133 Molesworth St
PO Box 5013
Wellington 6145
New Zealand
T+64 4 496 2000

[redacted]

Ref: H201806800

Dear [redacted]

Response to your request for official information

I write further to your request to the Ministry of Health of 5 October 2018 under the Official Information Act 1982 (the Act) for:

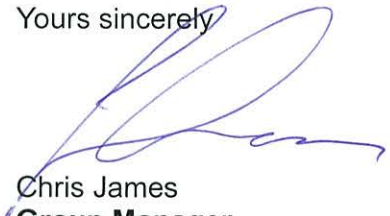
> *"Can I have copies of the original professional product information sheets and all iterations/updates since for all pandemic flu vaccines approved for use in New Zealand in the event of a pandemic?"*

The information covered by your request is itemised in the table below, and attached. I trust this information fulfils your request.

Vaccine	Date/Update
Celvapan H1N1 TT50-8404	28 January 2010
Panvax H1N1 vaccine TT50-7970	17 February 2010
Pandemic Influenza Vaccine H5N1 Baxter TT50-8146	20 July 2010
	15 December 2011
	14 August 2012
	16 July 2012
	28 May 2014
Pandemrix 3.75mcg H5N1 TT50-8267	28 October 2011
	13 March 2014
	26 March 2015
	16 May 2018
Panvax H5N1 vaccine TT50-7970-1	1 September 2008
	9 February 2011
	28 March 2014
Vepacel TT50-9096	9 July 2013
	1 May 2017

Please note this response (with your personal details removed) may be published on the Medsafe website.

Yours sincerely



Chris James
Group Manager
Medsafe

CELVAPAN

Pandemic influenza vaccine (whole virion, Vero cell derived, inactivated) suspension for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

Whole virion influenza vaccine, inactivated containing antigen of pandemic strain*:
A/California/07/2009 (H1N1) 7.5 micrograms** per 0.5 mL dose.

* propagated in Vero cells (continuous cell line of mammalian origin)
** expressed in micrograms haemagglutinin.

This vaccine complies with the WHO recommendation and EU decision for the pandemic.

This is a multidose container. See *Nature and Contents of the Container* for the number of doses per vial.

For a full list of excipients, see *List of Excipients*.

PHARMACEUTICAL FORM

Suspension for injection.
The vaccine is an off-white, opalescent, translucent suspension.

CLINICAL PARTICULARS

Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance.

Posology and method of administration

This pandemic influenza vaccine H1N1 has been authorised based on data obtained with a version containing H5N1 antigen supplemented with data obtained with the vaccine containing H1N1 antigen. The Clinical Particulars section will be updated in accordance with emerging additional data.

From clinical studies limited safety data are available for Celvapan (H1N1) in healthy adult and elderly subjects and in children (see *Special Warnings and Precautions for Use* and *Undesirable Effects*.).

The decision to use CELVAPAN (H1N1) in each age group defined below should take into account the extent of the clinical data available with a version of the vaccine

containing H5N1 antigen and the disease characteristics of the current influenza pandemic.

The dose recommendations are based on the available safety and immunogenicity data from clinical trials with CELVAPAN (adults, elderly and children and adolescents) and H5N1 (A/Vietnam/1203/2004; adults and elderly) where two doses of vaccine containing 7.5µg HA of either H1N1 or H5N1 were administered 21 days apart.

See *Special Warnings and Precautions for Use*, *Undesirable Effects* and *Pharmacodynamic Properties*.

Posology

Adults and elderly

One dose of 0.5 ml at an elected date.
A second dose of vaccine should be given after an interval of at least three weeks.

Children and adolescents aged 9 to 17 years of age

One dose of 0.5 ml at an elected date.
A second dose of vaccine should be given after an interval of at least three weeks.

Children aged 6 months to 8 years of age

Limited data are available in children 6 months to 8 years of age. Should vaccination be considered necessary, the experience with similarly constructed vaccines suggests that dosing in accordance with the adult dose may be appropriate.

The dosing used should take into account the extent of data and disease characteristics of the current influenza pandemic. Preliminary analysis of immunogenicity data from one clinical trial in children aged 6 months to 17 years suggests that an adequate immune response is achieved in this age group.

Children aged less than 6 months

Vaccination is not currently recommended in this age group.

