▼ This medicinal product is subject to additional monitoring **in Australia**. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

AUDENZ® [Influenza virus haemagglutinin]

1 NAME OF THE MEDICINE

Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted, prepared in cell cultures) suspension for injection containing influenza virus haemagglutinin as the active ingredient.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The vaccine is a purified, inactivated, monovalent, surface antigen (haemagglutinin and neuraminidase), adjuvanted vaccine containing antigen of the following type:

A/turkey/Turkey/1/2005 NIBRG-23

7.5 micrograms HA* per 0.5 mL dose

* haemagglutinin

AUDENZ® pandemic influenza vaccine is prepared from influenza virus propagated in Madin Darby Canine Kidney (MDCK) cells, adapted to grow freely in suspension culture medium. The virus is inactivated with propiolactone, disrupted by the detergent cetrimonium bromide and purified through several process steps and then combined 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 of fish origin. AUDENZ® may contain traces of propiolactone, cetrimonium bromide and polysorbate 80 (refer to **Section 4.3 CONTRAINDICATIONS**). For a full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS.**

3 PHARMACEUTICAL FORM

AUDENZ® is a suspension for injection. The vaccine appearance is a milky-white suspension for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AUDENZ® is indicated for active immunisation against influenza A in persons from 6 months of age and older in an officially declared pandemic.

AUDENZ® should be used in accordance with official recommendations.

4.2 DOSE AND METHOD OF ADMINISTRATION

Individuals 6 months of age and older: Administer two doses (0.5 mL each), at least 21 days apart.

Elderly: No dose adjustment is required in elderly individuals ≥ 65 years of age.

Booster dose: The need for a booster dose(s) following the primary vaccination schedule has not been established.

Method of administration

The vaccine should be administered by intramuscular injection.

For persons 12 months of age and over, the preferred injection site is the deltoid muscle of the upper arm; for those 6 to less than 12 months of age, the preferred injection site is the anterolateral thigh.

AUDENZ® must not be mixed with other products.

Instructions for Use and Handling

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.

AUDENZ® pre-filled syringes contains no antimicrobial preservative. Each pre-filled syringe is for use in one patient on one occasion only. Discard any residue.

Please refer to *The Australian Immunisation Handbook* for recommendations regarding the appropriate vaccination site, technique and needle size.

4.3 CONTRAINDICATIONS

AUDENZ® 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 an 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 until the fever is resolved.

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 AUDENZ® should be based on careful consideration of the potential benefits and risks.

Bleeding or bruising may occur in individuals receiving anticoagulant therapy or those with any coagulation disorder following intramuscular administration of any vaccine.

No post-marketing data is available following the use of AUDENZ®. Some cases of convulsions (with and without fever) were reported during the 2009 pandemic for an H1N1 vaccine manufactured with the MF59 adjuvant and from an egg-based manufacturing platform (Focetria®).

The majority of febrile convulsions occurred in paediatric subjects. Some cases were observed in subjects with a history of epilepsy. Particular attention should be given to subjects suffering from epilepsy and the physician should inform the vaccine recipients (or parents) about the possibility to experience convulsion (see Section 4.8).

Limitations of vaccine effectiveness

A protective immune response may not be elicited in all vaccine recipients. Some degree of cross-reactive immunity has been observed against H5N1 viruses of clades different to that of the vaccine strain (see Table 5). However, the degree of protection that may be elicited to H5N1 strains of other subtypes or clades is unknown (see Section 5.1).

Duration of protection

The duration of protection following the primary vaccination schedule is unknown.

A reduction of antibody titres was observed when assessed 6 and 12 months after the primary vaccination series with the A/turkey/Turkey/1/2005 (H5N1) strain.

Use in the elderly

Two clinical studies of aH5N1c included a total of 1,896 subjects 65 years of age and older. Of these, 533 subjects were 75 years of age and older.

Antibody responses to aH5N1c were lower in the geriatric (adults 65 years of age and older) population than in younger subjects (adults 18 to 64 years of age).

Refer to **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Clinical trials (Adults)** and **5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials** for elderly data.

Paediatric use

AUDENZ® may be used in children from 6 months of age.

