# AUSTRALIAN PRODUCT INFORMATION

**Flucelvax® Quad (Influenza virus haemagglutinin)**

**For Season xxxx**

## 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 XXXX influenza season representative of the following types:

| | |
|---|---|
| A/xxx-like virus (xxx) | 15 micrograms HA** |
| A/xxx-like virus (xxx) | 15 micrograms HA** |
| B/xxx-like virus (xxx) | 15 micrograms HA** |
| B/xxx-like virus (xxx) | 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 ß-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**.

The vaccine complies with the World Health Organization (WHO) recommendation and Australian Influenza Vaccine Committee (AIVC) for the xxxx 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 9 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**

**Adults and children from 9 year of age: a single 0.5 mL 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.

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 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 9 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 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 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). 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.

**Table 1: Incidence of Solicited Adverse Events[1] in the Adult and Elderly Safety Population[2] Reported Within 7 Days of Vaccination**

| | 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) |

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

[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.

The most commonly reported unsolicited adverse events (reported by ≥ 3% of subjects administered Flucelvax® Quad) in adults 18 to < 65 years, were upper respiratory tract infection (3.5%) and nasopharyngitis (3.0%), and in adults ≥ 65 years, were nasopharyngitis (4.4%) and upper respiratory tract infection (3.3%).

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

**Children and Adolescents 9 to less than 18 years of age**

Flucelvax® Quad is indicated for use in adults and children 9 years of age and older (See Section **4.1 THERAPEUTIC INDICATIONS**).

The safety of Flucelvax® Quad in children 4 to less than 18 years of age was evaluated in a randomised, double-blind, controlled study 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). Children 9 to less than 18 years of age received a single dose of Flucelvax® Quad or comparator vaccine. The collection and presentation of adverse events from this study is the same as the study in adults 18 years of age and older.

Solicited adverse events in the safety population of children 9 years to less than 18 years of age are shown in Table 2.

**Table 2: Incidence of Solicited Adverse Events[1] in the Safety Population[2] (Children 9 to less than 18 years of age) Reported After Any Dose Within 7 Days of Vaccination**

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

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

[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.

The most commonly reported unsolicited adverse event in children 9 to < 18 years, was upper respiratory tract infection (4.3%).

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

## 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.

***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). 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 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 3.

**Table 3 Non-inferiority of Flucelvax® Quad relative to TIVc in adults 18 years of age and above – Per protocol analysis set**

| | | **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.

[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). 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 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 4 in children and adolescents aged 4 to less than 18 years. Flucelvax® Quad is indicated for use in adults and children 9 years of age and older (See **Section 4.1 THERAPEUTIC INDICATIONS).**

**Table 4 Noninferiority [a] of Flucelvax® Quad relative to TIVc in children and adolescents 4 to less than 18 years of age)– Per-protocol analysis Set**

| | | 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 | 185 (171-200) | 185 (166-207) | 1 | - |

| | | | | | |
|---|---|---|---|---|---|
| | or 50 (95% CI) | | | (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

[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

The immunogenicity data in subjects 9 to less than 18 years of age are summarised in Table 5.

**Table 5 GMTs and seroconversion rates (with 95% CI) in subjects 9 to <18 years of age, 3 weeks after vaccination with Flucelvax Quad® or TIV1c/TIV2c - Per Protocol Set (V130_03)**

| | | **Flucelvax® Quad** | **TIV1c/TIV2c[a]** |
|---|---|---|---|
| **A/H1N1** | | N = 547 | N = 272 |
| | GMT (95% CI) | 1139 (1045-1242) | 1138 (1007-1286) |
| | Seroconversion Rate[b] (95% CI) | **70%** (66%-74%) | **72%** (67%-78%) |
| **A/H3N2** | | N = 546 | N = 272 |
| | GMT (95% CI) | 719 (673-767) | 762 (694-836) |
| | Seroconversion Rate[b] (95% CI) | **42%** (38%-47%) | **53%** (46%-59%) |
| **B1** | | N = 546 | N = 272 |
| | GMT (95% CI) | 200 (185-218) | 200 (178-224) |
| | Seroconversion Rate[b] (95% CI) | **63%** (58%-67%) | **63%** (57%-69%) |
| **B2** | | N = 545 | N = 265 |
| | GMT (95% CI) | 212 (192-235) | 203 (175-234) |
| | Seroconversion Rate[b] (95% CI) | **72%** (68%-75%) | **68%** (62%-74%) |

[a] For H1N1, H3N2 and B1 influenza strains TIV1c data are presented, whereas for B2 influenza strain TIV2c data are presented.

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

**Bold**- CHMP immunogenicity criteria met. The percentage of subjects with seroconversion or significant increase in HI antibody titre is >40%.

**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 2007-2008 influenza season in adults aged 18 to 49 years (NCT00630331, see http://clinicaltrials.gov). 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 ≥ 100.0°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 6).

**Table 6: Efficacy of TIVc against culture confirmed influenza by influenza viral subtype**

| | | 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.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

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

**Table 7 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 |
| **Dibasic potassium phosphate** | 0.1865 mg |
| **Water for injections** | Up to 0.5 mL |

## 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.

**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

## 9 DATE OF FIRST APPROVAL

14 August 2020

## 10 DATE OF REVISION

Not applicable.

### SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| | |