

NAME OF THE MEDICINE

CSL H1N1 Pandemic Influenza Vaccine
Pandemic influenza vaccine (H1N1) (split virion, inactivated).

DESCRIPTION

CSL H1N1 Pandemic Influenza Vaccine is a purified, inactivated, monovalent, split virion (split virus) vaccine containing antigen of the following type:

A/California/7/2009 (H1N1) (A/California/7/2009 (H1N1)v-like)
7.5 µg haemagglutinin (HA) per 0.25 mL dose
15 µg HA per 0.5 mL dose

Each 0.5 mL dose contains, nominally: sodium chloride 4.1 mg, sodium phosphate – dibasic anhydrous 0.3 mg, sodium phosphate – monobasic 0.08 mg, potassium chloride 0.02 mg, potassium phosphate – monobasic 0.02 mg, calcium chloride 1.5 µg and thiomersal 50 µg. Each 0.25 mL dose contains half of these quantities.

The following are also present in each 0.5 mL dose: sodium taurodeoxycholate ≤ 5 µg, ovalbumin ≤ 1.0 µg, sucrose < 10 µg, neomycin ≤ 0.7 ng, polymyxin B sulfate ≤ 0.11 ng and beta-propiolactone ≤ 1.4 ng.

The virus strain in this vaccine complies with the World Health Organization recommendation for the influenza A(H1N1) vaccine.

CSL H1N1 Pandemic Influenza Vaccine is prepared from influenza virus propagated in the allantoic fluid of embryonated chicken eggs. The virus is harvested from the eggs, purified by zonal centrifugation, inactivated with beta-propiolactone and disrupted with sodium taurodeoxycholate to produce split virion particles.

PHARMACOLOGY

Immunisation with inactivated influenza vaccines has been shown to induce antibodies to the viral surface glycoproteins, haemagglutinin and neuraminidase. These antibodies are important in the prevention of natural infection.

CLINICAL TRIALS

Clinical trials are being conducted to assess the immunogenicity and safety of the vaccine in healthy children and adults. Additionally, these trials will inform the dose and vaccination schedule for the vaccine. These studies are ongoing; however preliminary data in adults and children show that a single dose of vaccine is sufficient to elicit a protective antibody response.

Adults

A total of 240 participants, aged ≥ 18 to < 65 years, were randomised to receive either a 15 μg or 30 μg HA dose. The serum antibody response after the first vaccine dose was assessed by the haemagglutination inhibition (HI) and viral microneutralisation (MN) assays. Similar immunogenicity results were observed for both antigen doses showing that the vaccine elicits a satisfactory immune response in a large proportion of participants. Results are provided for the 15 μg HA antigen dose, with $> 96\%$ of participants by HI (Table 1a) and $> 89\%$ of participants by MN (Table 1b) achieving seroprotective antibody titres of ≥ 40 .

Table 1a: Immunogenicity Results for Adult Population (HI assay)

Serum HI antibody	15 μg HA dose n=120 (95% CI)
Fold increase in GMT ^a	10.6 (7.9, 14.2)
Seroconversion or significant increase ^b	70.8% (61.8, 78.8)
Proportion with HI ≥ 40	96.7% (91.7, 99.1)

^a Fold increase in GMT (geometric mean titre) is the fold increase in antibody titre over the pre-vaccination GMT. ^b 'Seroconversion' is defined as the number of participants with a pre-vaccination titre of $< 1:10$ achieving a post-vaccination titre value of at least 40 and 'significant increase' is defined as the number of participants with a pre-vaccination titre of $\geq 1:10$ achieving at least a four fold increase over the pre-vaccination titre.

Table 1b: Immunogenicity Results for Adult Population (MN assay)

Serum HI antibody	15 μg HA dose n=120 (95% CI)
Fold increase in GMT ^a	24.3 (17.2, 34.3)
Seroconversion or significant increase ^b	74.2% (65.4, 81.7)
Proportion with MN ≥ 40	89.2% (82.2, 94.1)

^a Fold increase in GMT (geometric mean titre) is the fold increase in antibody titre over the pre-vaccination GMT. ^b 'Seroconversion' is defined as the number of participants with a pre-vaccination titre of $< 1:10$ achieving a post-vaccination titre of at least 40 and 'significant increase' is defined as the number of participants with a pre-vaccination titre of $\geq 1:10$ achieving at least a four fold increase over the pre-vaccination titre.