The safety and efficacy of aH5N1c in infants aged less than 6 months have not yet been established. No data are available.

Refer to **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Clinical trials (Paediatric)** and **5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials.**

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There are no data on co-administration of AUDENZ® vaccine with other vaccines.

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

If AUDENZ® is 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

A reproductive and development toxicity study in female rabbits dosed intramuscularly with AUDENZ® at 12.5-fold margin on a µg/kg basis had no effects on fertility.

Use in pregnancy – Pregnancy Category B1

Healthcare providers should assess the benefit and potential risks of administering the vaccine to pregnant women taking into consideration official recommendations.

The safety of AUDENZ® in pregnancy has not been assessed in clinical trials.
A reproductive and developmental toxicity study in female rabbits dosed intramuscularly with AUDENZ® at 12.5-fold margin on a µg/kg basis did not reveal any maternal, fetal or pre-weaning developmental toxicity.

Use in lactation

AUDENZ® has not been evaluated in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

AUDENZ® has no or negligible influence on the ability to drive and use machines. However, some of the undesirable effects mentioned under **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)** may affect the ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials – Adults 18 Years of Age and Older

Clinical safety data for aH5N1c in adults (18 years of age and older) have been collected from three studies: Study V89_04 was a dose comparison trial in adults 18 to less than 65 years of age; Study V89_13 was a dose comparison trial in adults 65 years of age and older, and V89_18 was a placebo-controlled trial in adults 18 years of age and older. Subjects in all studies received 2 doses of aH5N1c, 21 days apart. The total safety population includes 3579 subjects who received at least one dose of aH5N1c. Of these, 1683 were adults 18 to less than 65 years of age and 1896 were adults 65 years of age and older.

Study V89_18 was a randomised, observer-blind, multicentre, controlled study conducted in the US, in adults 18 years of age and older. Subjects were randomised in a 3:1 ratio to receive two doses of either aH5N1c or saline placebo, 21 days apart. In total, 3191 subjects (18 to <65 years: N=1596; 65 years and older: N=1595) in the safety population received at least one dose of aH5N1c (N=2395) or placebo (N=796).

In the pivotal clinical trial, Study V89_18, the most common (≥10%) local and systemic reactions in adults (18 to <65 years) reported within 7 days following administration of aH5N1c were injection site pain (64%), fatigue (25%), headache (25%), malaise (22%),

myalgia (14%), arthralgia (10%) and nausea (10%).

The frequencies of solicited local and systemic adverse reactions reported from Study V89_18 are presented in Table 1. Adults 65 years and older generally reported fewer solicited local and systemic reactions compared to younger persons. The majority of solicited local and systemic adverse reactions were mild or moderate in intensity. Severe reactions in subjects receiving aH5N1c were reported in 1% or fewer subjects for each reaction; these rates were similar to those reported in subjects receiving placebo. Reactogenicity was higher after the first dose than after the second dose.

Table 1. Incidence of Solicited Local and Systemic Adverse Reactions in Adult and Elderly Subjects Within 7 Days of Vaccination with aH5N1c (Study V89_18)

System Organ Class Solicited Reaction	**Adults 18 to <65 Years**		**Elderly ≥65 Years**	
	aH5N1c (N=1163)[a]	**Placebo (N=387)[a]**	**aH5N1c (N=1189)[a]**	**Placebo (N=397)[a]**
	Frequency Category[b] (%)[c]		**Frequency Category[b] (%)[c]**	
Nervous system disorders				
Headache	Very common (25%)	23%	Very common (16%)	16%
Gastrointestinal disorders				
Nausea	Very common (10%)	11%	Common (7%)	6%
Loss of appetite	Common (8%)	9%	Common (6%)	6%
Musculoskeletal and connective tissue disorders				
Myalgia	Very common (14%)	11%	Common (9%)	8%
Arthralgia	Very common (10%)	9%	Very common (10%)	9%
General disorders and administration site conditions				
Injection site pain	Very common (64%)	20%	Very common (36%)	10%
Fatigue	Very common (25%)	21%	Very common (20%)	19%
Malaise	Very common (22%)	12%	Very common (16%)	12%
Chills	Common (4%)	4%	Common (4%)	3%
Fever (Oral) (≥38°C)	Uncommon (0.6%)	2%	Uncommon (0.7%)	0.3%
Erythema	Uncommon (0.6%)	0%	Uncommon (0.4%)	0%
Induration	Uncommon (0.4%)	0%	Uncommon (0.7%)	0%
Ecchymosis	Uncommon (0.3%)	0%	Uncommon (0.6%)	0.3%