For further information, see *Undesirable Effects* and *Pharmacodynamic Properties*.

It is recommended that subjects who receive a first dose of CELVAPAN, complete the vaccination course with CELVAPAN (see *Special Warnings and Precautions for Use*).

Method of administration

Immunisation should be carried out by intramuscular injection preferably into the deltoid muscle or anterolateral thigh, depending on the muscle mass.

Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (e.g. formaldehyde, benzonase, sucrose) of this vaccine. However, if vaccination is considered necessary, it may be appropriate to give the vaccine, provided that facilities for resuscitation are immediately available in case of need.

See *Special Warnings and Precautions for Use*.

Special warnings and precautions for use

Caution is needed when administrating this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance(s), to any of the excipients and to trace residues e.g. formaldehyde, benzonase, or sucrose.

Hypersensitivity reactions, including anaphylaxis, have been reported following vaccination with Baxter's H5N1 vaccine (see *Undesirable Effects*). Such reactions have occurred both in patients with a history of multiple allergies and in patients with no known allergy.

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.

If the pandemic situation allows, immunisation shall be postponed in patients with severe febrile illness or acute infection.

CELVAPAN should under no circumstances be administered intravascularly.

There are no data with CELVAPAN using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleedings.

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

A protective response may not be induced in all vaccinees (see *Pharmacodynamic Properties*).

There are no safety, immunogenicity or efficacy data to support interchangeability of CELVAPAN with other H1N1 pandemic vaccines.

Interactions with other medicinal products and other forms of interaction

There are no data on co-administration of CELVAPAN with other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

Following influenza vaccination, published literature have reported 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.

Pregnancy and lactation

The safety of CELVAPAN in pregnancy and lactation has not been assessed in clinical trials. Animal studies with H5N1 strain vaccines (A/Vietnam/1203/2004 and A/Indonesia/05/2005) do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/fetal development, parturition or post-natal development (see *Preclinical Safety Data*). Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing CELVAPAN.

(see *Preclinical Safety Data*).

The use of CELVAPAN may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations.

Effects on ability to drive and use machines

Some undesirable effects such as dizziness and vertigo may affect the ability to drive or use machines.

Undesirable effects

- Clinical trials with H5N1 mock-up vaccine

In clinical trials with the mock-up vaccine using an H5N1 vaccine strain (see *Pharmacodynamic Properties*) in 3576 subjects (3116 between 18 and 59 years old, and 460 aged 60 and above), the following adverse reactions were assessed as at least possibly related by the investigator. Most of the reactions were mild in nature, of short duration and qualitatively similar to those induced by influenza vaccines. There were fewer reactions after the second dose of the vaccine compared with the first dose. The most frequently occurring adverse reaction was injection site pain, which was usually mild.

Adverse reactions from clinical trials with the mock-up vaccine are listed below (see *Pharmacodynamic Properties* for more information on mock-up vaccines).

Adverse reactions are listed according to the following frequency.
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000).
Not known (cannot be estimated from the available data)

Infections and infestations
Common: nasopharyngitis

Blood and the lymphatic system disorders
Uncommon: lymphadenopathy

Psychiatric disorders
Uncommon: insomnia, restlessness

Nervous system disorders
Common: headache, dizziness
Uncommon: somnolence, dysaesthesia, paresthesia

Eye disorders
Uncommon: conjunctivitis

Ear and labyrinth disorders
Common: vertigo
Uncommon: sudden hearing loss
Rare: ear pain

Vascular disorders
Uncommon: hypotension

Respiratory, thoracic and mediastinal disorders
Common: pharyngolaryngeal pain
Uncommon: dyspnoea, cough, rhinorrhoea, nasal congestion, dry throat

Gastrointestinal disorders
Uncommon: gastro-intestinal symptoms (such as nausea, vomiting, diarrhoea and upper abdominal pain)

Skin and subcutaneous tissue disorders
Common: hyperhidrosis
Uncommon: rash, pruritus, urticaria

Musculoskeletal and connective tissue disorders
Common: arthralgia, myalgia

General disorders and administration site conditions
Very common: injection site pain
Common: pyrexia, chills, fatigue, malaise, induration, erythema, swelling and haemorrhage at the injection site
Uncommon: injection site irritation
Rare: injection site movement impairment

- Clinical Trials with CELVAPAN (H1N1)

Limited preliminary safety data after the first and second dose from clinical trials in adults aged over 18 years (N=408) and after the first dose in children aged from 9 to 17 years (N=101), 3 to 8 years (N=100) and 6 to 35 months (N=96) investigating two different dose levels (3.75µg or 7.5µg) of CELVAPAN H1N1 suggest a comparable safety profile with that reported for the influenza vaccines using a H5N1 strain.