Children

In a placebo-controlled clinical trial conducted in children, aged ≥ 6 months to < 9 years, a total of 473 participants were randomised to receive two doses of either a 7.5 μg or 15 μg HA antigen dose of vaccine, or placebo. Participants were further stratified into two age groups: Group A, ≥ 6 months to < 3 years, and Group B, ≥ 3 years to < 9 years.

After the first vaccine dose, immunogenicity results (by HI) were comparable across the age groups and antigen doses, showing that a single vaccine dose elicits a satisfactory immune response in a large proportion of participants. Results are provided for the 7.5 μg HA antigen dose for Group A and for the 15 μg HA antigen dose for Group B, as these are the dosages to be administered. More than 88% of

Group A participants and > 91% of Group B participants achieved seroprotective antibody titres of ≥ 40 (Table 2).

Table 2: Immunogenicity Results for Paediatric Population (HI assay) After a Single Vaccine Dose

Serum HI antibody	Group A ≥ 6 mths to < 3 yrs (95% CI)		Group B ≥ 3 yrs to < 9 yrs (95% CI)	
	Placebo n = 25	7.5 μ g HA dose n = 102	Placebo n = 27	15 μ g HA dose n = 102
Fold increase in GMT ^a	1.3 (0.9, 1.7)	13.6 (11.5, 16.0)	1.1 (0.9, 1.5)	17.2 (13.9, 21.4)
Seroconversion or significant increase ^b	8.0% (1.0, 26.0)	87.3% (79.2, 93.0)	3.7% (0.1, 19.0)	89.2% (81.5, 94.5)
Proportion with HI ≥ 40	12.0% (2.5, 31.2)	88.2% (80.4, 93.8)	22.2% (8.6, 42.3)	91.2% (83.9, 95.9)

^a Fold increase in GMT (geometric mean titre) is the fold increase in antibody titre over the pre-vaccination GMT. ^b 'Seroconversion' is defined as the number of participants with a pre-vaccination titre of < 1:10 achieving a post-vaccination titre value of at least 40 and 'significant increase' is defined as the number of participants with a pre-vaccination titre of $\geq 1:10$ achieving at least a four fold increase over the pre-vaccination titre.

INDICATIONS

For active immunisation to prevent influenza disease caused by the influenza A(H1N1) virus in persons from 6 months of age.

CONTRAINDICATIONS

Anaphylactic hypersensitivity to previous influenza vaccination, or to eggs, thiomersal (for thiomersal-containing vaccine only), neomycin, polymyxin B sulfate or any of the constituents or trace residues (see Description section) of this vaccine.

Immunisation must be postponed in people who have febrile illness or acute infection.

PRECAUTIONS

As with all injectable vaccines, appropriate medical treatment and supervision should always be available to manage the rare event of an anaphylactic reaction following administration of the vaccine.

Minor illness, with or without fever, should not contraindicate the use of influenza vaccine.

In immunocompromised patients, the antibody response may be lower.

If Guillain-Barré syndrome has occurred within six weeks of previous influenza vaccination, the decision to give H1N1 Pandemic Influenza Vaccine should be based on careful consideration of the potential benefits and risks.

Use in pregnancy: (Category B2)

The safety profile of CSL H1N1 Pandemic Influenza Vaccine in pregnant women is unknown. An animal reproduction study conducted with CSL's seasonal influenza vaccine did not demonstrate any maternal or developmental toxicity. Healthcare professionals should assess the potential benefits and risks of administering CSL H1N1 Pandemic Influenza Vaccine to pregnant women on a case by case basis, taking into account Health Authorities' recommendations.

Use in lactation:

The safety profile of the vaccine in lactating women is unknown. Healthcare professionals should assess the potential benefits and risks of administering CSL H1N1 Pandemic Influenza Vaccine to lactating women on a case by case basis, taking into account Health Authorities' recommendations.

Paediatric use:

There are no clinical data for children under 6 months of age.

Interactions with other medicines:

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

There are no data to assess the concomitant administration of CSL H1N1 Pandemic Influenza Vaccine with other vaccines. If the vaccine is to be given at the same time as another injectable vaccine, the vaccines should be administered at different injection sites.