[a] N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any

solicited safety data) for each study vaccine group

[b] Frequency category definitions: Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100)

[c] Percent (%) is derived from the number of subjects that reported the event divided by the Solicited Safety Population in each vaccine group and age cohort

Unsolicited Adverse Events:

Unsolicited adverse events (AEs) were collected for 21 days following each vaccination in the three studies.

In Study V89_18, the proportion of subjects who reported unsolicited AEs in the 21 days after each vaccination was similar for the aH5N1c and the placebo groups (23% vs. 22%). There was no clear increase in the frequency, or difference in the nature of unsolicited AEs in the aH5N1c group compared with the placebo group. The following unsolicited AE was reported as possibly or probably related at a rate ≥1%: Injection site bruising (1.5%) in subjects who received aH5N1c.

Serious adverse events (SAEs), adverse events of special interest (AESIs) and new onset of chronic disease (NOCD) were collected for one year following vaccination.

Across all 3 studies no SAEs, AESIs or deaths were considered related to vaccination with aH5N1c.

Across all three studies, NOCDs (9.7% vs 9.2%) and Medically Attended AEs (47.1% vs 46.0%) occurred with similar frequencies between aH5N1c and placebo recipients, respectively, with larger proportions of these events occurring in subjects ≥ 65 years. No large imbalances in types of event were observed between treatment groups.

Paediatric Population 6 months to less than 18 years of age

Clinical safety data for aH5N1c in children 6 months to less than 18 years of age was collected in Study V89_11.

This was a phase 2, randomised, controlled, observer-blind multicentre study conducted in the US and Thailand in children 6 months to less than 18 years of age who received either two 0.5 mL (7.5 mcg HA of H5N1 with 0.25 mL MF59) or 0.25 mL (3.75 mcg HA of H5N1

with 0.125 mL MF59) doses of vaccine, 21 days apart. In total, 658 subjects in the safety population received at least one dose (7.5 mcg dose N=329; 3.75 mcg dose N=329).

Solicited local and systemic adverse reactions were collected for 7 days after each vaccination in all children, divided into two age cohorts (6 months to <6 years, and 6 to <18 years of age).

In both the 7.5 mcg and 3.75 mcg dose groups, the majority of solicited local and systemic adverse reactions were mild or moderate in intensity and resolved within a few days. The frequency of solicited local and systemic adverse reactions was similar between the 7.5 mcg and 3.75 mcg doses.

The most common (≥10%) solicited local and systemic reactions reported within 7 days following administration of aH5N1c in children 6 months to less than 6 years of age were tenderness (56%), irritability (30%), sleepiness (25%), change in eating habits (18%) and fever (16%). The most common (≥10%) solicited local and systemic reactions reported within 7 days following administration of aH5N1c in children 6 to less than 18 years of age were pain (68%), myalgia (30%), fatigue (27%), malaise (25%), headache (22%), loss of appetite (14%), nausea (13%), and arthralgia (13%).

Solicited local and systemic adverse reactions in subjects who received aH5N1c from Study V89_11 are shown below.

Table 2. Incidence of Solicited Local and Systemic Adverse Reactions in Children 6 Months to Less Than 6 Years of Age Within 7 Days of Vaccination with aH5N1c (7.5 mcg HA of H5N1 with MF59) (Study V89_11)

	6 Months to <6 Years	**6 to <18 Years**
System Organ Class Solicited Reaction	**aH5N1c (N=159)[a]** **Frequency Category[b] (%)[c]**	**aH5N1c (N=163)[a]** **Frequency Category[b] (%)[c]**
Nervous system disorders		
Headache	-	Very common (22%)
Gastrointestinal disorders		
Nausea	-	Very common (13%)