Post-marketing surveillance

CELVAPAN H1N1

The following additional adverse reactions have been reported in the post-marketing experience in adults and children receiving CELVAPAN H1N1.

The frequency of these adverse reactions is not known.

Immune system disorder:
Anaphylactic reaction*, Hypersensitivity*

*Such reactions have been manifested by respiratory distress, hypotension, tachycardia, tachypnea, cyanosis, pyrexia, flushing, angioedema, and urticaria

Nervous system disorders:
Convulsion

Skin and subcutaneous tissue disorders:
Angioedema

Musculoskeletal and connective tissue disorders:
Pain in extremity

General disorders and administration site conditions
Influenza-like illness

Interpandemic trivalent vaccines

From post-marketing surveillance with other manufacturers' egg-derived interpandemic trivalent vaccines, the following serious adverse reactions have been reported:

Uncommon:
Generalised skin reactions
Rare:
Neuralgia, paraesthesia, convulsions, transient thrombocytopenia.
Allergic reactions, in rare cases leading to shock, have been reported.

Very rare:
Vasculitis with transient renal involvement.
Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

Overdose

No case of overdose has been reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This section describes the clinical experience with the mock-up vaccine using a H5N1 strain (adults and elderly) following a two-dose administration and with CELVAPAN H1N1 (adults, elderly, children and adolescents) following a two-dose administration. The children and adolescent data are only available after the first dose at this time.

Mock-up 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 mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Immune response against CELVAPAN H1N1

In a clinical study in adults aged 18 – 59 years (N=100) and elderly subjects aged 60 years and above (N=101) investigating the immunogenicity of the vaccine containing 7.5 mcg non-adjuvanted HA derived from strain A/California/07/2009 (H1N1) the seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody as measured by hemagglutination inhibition (HI) were as follows:

HI Assay	21 Days After 1st Dose			
	Total enrolled subjects		Seronegative subjects prior to vaccination	
	18 – 59 years (N=100)	60 years and above (N=101)	18 – 59 years (N=4)	60 years and above (N=4)
Seroprotection rate*	85.0%	72.3%	50.0%	75.0%
Seroconversion rate**	63.0%	33.7%	50.0%	75.0%
Seroconversion factor***	5.6	2.5	6.7	8.0

* HI titer ≥ 40

** ≥ 4-fold increase in HI titer or a reciprocal HI titer ≥ 40 when there is no detectable titer at baseline

*** geometric mean increase

HI Assay	21 Days After 2nd Dose			
	Total enrolled subjects		Seronegative subjects prior to vaccination	
	18 – 59 years (N=99)	60 years and above (N=101)	18 – 59 years (N=12)	60 years and above (N=7)
Seroprotection rate*	93.9%	87.1%	91.7%	71.4%
Seroconversion rate**	66.7%	43.6%	91.7%	71.4%
Seroconversion factor***	7.6	3.3	28.5	13.1

* HI titer ≥ 40

** ≥ 4-fold increase in HI titer or a reciprocal HI titer ≥ 40 when there is no detectable titer at baseline

*** geometric mean increase

After the first vaccination the rate of subjects with neutralizing antibody titers ≥ 40, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

MN Assay	21 Days After 1st Dose			
	Total enrolled subjects		Seronegative subjects prior to vaccination	
	18 – 59 years (N=100)	60 years and above (N=101)	18 – 59 years (N=39)	60 years and above (N=34)
Seroneutralization rate*	87.0%	70.3%	74.4%	55.9%
Seroconversion rate**	80.0%	55.4%	84.6%	73.5%
Seroconversion factor***	21.3	5.0	28.8	7.1