ADVERSE EFFECTS

Clinical Trial (Adults):

Clinical data show CSL H1N1 Pandemic Influenza Vaccine is safe and well tolerated in adults, ≥ 18 to < 65 years of age. A total of 240 participants were administered a single dose of vaccine containing 15 μg or 30 μg HA. Data for solicited local and systemic and unsolicited adverse events for the 15 μg HA antigen dose are presented as this is the dosage to be administered.

The most common solicited local (injection-site) adverse events observed within 7 days of administration of the vaccine were injection-site tenderness, pain and induration, with the majority of reactions of mild intensity and self-limiting. The most common solicited systemic adverse reactions were headache, myalgia and malaise, with the majority of these events mild to moderate in intensity and similarly self-limiting (Table 3).

In addition, headache was identified as the most common unsolicited adverse event, reported in 11.7 % of participants. Other unsolicited adverse events, reported by more than 2 % of participants, were back pain, arthralgia, seasonal allergy, cough, oropharyngeal pain, nasal congestion, diarrhoea and toothache. There were no reports of serious adverse events.

Table 3: Proportion of Adult Participants with Solicited Local and Systemic Adverse Events within 7 Days of Administration of CSL H1N1 Pandemic Influenza Vaccine, Irrespective of Causality

Solicited Adverse Event	Proportion of Participants (%) Adults (n = 120) (≥ 18 to < 65 years)
Local (injection-site)	
Tenderness	30.8
Pain	20.8
Induration	10.0
Ecchymosis	5.0
Erythema	0.8
Systemic	
Headache	25.8
Myalgia	15.8
Malaise	11.7
Fever	5.8
Nausea	5.8
Chills	0.8
Vomiting	0

Clinical Trial (Children):

Preliminary clinical data show that CSL H1N1 Pandemic Influenza Vaccine is well tolerated in children, ≥ 6 months to < 9 years of age. In the placebo-controlled trial, 473 participants were administered a single 7.5 µg or 15 µg HA dose of vaccine, or placebo, and were stratified according to age at the date of vaccination: Group A (≥ 6 months to < 3 years) or Group B (≥ 3 years to < 9 years). Data were similar across the antigen doses for each age group. Preliminary results are provided for solicited local and systemic adverse events for the 7.5 µg HA antigen dose for Group A, and for the 15 µg HA antigen dose for Group B, as these are the dosages to be administered.

There were no reports of serious adverse events related to the vaccine. The most common solicited local (injection-site) adverse events observed within 7 days of administration of the vaccine were injection-site pain and erythema, with the majority of reactions of mild intensity and short-lived. The most common solicited systemic adverse reactions for the younger age group (Group A) were irritability, diarrhoea and fever (Table 4). The most common solicited systemic adverse reactions for the older age group, Group B, were headache, fever and malaise (Table 5). The majority of all solicited systemic adverse events were similarly mild in intensity and short-lived.

Table 4: Proportion of Paediatric Participants with Solicited Local and Systemic Adverse Events within 7 Days of Administration of CSL H1N1 Pandemic Influenza Vaccine, Irrespective of Causality (Group A, ≥ 6 months to < 3 years)

Solicited Adverse Event	Proportion of Participants (%) Group A ≥ 6 mths to < 3 years	
	Placebo n = 24	7.5 µg HA dose n = 103
Local (injection-site)		
Pain	29.2	30.1
Erythema	16.7	27.2
Induration	8.3	17.5
Systemic		
Irritability	8.3	40.8
Diarrhoea	33.3	24.3
Fever	8.3	21.4
Loss of appetite	4.2	12.6
Nausea / Vomiting	4.2	5.8

Table 5: Proportion of Paediatric Participants with Solicited Local and Systemic Adverse Events within 7 Days of Administration of CSL H1N1 Pandemic Influenza Vaccine, Irrespective of Causality (Group B, ≥ 3 years to < 9 years)

Solicited Adverse Event	Proportion of Participants (%) Group B ≥ 3 to < 9 years	
	Placebo n = 27	15 µg HA dose n = 108
Local (injection-site)		
Pain	18.5	34.3
Erythema	22.2	24.1
Induration	7.4	13.9
Systemic		
Headache	14.8	23.1
Fever	14.8	16.7
Malaise	18.5	16.7
Myalgia	18.5	16.7
Diarrhoea	22.2	7.4
Nausea / Vomiting	7.4	7.4

Post-marketing surveillance:

Post-marketing data for CSLH1N1 Pandemic Influenza Vaccine are limited and have not identified any new safety concerns. It is anticipated that the adverse events after vaccination will be similar to those spontaneously reported during post-approval use of CSL's seasonal influenza vaccine. The adverse events reported are presented below according to System Organ Class and frequency. These data reflect experience in children and adults with seasonal influenza vaccine.