	6 Months to <6 Years	6 to <18 Years
System Organ Class Solicited Reaction	**aH5N1c (N=159)[a]** **Frequency Category[b] (%)[c]**	**aH5N1c (N=163)[a]** **Frequency Category[b] (%)[c]**
Loss of appetite	-	Very common (14%)
Change in eating habits	Very common (18%)	-
Musculoskeletal and connective tissue disorders		
Myalgia	-	Very common (30%)
Arthralgia	-	Very common (13%)
General disorders and administration site conditions		
Injection site pain/Tenderness	Very common (56%)	Very common (68%)
Fatigue	-	Very common (27%)
Sleepiness	Very common (25%)	-
Malaise	-	Very common (25%)
Irritability	Very common (30%)	-
Fever (Oral) (≥38°C)	Very common (16%)	Common (4%)
Erythema	Common (3%)	Common (1%)
Induration	Common (1%)	Common (1%)
Ecchymosis	0%	0%

[a] N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data) for each study vaccine group
[b] Frequency category definitions: Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100)
[c] Percent (%) is derived from the number of subjects that reported the event divided by the Solicited Safety Population in each vaccine group and age cohort

In Study V89_11, unsolicited AEs were collected for 21 days following vaccination for children 6 months to less than 18 years of age. Serious AEs and AESIs were monitored for one year after the last vaccination. In children 6 months to less than 18 years of age (N=658), 26% of subjects who received aH5N1c (7.5 mcg with MF59/0.5 mL) and 29% of subjects who received 3.75 mcg with MF59/0.25 mL reported at least one unsolicited adverse event within 21 days after any vaccination.

No SAEs were assessed as related to aH5N1c. No deaths, AESIs or NOCDs were reported.

Post-marketing adverse reactions

There is no post-marketing experience following administration of AUDENZ®. However, the post-marketing adverse events that have been reported after use of seasonal influenza vaccines are shown below in Table 3.

Table 3. Post-marketing experience reported after use of seasonal influenza vaccines[a]

System Organ Class Unsolicited reaction	Adverse Reaction[b]
Immune system disorders	Allergic reactions, such as immediate hypersensitivity, anaphylaxis including dyspnoea, bronchospasm, laryngeal oedema, in rare cases leading to anaphylactic shock
Nervous system disorders	Neuralgia, paraesthesia, neuritis, convulsions, encephalomyelitis, Guillain-Barré syndrome, vaccination anxiety-related reactions including presyncope and syncope
Vascular disorders	Vasculitis which may be associated with transient renal involvement
Skin and subcutaneous tissue disorders	Generalised skin reactions such as urticaria, non-specific rash, and local allergic reactions including angioedema
General disorders and administration site conditions	Extensive swelling of vaccinated limb

[a] Reports are from cell-based and egg-based seasonal influenza vaccines with and without MF59 adjuvant and include Flucelvax® Quad (AUST R 319093 & AUST R 341450) and Fluad® Quad (AUST R 313724 & AUST R 316323)
[b] Frequency not known (cannot be estimated from the available data)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

There is no experience of overdose with AUDENZ®.

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 764 766 (New Zealand).

5 Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action

Pandemic preparedness vaccines contain influenza antigens that are different from those in the currently circulating influenza viruses. These antigens can be considered as "novel" antigens and simulate a situation where the target population for vaccination is immunologically naïve. Data obtained with the pandemic preparedness vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with pandemic preparedness vaccines are relevant for the pandemic vaccines.

Clinical trials

Immunological evaluation

Four studies evaluated immunological responses in adults, including elderly (studies V89_13, V89_04, V89_18), or children (Study V89_11). All studies demonstrated that aH5N1c met the pre-specified immunological criteria at day 43 (21 days after the second vaccination).

Adults 18 years of age and older:

Study V89_18 was a phase 3, randomised, observer-blind, multicentre, controlled study conducted in the US in adults 18 years of age and older, who received either two doses of 7.5 mcg HA of aH5N1c with 0.25 mL of MF59 or saline placebo, 21 days apart. In total, 2988 subjects (18 to <65 years N=1488; ≥65 years N=1500) in the per protocol population received both doses of aH5N1c (N=2249) or saline placebo (N=739). Haemagglutination-inhibition

(HI) antibody titres against the A/turkey/Turkey/1/2005 (H5N1) strain were evaluated in sera obtained 21 days after the second dose.