* MN titer ≥ 40

** ≥ 4-fold increase in MN titer or a reciprocal MN titer ≥ 40 when there is no detectable titer at baseline

*** geometric mean increase

In a clinical study in children and adolescents aged 9 – 17 years (N=52) investigating the immunogenicity of the vaccine containing 7.5 mcg non-adjuvanted HA derived from strain A/California/07/2009 (H1N1) the seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody as measured by hemagglutination inhibition (HI) were as follows:

HI Assay	21 Days After 1st Dose	
	Total enrolled subjects	Seronegative subjects prior to vaccination
	9 – 17 years (N=52)	9 – 17 years (N=3)
Seroprotection rate*	88.5%	66.7%
Seroconversion rate**	78.8%	66.7%
Seroconversion factor***	7.4	25.4

* HI titer ≥ 40

** ≥ 4-fold increase in HI titer or a reciprocal HI titer ≥ 40 when there is no detectable titer at baseline

*** geometric mean increase

Immune response against the vaccine strain H5N1 A/Vietnam/1203/2004

The immunogenicity of the 7.5 µg non-adjuvanted formulation of CELVAPAN (strain A/Vietnam/1203/2004) has been evaluated in two clinical studies in adults aged 18 – 59 years (N=312) and in elderly subjects aged 60 years and older (N=272) following a 0, 21 day schedule.
After primary vaccination the seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody as measured by single radial haemolysis (SRH) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

SRH Assay	18 – 59 years 21 Days After		60 years and above 21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroprotection rate*	55.5%	65.4%	57.9%	67.7%
Seroconversion rate**	51.3%	62.1%	52.4%	62.4%
Seroconversion factor***	3.7	4.8	3.6	4.6

* SRH area ≥ 25 mm²

** either SRH area ≥ 25 mm^2 if baseline sample negative or 50% increase in SRH area if baseline sample >4 mm²

*** geometric mean increase

After primary vaccination the rate of subjects with neutralizing antibody titres > 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

Microneutralisation assay	18 – 59 years		60 years and above	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	49.4%	73.0%	54.4%	74.1%
Seroconversion rate**	39.1%	61.9%	14.3%	26.7%
Seroconversion factor***	3.4	4.7	2.1	2.8

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Cross-reactive Immune Response Against Related H5N1 Strains

In the phase 3 study in adults (N=265) and elderly subjects (N=270) after vaccination with the A/Vietnam/1203/2004 strain vaccine the rate of subjects with cross-neutralising antibodies as measured by MN (titre > 20) was as follows:

	18 – 59 years		60 years and above	
	Day 42 [a]	Day 180	Day 42 [a]	Day 180
Tested against	Strain A/Indonesia/05/2005			
Seroneutralisation rate*	35.1%	14.4%	54.8%	28.0%

* MN titre ≥ 20
a 21 days after 2nd dose

In a dose-finding study in adults aged 18 – 45 years investigating various dose levels of adjuvanted and non-adjuvanted formulations of the A/Vietnam/1203/2004 strain vaccine the rates of subjects with neutralising antibody titres > 20, seroconversion rates and seroconversion factor for cross-neutralising antibodies as measured by MN in subjects who received the 7.5 µg non-adjuvanted formulation (N=42) were as follows:

Tested against	Strain A/Indonesia/05/2005	
	Day 42 [a]	Day 180
Seroneutralisation rate*	45.2%	33.3%
Seroconversion rate**	31.0%	21.4%
Seroconversion factor***	3.2	2.5

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase
a 21 days after 2nd dose

Antibody Persistence and Booster Vaccination with Homologous and Heterologous Vaccine Strains

Antibody persistence after vaccination with the 7.5 µg non-adjuvanted formulation of CELVAPAN (strain A/Vietnam/1203/2004) has been evaluated in two clinical studies in adults aged 18 – 59 years (N=285) and in one clinical study in elderly subjects aged 60 years and above (N=258) up to 6 months after the start of the primary vaccination series. The results indicate an overall decline in antibody levels over time. Data on later time points (months 12 and 24) are not yet available.

Seroprotection*/	18 – 59 years		60 years and above	
Seroneutralisation rate**	SRH Assay	MN Assay	SRH Assay	MN Assay
Month 6	28.1%	37.9%	26.7%	40.5%

* SRH area $\geq$ 25 mm²
** MN titre $\geq$ 20

To date a booster vaccination with homologous and heterologous vaccine strains has been administered in the phase 3 study 6 months after primary vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine. Two dose levels (3.75 µg and 7.5 µg) of both the A/Vietnam/1203/2004 and A/Indonesia/05/2005 strain vaccines were investigated for the booster vaccination.