Adverse event frequencies are defined as follows:

Very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10\ 000$ and $< 1/1000$) and very rare ($< 1/10\ 000$).

Blood and Lymphatic System Disorders

Rare: Transient thrombocytopenia

Immune System Disorders

Rare: Allergic reactions including anaphylactic shock

Nervous System Disorders

Rare: Neuralgia, paraesthesia and convulsions

Very rare: Encephalitis, neuritis or neuropathy and Guillain-Barré syndrome

Vascular Disorders

Very rare: Vasculitis with transient renal involvement

Skin and Subcutaneous Tissue Disorders

Uncommon: Pruritus, urticaria and rash

General Disorders and Administration Site Conditions

These reactions usually resolve within 1-2 days without treatment.

Very common:	Injection site inflammation Influenza-like illness (for thiomersal-containing vaccine only)
Common:	Injection site ecchymosis and induration Influenza-like illness (for thiomersal-free vaccine only)

Influenza-like illness may include pyrexia, chills, headache, malaise and myalgia.

DOSAGE AND ADMINISTRATION

Dosage:

Children 6 months to 35 months:	0.25 mL dose (7.5 µg HA)
Adults and children from 36 months:	0.5 mL dose (15 µg HA)

Children from 6 months to less than 10 years should receive two doses of vaccine, with the second dose given after an interval of at least 4 weeks.

Adults, adolescents and children 10 years of age and older should receive a single dose.

Administration:

The vaccine should be administered by intramuscular or deep subcutaneous injection.

It is important that the contents of the container be shaken thoroughly immediately before use. The vaccine should appear as a clear to slightly opaque liquid with some sediment that resuspends upon shaking.

For the multi-dose vials, the conditions for use are:

- the vaccine is stored at 2 - 8°C prior to and immediately after each use
- the vaccine is protected from light during storage
- the vaccine in the vial must be used **within 24 hours** once the stopper has been pierced
- the stopper is to be pierced no more than 18 times to ensure stopper integrity
- aseptic technique must be used to withdraw each dose, using a separate sterile needle and syringe
- following withdrawal of vaccine from the vial, the syringe must be used within the one vaccination session (up to a maximum time interval of 4 hours) and cannot be stored for use at a later date
- at the end of the 24 hour period, any remaining contents within the vials should be discarded in accordance with local requirements.

Ensuring the conditions for vial use are maintained is the responsibility of the healthcare professional administering the vaccine.

OVERDOSAGE

There is no specific information on overdose of CSL H1N1 Pandemic Influenza Vaccine.

PRESENTATION AND STORAGE CONDITIONS

Presentations:

CSL H1N1 Pandemic Influenza Vaccine is provided in a multi-dose vial presentation. Thiomersal is added as a preservative; each 0.5 mL dose contains 50 µg of thiomersal.

Each multi-dose vial contains a nominal 5 mL of vaccine and is closed with a latex-free stopper and sealed with an aluminium crimp seal. The aluminium seal has a plastic tear-away cap attached that is removed to gain access to the vial closure. The cap is present to protect the vial closure and to indicate if the vial has been tampered with. Once removed, the cap cannot be re-affixed to the vial. The sealed units are packed into a cardboard carton.

Pack size is 10 vials.

Storage Conditions:

CSL H1N1 Pandemic Influenza Vaccine should be stored, protected from light, at 2°C to 8°C. IT MUST NOT BE FROZEN.

The shelf life of the vaccine is 12 months when stored at 2°C to 8°C. The expiry date is indicated on the container label.

PREQUALIFICATION HOLDER

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VICTORIA 3052 AUSTRALIA

PREQUALIFICATION AUTHORISATION NUMBER(S)

XXXXX

DATE OF FIRST PREQUALIFICATION AUTHORISATION

01/12/2009

DATE OF REVISION OF THE TEXT

XX/XX/XXXX