HI titres were assessed according to pre-specified criteria for the proportion of subjects with seroconversion (defined as a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or a pre-vaccination HI titre ≥1:10 and ≥4-fold increase in HI titre) and the proportion of subjects with an HI titre ≥1:40. Assessment of the proportion of subjects with seroconversion or an HI titre ≥1:40 after vaccination was performed by age group (18 to <65 years and ≥65 years). Success criteria required the lower bound of the 2-sided 95% CI for the proportion of subjects with seroconversion, to be ≥40% for subjects 18 to less than 65 years, and ≥30% for subjects ≥65 years of age. For the proportion of subjects with an HI titre ≥1:40, the lower bound of the 2-sided 95% CI was required to be ≥70% for subjects ≥18 to less than 65 years of age, and ≥60% for subjects ≥65 years of age.

In subjects 18 to less than 65 years of age and subjects ≥65 years of age, the pre-specified criteria for proportion of subjects with seroconversion and an HI titre ≥1:40 were met 21 days after the second vaccination (Table 4). In Study V89_13 (NCT01776541) for adults 18 to less than 65 years of age, and Study V89_04 (NCT01766921) for adults 65 years of age and older, similar immunogenicity results were observed.

Table 4. Seroconversion Rates, Percentage of Subjects with HI Titres ≥1:40 and Geometric Mean Titre Ratios (GMR) following aH5N1c or Placebo (21 Days after 2 vaccinations) (PPS[a] – Study V89_18[b])

	Adults 18 to <65 years of age		**Adults ≥65 years of age**	
	aH5N1c (N=1076)	**Placebo (N=349)**	**aH5N1c (N=1080)**	**Placebo (N=351)**
Seroconversion[c] (95% CI)	79.9% (**77.4**; 82.3)	0.3% (0.0; 1.6)	54.0% (**51.0**; 57.0)	1.7% (0.6; 3.7)
HI Titre ≥1:40 (95% CI)	95.0% (**93.4**, 96.2)	8.5% (5.9, 12.1)	85.7% (**83.3**, 87.9)	20.8% (16.6, 25.8)
GMR Day 43/ Day 1[d]	12.7 (11.9, 13.5)	0.8 (0.7, 0.9)	4.9 (4.6, 5.2)	0.8 (0.8, 0.9)

[a] PPS: Per Protocol Set, subjects who correctly received 2 doses of aH5N1c according to the study protocol
[b] NCT02839330
[c] Seroconversion is defined as a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or a pre-

vaccination HI titre ≥1:10 and ≥4-fold increase in HI titre.
[d] Geometric mean HI titres on Day 43 compared to Day 1

Bold shows that the pre-specified criterion was met, ie, a lower bound of the 2-sided 95% confidence interval for seroconversion ≥40%, and for the proportion of subjects with HI antibody titres of ≥1:40 a lower bound of the 2-sided 95% confidence interval ≥70% for subjects 18 to less than 65 years and ≥60% for subjects 65 years and older.

The MicroNeutralisation (MN) assay was used to measure immunological response against the homologous strain in a subset of 76 adults 18 to <65 years of age in Study V89_18. Using the MN assay an at least 4-fold increase from baseline titres at Day 43 was achieved in 90% of subjects and a 24-fold increase in geometric mean titres (GMTs) was achieved on Day 43 compared to Day 1.

Cross reactivity data in adults

Cross-reactive immune response elicited by A/turkey/Turkey/1/2005 (clade 2.2.1)

In the phase 2 studies, V89_04 and V89_13, immune responses were evaluated against five H5N1 heterologous strains: A/Anhui/1/2005 (clade 2.3.4); A/Egypt/N03072/2010 (clade 2.2.1); A/Hubei/1/2010 (clade 2.3.2); A/Indonesia/5/2005 (clade 2.1.3) and A/Vietnam/1203/2004 (clade 1) three weeks after the second vaccination. HI GMTs on Day 43 compared to Day 1 increased between 2- and 7.3-fold in subjects 18 to <65 years of age (Study V89_04), and between 1.5- and 4.8-fold in subjects ≥65 years of age (Study V89_13). The percentage of subjects with seroconversion or an HI titre ≥1:40 at Day 43 ranged from 28% to 64% in subjects 18 to <65 years of age and from 17% to 57% in subjects ≥65 years of age. Table 5 presents data on immune responses against the H5N1 heterologous strains.