Seroprotective titres as determined by SRH assay against the homologous vaccine strain (A/Vietnam/1203/2004) were observed in 65.5% of subjects aged 18 – 59 years and in 59.4% of subjects aged 60 years and older at 21 days after a booster vaccination with the 7.5 µg dose of the A/Vietnam strain vaccine. Twenty-one days after a booster vaccination with the 7.5 µg dose of the A/Indonesia/05/2005 strain vaccine a cross reactive response against the A/Vietnam strain was obtained in 69.0% of subjects aged 18 – 59 years and in 40.6% of subjects aged 60 years and older.

Antibody responses as measured by MN 21 days after the booster vaccination were generally slightly higher with the A/Indonesia/05/2005 than with the A/Vietnam/1203/2004 strain vaccine. Seroneutralisation rates (MN titre > 20) at 21 days after a booster vaccination with the 7.5 µg dose of the A/Vietnam and A/Indonesia vaccines, tested against both the homologous and heterologous strains were as follows:

6-Month Booster	18 – 59 years		60 years and above	
	Vaccination with 7.5 µg strain A/Vietnam			
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
Seroneutralisation rate*	86.2%	65.5%	64.5%	54.8%
	Vaccination with 7.5 µg strain A/Indonesia			
Seroneutralisation rate*	86.2%	93.1%	65.6%	71.9%

* MN titer $\geq$ 1:20

Another study investigated a booster vaccination with 7.5 µg of the heterologous A/Indonesia/05/2005 vaccine strain administered 12 – 15 months after an initial 2-dose priming with various dose levels of adjuvanted and non-adjuvanted formulations of the A/Vietnam/1203/2004 strain vaccine in subjects aged 18 – 45 years. In subjects who received the 7.5 µg non-adjuvanted formulation for primary vaccination (N = 12) seroprotection rates as measured by SRH 21 days after the booster vaccination were 66.7% and 83.3%, and 100% and 91.7% of subjects achieved neutralising antibody titres > 20 when tested against the homologous A/Indonesia and the heterologous A/Vietnam strain, respectively.

No H5N1 clinical data have been generated in subjects below 18 years of age.

Information from non-clinical studies:

Baxter has produced an inactivated A/H1N1 wild-type whole virus candidate vaccine based on the A/California/07/2009 H1N1 influenza virus strain at 100 L GMP fermentation scale.
The immunogenicity of this pandemic A/H1N1 candidate vaccine, produced according to the final large scale GMP process established previously for H5N1 candidate vaccines, has been evaluated in a dose-response study in mice. Groups of ten female CD1 mice were immunized subcutaneously, twice, three weeks apart with one of six doses of pandemic H1N1 candidate vaccine (ranging from 3.75µg to 0.0012µg haemagglutinin). The pandemic H1N1 candidate vaccine was shown to be immunogenic in mice using the haemagglutination inhibition assay (HI) inducing titers up to 160 three weeks after the primary immunization and up to 5120 three weeks after the second dose.. A clear dose response was seen even after a single immunization and the anti-H1N1 antibody response was boosted further by a second immunization given three weeks after the first immunization. The effective dose 50% (that is, the dose inducing an HIA titre of at least 1:40 in half of the immunized mice) was found to be 300 ng for a single immunization and 7 ng for sera collected two weeks after a second immunization.

The protective efficacy of the mock-up vaccine using an H5N1 strain against morbidity and mortality induced by the infection with lethal doses of highly pathogenic avian Influenza H5N1 virus was assessed non-clinically in a ferret challenge model. Two studies have been performed using either the H5N1 A/Vietnam/1203/2004 or the A/Indonesia/05/2005 vaccine.

