium chloride	4mg
Potassium chloride	0.1mg
Monobasic potassium phosphate	0.1mg
Dibasic sodium phosphate dihydrate	0.66mg
Magnesium chloride hexahydrate	0.05mg
Calcium chloride dihydrate	0.06mg
Water for injections	q.s.

Fluad® may also contain kanamycin sulfate, neomycin sulfate, formaldehyde, chicken proteins (such as ovalbumin), cetyltrimethylammonium bromide (CTAB), sucrose, barium sulfate, and hydrocortisone 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

Fluad® has a shelf life of 12 months when stored at +2°C to +8°C.

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 presentations or pack sizes may be marketed.

AUST R 306718
Fluad® inactivated influenza vaccine (surface antigen) suspension for injection, adjuvanted, 0.5ml syringe, needle-free (AUST R 306718) is a 0.5 mL suspension for injection in a needle-free pre-filled syringe (type I glass).

The syringe and all associated syringe components do not contain natural rubber latex.

Pack sizes: 1's, 10's.

AUST R 90399
Fluad® inactivated influenza vaccine (surface antigen) suspension for injection, adjuvanted, 0.5ml syringe, fixed needle (AUST R 90339) 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 STANDARDS)

Prescription only Medicine (S4)

8. SPONSOR

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

9. DATE OF FIRST APPROVAL

AUST R 90339 15 October 2002
AUST R 306718 2 November 2018

10. DATE OF REVISION

2 November 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information

All	Updated as per TGA Form for providing PI dated Mar 2018.
2	Influenza strains updated for Southern Hemisphere 2019 season.