Table 5. Seroconversion Rates, Percentage of Subjects with HI Titres ≥1:40 and Geometric Mean Titre Ratios (GMR) following aH5N1c (21 Days after 2 vaccinations) against heterologous H5N1 strains in subjects 18 to <65 years of age and ≥65 years of age (FAS[a] – Study V89_04 and V89_13)[b]

	Adults 18 to <65 years of age (V89_04) N=69				
	A/Anhui/1/ 2005	**A/Egypt/N03072/ 2010**	**A/Hubei/1/ 2010**	**A/Indonesia/5/ 2005**	**A/Vietnam/1203/ 2004**
Seroconversion[c] (97.5% CI)	28% (16, 41)	55% (41, 69)	55% (41, 69)	35% (22; 49)	52% (38, 66)
HI Titre ≥1:40 (97.5% CI)	28% (16, 41)	58% (44, 71)	64% (50, 76)	35% (22, 49)	54% (40, 67)

	Adults 18 to <65 years of age (V89_04) N=69				
	A/Anhui/1/ 2005	**A/Egypt/N03072/ 2010**	**A/Hubei/1/ 2010**	**A/Indonesia/5/ 2005**	**A/Vietnam/1203/ 2004**
GMR Day 43/Day 1[d]	2.1 (1.3, 3.4)	6.5 (3.6, 12)	7.3 (4.0; 13)	3.1 (1.8, 5.4)	7.0 (3.8, 13)
	Adults ≥65 years of age (V89_13) N=35				
Seroconversion[c] (97.5% CI)	17% (6, 36)	43% (24, 63)	46% (27, 66)	26% (11, 46)	43% (24, 63)
HI Titre ≥1:40 (97.5% CI)	17% (6, 36)	49% (29, 68)	57% (37, 76)	26% (11, 46)	51% (32, 71)
GMR Day 43/Day 1[d]	1.5 (0.9; 2.6)	3.6 (1.6; 8.2)	4.8 (2.3; 10)	2.1 (1.1; 3.8)	4.3 (2.0; 9.2)

[a] FAS: Full Analysis Set, subjects who received at least one study vaccination and provided immunogenicity data at day 1 and day 43
[b] Exploratory objective of Study V89_04 and V89_13
[c] Seroconversion is defined as a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or a pre-vaccination HI titre ≥1:10 and ≥4-fold increase in HI titre.
[d] Geometric mean HI titres on Day 43 compared to Day 1

Using the MicroNeutralisation (MN) assay against the 5 heterologous strains, an at least 4-fold increase from baseline titres at Day 43 was achieved by 32% to 88% of subjects 18 to <65 years of age, and by 26% to 74% of subjects ≥65 years of age. MN GMTs on Day 43 compared to Day 1 increased between 4.8- and 34-fold in subjects 18 to <65 years of age (Study V89_04), and between 3.7- and 12-fold in subjects ≥65 years of age (Study V89_13).

Paediatric population 6 months to less than 18 years old

Immunogenicity data for aH5N1c in children 6 months to 17 years of age was assessed in Study V89_11. Study V89_11 was a randomised, controlled, observer-blind multicentre study conducted in Thailand and the US in children 6 months to less than 18 years of age who received two doses of either 7.5 mcg HA of H5N1 with MF59 per 0.5 mL or 3.75 mcg HA of H5N1 with MF59 per 0.25 mL, 21 days apart.