In one study, sixteen ferrets were divided into two cohorts and were vaccinated on days 0 and 21 with 7.5 µg of the A/Vietnam/1203/2004 vaccine or were sham vaccinated. All ferrets were challenged intranasally on day 35 with a high dose of the highly virulent H5N1 virus strain A/Vietnam/1203/2004 and monitored for 14 days. Ferrets vaccinated with the 7.5 µg dose of the A/Vietnam/1203/2004 vaccine demonstrated a high rate of seroconversion. The A/Vietnam/1203/2004 vaccine afforded protection against homologous challenge as evidenced by full survivorship, reduced weight loss, a less pronounced and shorter increase in temperature, a less marked reduction in lymphocyte counts and in reduction of inflammation and necrosis in brain and olfactory bulb in the vaccinated cohorts as compared to control animals. All controls animals succumbed to the infection.

In a second study, sixty-six ferrets were divided into 6 cohorts of 11 ferrets and were immunized on days 0 and 21 with 3.75 µg or 7.5 µg of the Indonesia vaccine or were sham vaccinated. The ferrets were challenged intranasally on day 35 with a high dose of either the clade 2 H5N1 virus A/Indonesia/05/2005 or the clade 1 H5N1 virus A/Vietnam/1203/2004 and monitored for 14 days. The A/Indonesia/05/2005 vaccine was shown to be efficacious with 100% survival, reduced incidence of fever, reduced weight loss, reduced virus burden, and reduced haematological (leukopenia and lymphopenia) changes in the vaccinated cohorts following homologous challenge. Similarly, the A/Indonesia/05/2005 vaccine was efficacious against a heterologous challenge, showing a vaccine dose dependent survivorship in the vaccinated cohorts as compared to the control cohort. Similar to the homologous challenge, vaccination against a heterologous challenge reduced virus burden, and reduced haematological (leukopenia) changes associated with highly pathogenic avian influenza infection.

Pharmacokinetic properties

Not applicable.

Preclinical safety data

Non-Clinical studies with mock-up vaccine using an H5N1 vaccine strain demonstrated alterations in liver enzymes and calcium levels in repeat dose toxicity studies in rats. Such alterations in liver function have not been seen to date in human clinical studies. Alterations in calcium metabolism have not been examined in human clinical studies.

Animal reproductive toxicology studies do not indicate harmful effects in regard to female fertility, embryo-foetal and pre- and post-natal toxicity.

PHARMACEUTICAL PARTICULARS

List of excipients

Trometamol
Sodium chloride
Water for injections
Polysorbate 80

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf-life

1 year
After first opening, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

Nature and contents of the container

One pack of 20 multidose vials (type I glass) of 5 ml suspension (10 x 0.5 ml doses) with a stopper (bromobutyl rubber)

Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use. Shake before use.
Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection.
Any unused vaccine or waste material should be disposed of in accordance with local requirements.

NAME AND ADDRESS

Manufacturer

Baxter AG
Industriestrasse 67
A-1221 Vienna
Austria

Distributor

Baxter Healthcare Ltd
PO Box 14-062
Panmure
Auckland 1741

Medicine Classification

Prescription Only Medicine.

Date of Preparation

28 January 2010

NAME OF THE MEDICINE

Panvax® H1N1 Vaccine
H1N1 Pandemic influenza vaccine (split virion, inactivated).

DESCRIPTION

Panvax® H1N1 Vaccine is a purified, inactivated, monovalent, split virion (split virus) vaccine. A single 0.5 mL dose contains antigen of the following type:

A/California/7/2009 (H1N1) (NYMC X-179A) (A/California/7/2009 (H1N1)v-like)
15 µg haemagglutinin (HA) per 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 (for multi-dose vial presentation only).

The following are 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 Australian Influenza Vaccine Committee (AIVC) decision, endorsing the World Health Organisation recommended virus for the influenza A(H1N1) vaccine.

Panvax® H1N1 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 still ongoing; however preliminary data available from the study in adults have shown that a single dose of vaccine is sufficient to elicit a protective antibody response. Results from the trial in children are not yet available.

A total of 240 adult 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	15µg 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 ≥ 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	15µg 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 < 1:20 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 ≥ 1:20 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 adults, adolescents and children 10 years of age and older.

CONTRAINDICATIONS

Anaphylactic hypersensitivity to previous influenza vaccination, or to eggs, chicken protein, 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.

In immunocompromised patients, the antibody response may be lower.

Use in pregnancy: (Category B2)
The safety profile of the vaccine in pregnant women is unknown. Healthcare professionals should assess the potential benefits and risks of administering Panvax® H1N1 Vaccine to pregnant women on a case by case basis, taking into account Australian 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 Panvax® H1N1 Vaccine to lactating women on a case by case basis, taking into account Australian Health Authorities' recommendations.