In total, 577 subjects in the full analysis population received the 7.5 mcg dose (N=329) or 3.75 mcg dose (N=329). The mean age of the subjects was 80.5 months; 53% of the subjects were male. 73% of the participants were Asian, 22% were White, 3% were Black or African American. HI antibody titres against the A/turkey/Turkey/1/2005 (H5N1) strain were evaluated in sera obtained 21 days after the second dose in three age cohorts (6 to <36 months, 3 to <9 years, and 9 to <18 years). The proportion of subjects with seroconversion and an HI titre of

≥1:40 after vaccination was evaluated according to pre-specified criteria. The success criteria for proportion of subjects with seroconversion were that the lower bound of the 2-sided 97.5% CI should be ≥40% and for the proportion of subjects with an HI titre >1:40, the lower bound of the 2-sided 97.5% CI should be ≥70% for all three age cohorts.

In all three age cohorts (6 to <36 months, 3 to <9 years, and 9 to <18 years) the pre- specified criteria for proportion of subjects with seroconversion and an HI titre ≥1:40 were met 21 days after the second vaccination with either the 7.5 mcg or 3.75 mcg dose. Table 6 presents data for the recommended dose (7.5 mcg).

Table 6. Seroconversion Rates, Percentage of Subjects with HI Titres ≥1:40 and Geometric Mean Titre Ratios (GMR) following vaccination with aH5N1c in Study V89_11[a] (FAS[b])

	Overall population	**Age Subgroups**		
	6 months to <18 years	**6 to <36 months**	**3 to <9 years**	**9 to <18 years**
Formulation: 7.5 mcg HA / 100% MF59				
Seroconversion[c] (97.5% CI, overall) (95% CI, subgroups)	96% (**93**-98) N=279	99% (**94**; 100) N=84	98% (**92**; 100) N=93	92% (**85**; 97) N=102
HI Titre ≥1:40 (97.5% CI)	96% (**92**-98) N=287	98% (**92**; 100) N=91	98% (**93**; 100) N=94	92% (**85**; 97) N=102
GMR Day 43/Day 1[d]	262 (190-361) N=279	302 (192-476) N=84	249 (153-404) N=93	186 (105-328) N=102
Formulation: 3.75 mcg HA / 50% MF59[e]				
Seroconversion[c] (97.5% CI) (95% CI, subgroups)	86% (81-90) N=288	94% (87-98) N=85	86% (77-92) N=98	79% (70-86) N=105
HI titre ≥1:40 (97.5% CI)	86% (81-90) N=288	94% (87-98) N=85	86% (77-92) N=98	79% (70-86) N=105
	84	116	73	58

	Overall population	Age Subgroups		
	6 months to <18 years	**6 to <36 months**	**3 to <9 years**	**9 to <18 years**
Formulation: 7.5 mcg HA / 100% MF59				
GMR Day 43/Day 1[d]	(61-116) N=288	(74-181) N=85	(44-121) N=98	(34-101) N=105

[a] NCT01776554

[b] FAS: Full Analysis Set, subjects who received at least one 7.5 mcg dose of aH5N1c.

[c] Seroconversion is defined as a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or a pre-vaccination HI titre ≥1:10 and ≥4-fold increase in HI titre.

[d] Geometric mean HI titres on Day 43 compared to Day 1

[e] The TGA approved dose for adults and children 6 months of age and older is 7.5 mcg HA/100% MF59

Bold shows that the pre-specified criterion was met, i.e., a lower bound of the 2-sided 97.5% confidence interval for seroconversion ≥40% and for the proportion of subjects with an HI titre of ≥1:40 a lower bound of the 2-sided 97.5% confidence interval ≥70%.

The MicroNeutralisation (MN) assay was used to evaluate immunological response against the homologous strain (A/turkey/Turkey/1/2005) in subjects 6 months to <18 years of age (N=69) who received the 7.5 mcg dose in Study V89_11. Using the MN assay an at least 4 fold increase from baseline titres at Day 43 was achieved in 100% of subjects and a 257-fold increase in GMTs was achieved on Day 43 compared to Day 1.