Paediatric use:
Data in children are not yet available.

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 Panvax® H1N1 Vaccine with other vaccines. If Panvax® H1N1 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 Trials:

Clinical data specific to Panvax® H1N1 Vaccine show that the 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 2).

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 2: Proportion of Adult Participants with Solicited Local and Systemic Adverse Events within 7 Days of Administration of Panvax® H1N1 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

Post-marketing surveillance:
There are currently no post-marketing data for Panvax® H1N1 vaccine. 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, Fluvax® vaccine. The adverse events reported are presented below according to System Organ Class and frequency. These data reflect experience in children and adults with Fluvax® vaccine.

Adverse event frequencies are defined as follows:

Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1000 and < 1/100), rare (≥ 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:
Adults, adolescents and children from 10 years 0.5 mL

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.

The pre-filled syringe is for single use and any remaining contents should be discarded in accordance with local requirements.

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

- the vaccine is stored at 2 - 8^{o}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 Panvax® H1N1 Vaccine.

For general advice on overdose management, call the New Zealand Poisons Centre on 0800 POISON or 0800 764 766.

PRESENTATION AND STORAGE CONDITIONS

Presentations:
Panvax® H1N1 Vaccine is presented in a single-dose pre-filled glass syringe with an attached needle for injection and a multi-dose glass vial.

Multi-dose Vial
Each multi-dose vial contains a nominal 5 mL or 10mL 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 or 50 vials.

Pre-filled Syringe
Each disposable syringe contains a single 0.5 mL dose of vaccine and is supplied encased within a clear film wrapper. The presence of the film wrapper provides assurance that the product has not been opened. Do not use if the film wrap is damaged or missing.

Pack size is 1 or 10 syringes.

Storage Conditions:
Panvax® H1N1 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.

NAME AND ADDRESS OF THE SPONSOR

Manufactured by:
CSL Limited ABN 99 051 588 348
45 Poplar Road, Parkville
VICTORIA 3052 AUSTRALIA

Distributed by:
CSL Biotherapies (NZ) Ltd
Level 9, Building 5
666 Great South Road
Central Park
Penrose
AUCKLAND

MEDICINE CLASSIFICATION

Prescription only medicine

DATE OF PREPARATION

17 February 2010

® Registered Trademark of CSL Limited

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Whole virion, Vero cell derived, inactivated

Suspension for injection

QUALITATIVE & QUANTITATIVE COMPOSITION

Whole virion influenza vaccine, inactivated containing antigen of pandemic strain*:

A/Vietnam/1203/2004 (H5N1) 7.5 micrograms** per 0.5mL dose.

* propagated in Vero cells (continuous cell line of mammalian origin)
** expressed in micrograms haemagglutinin.

This vaccine complies with the WHO recommendation and EU decision for the pandemic.

This is a multidose container, *see Nature and Contents of the Container for the number of doses per vial.*

For a full list of excipients, *see List of Excipients.*

The vaccine is an off-white, opalescent, translucent suspension.

CLINICAL PARTICULARS

Therapeutic Indications

Prophylaxis of influenza in an officially declared pandemic situation. PANDEMIC INFLUENZA VACCINE H5N1 BAXTER should be used in accordance with official guidance.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been evaluated in adults 18 - 59 years of age and in elderly 60 years of age and above.

Dosage and Method of Administration

Adults

First dose of 0.5mL at an elected date.

A second dose of vaccine should be given after an interval of at least 3 weeks.

Individuals with hypersensitivity to egg and/or chicken proteins can be vaccinated with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER since the vaccine does not contain either egg or chicken proteins.

There is no data on PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccination dose and schedule for subjects under 18 years old and for subjects with co-morbidities (e.g. immunosuppressed subjects). In a pandemic situation administration of the vaccine in those populations shall follow national recommendations.

For further information, *see Pharmacodynamic Properties*.

Immunization should be carried out by intramuscular injection into the deltoid muscle, *see Special Warnings and Precautions for Use*.

Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (e.g. formaldehyde, benzonase, sucrose) of this vaccine.