Cross reactivity data in the paediatric population 6 months to less than 18 years of age

Cross-reactive immune response elicited by A/turkey/Turkey/1/2005 (clade 2.2.1)

In subjects 6 months to less than 18 years of age (Study V89_11), immune responses were evaluated against five H5N1 heterologous strains: A/Anhui/1/2005 (clade 2.3.4); A/Egypt/N03072/2010 (clade 2.2.1); A/Hubei/1/2010 (clade 2.3.2); A/Indonesia/5/2005 (clade 2.1.3) and A/Vietnam/1203/2004 (clade 1) three weeks after the second vaccination. HI GMTs on Day 43 increased between 8- and 40-fold compared to Day 1. The percentage of subjects with seroconversion or an HI titre ≥1:40 at Day 43 ranged from 32% to 72% in subjects 6 months to <18 years of age. Table 7 presents data on immune responses against the H5N1 heterologous strains.

Table 7. Seroconversion Rates, Percentage of Subjects with HI Titres ≥1:40 and Geometric Mean Titre Ratios (GMR) following aH5N1c (21 Days after 2 vaccinations) against heterologous H5N1 strains in subjects 6 months to <18 years of age (FAS[a] – Study V89_11)[b]

	Children 6 months to <18 years of age (V89_11) N=69				
	A/Anhui/1/ 2005	**A/Egypt/N03072/ 2010**	**A/Hubei/1/ 2010**	**A/Indonesia/5/ 2005**	**A/Vietnam/1203/ 2004**
Seroconversion[c] (97.5% CI)	32% (20, 46)	72% (59, 84)	54% (40, 67)	36% (24; 50)	54% (40, 68)
HI Titre ≥1:40 (97.5% CI)	32% (20, 46)	72% (59, 84)	54% (40, 67)	36% (24, 50)	54% (40, 68)
GMR Day 43/Day 1[d]	8.4 (4.0; 17)	40 (15; 109)	34 (11; 105)	11 (4.9; 25)	23 (8.5; 60)

[a] FAS: Full Analysis Set, subjects who received at least one study vaccination and provided immunogenicity data at day 1 and day 43
[b] Exploratory objective of Study V89_11
[c] Seroconversion is defined as a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or a pre-vaccination HI titre ≥1:10 and ≥4-fold increase in HI titre.
[d] Geometric mean HI titres on Day 43 compared to Day 1

MN assay results against the 5 heterologous strains showed a substantial percentage of paediatric subjects achieving an at least 4-fold increase in MN titres at Day 43, ranging from 83% to 100%. MN GMTs on Day 43 compared to Day 1 increased between 13- and 160-fold in subjects 6 months to <18 years of age (Study V89_11).

5.2 PHARMACOKINETIC PROPERTIES

Not applicable.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

AUDENZ® has not been evaluated for potential to cause genotoxicity.

Carcinogenicity

AUDENZ® has not been evaluated for potential to cause carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 0.5 mL dose of AUDENZ® also contains the following:

Table 8. List of excipients

Sodium chloride	4.0 milligrams
Potassium chloride	0.10 milligrams
Magnesium chloride hexahydrate	0.05 milligrams
Dibasic sodium phosphate dihydrate	0.646 milligrams
Monobasic potassium phosphate	0.186 milligrams
Water for injections	To 0.5 millilitres

Table 9. Adjuvant

MF59C.1 is a proprietary adjuvant that is composed of the following:

Squalene	9.75 milligrams
Polysorbate 80	1.175 milligrams
Sorbitan trioleate	1.175 milligrams
Sodium citrate dihydrate	0.66 milligrams
Citric acid monohydrate	0.04 milligrams

AUDENZ® may contain traces of propiolactone, cetrimonium bromide and polysorbate 80 as residues of the manufacturing process.

6.2 INCOMPATIBILITIES

AUDENZ® must not be mixed with other products.

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

AUST R 446671

Pre-filled syringe

Each pre-filled syringe contains 1 dose of 0.5 mL suspension for injection in a needle-free Type 1 glass syringe with a Plastic Rigid Tip Cap (PRTC) and closed with a Bromobutyl plunger stopper. The syringe and all associated syringe components do not contain natural rubber latex.

Pack size of 10 pre-filled syringes.

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)

Prescription Only Medicine (S4)

8 SPONSOR

Seqirus Pty Ltd
ABN 26 160 735 035
63 Poplar Road
Parkville, VIC 3052
Australia
Telephone: +61 3 9389 2000

Website: www.cslseqirus.com.au

9 DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods – *to be included following TGA approval.*

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	Initial registration