However, in a pandemic situation, it may be appropriate to give the vaccine, provided that facilities for resuscitation are immediately available in case of need.

See Special Warnings and Precautions for Use.

Special Warnings and Precautions for Use

Caution is needed when administrating this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance(s), to any of the excipients and to trace residues e.g. formaldehyde, benzonase, or sucrose.

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.

If the pandemic situation allows, immunisation shall be postponed in patients with severe febrile illness or acute infection.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER should under no circumstances be administered intravascularly.

There are no data with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleedings.

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

A protective response may not be induced in all individuals receiving the vaccine, *see Pharmacological Properties/Pharmacodynamic Properties*.

Interactions with other Medicinal Products and other forms of Interaction

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER should not be given at the same time as other vaccines as it has not been studied. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

Immunoglobulin is not to be given with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER. If it is necessary to provide immediate protection, PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may be given at the same time as normal or specific immunoglobulin. Injections of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER and immunoglobulin should be made into separate limbs.

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

Following seasonal 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 by the vaccine.

Pregnancy and Lactation

The safety of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in pregnancy and lactation has not been assessed in clinical trials. In general, data from influenza vaccinations in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryo-foetal development, parturition or post-natal development, *see Pharmacological Properties/Preclinical Safety Data*.

Effects on Ability to Drive and Use Machines

Some undesirable effects mentioned under *Clinical Particulars/Adverse Reactions* such as dizziness and vertigo may affect the ability to drive or use machines.

Adverse Reactions

Adverse Reactions for Clinical Trials

In clinical trials with the mock-up vaccine (*see Pharmacological Properties/ Pharmacodynamic Properties*) in 606 subjects (326 between 18 and 59 years old, and 280 aged 60 and above), the following adverse reactions were assessed as at least possibly related by the investigator. Most of the reactions were mild in nature, of short duration and qualitatively similar to those induced by conventional seasonal influenza vaccines. There were fewer reactions after the second dose of the vaccine compared with the first dose. The most frequently occurring adverse reaction was injection site pain, which was usually mild.

Clinical Trial Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
INFECTIONS AND INFESTATIONS	Nasopharyngitis	Common
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy	Uncommon
PSYCHIATRIC DISORDERS	Insomnia Restlessness	Uncommon Uncommon
NERVOUS SYSTEM DISORDERS	Headache Dizziness Somnolence Dysesthesia	Common Common Uncommon Uncommon
EYE DISORDERS	Conjunctivitis	Uncommon
EAR AND LABYRINTH DISORDERS	Vertigo Sudden hearing loss	Common Uncommon
VASCULAR DISORDERS	Hypotension	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Pharyngolaryngeal pain Dyspnoea Cough Rhinorrhoea Nasal congestion	Common Uncommon Uncommon Uncommon Uncommon
GASTROINTESTINAL DISORDERS	Nausea Vomiting Diarrhoea Upper abdominal pain	Uncommon Uncommon Uncommon Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis Rash Pruritis	Common Uncommon Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia Myalgia	Common Common

Clinical Trial Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Injection site pain	Very Common
	Pyrexia	Common
	Chills	Common
	Fatigue	Common
	Malaise	Common
	Injection site Induration	Common
	Injection site Eyrthema	Common
	Injection site swelling	Common
	Injection site haemorrhage	Common
	Injection site irritation	Uncommon

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)

Post-marketing Surveillance

There are no post-marketing data available for PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

From post-marketing surveillance with egg-derived interpandemic trivalent vaccines, the following serious adverse events have been reported:

Uncommon: Generalised skin reactions including pruritus, urticaria, and non-specific rash.

Rare: Neuralgia, paraesthesia, convulsions, transient thrombocytopoenia.
Allergic reactions, in rare cases leading to shock, have been reported.

Very rare: Vasculitis with transient renal involvement and neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

Overdose

No case of overdose has been reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This section describes the clinical experience with the mock-up vaccine following a two-dose administration.

Mock-up 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 mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Immune response against the vaccine strain contained in PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (A/Vietnam/1203/2004)

The immunogenicity of the 7.5µg non-adjuvanted formulation of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (strain A/Vietnam/1203/2004) has been evaluated in two clinical studies in adults aged 18 - 59 years (N = 312) and in elderly subjects aged 60 years and older (N = 272) following a 0, 21 day schedule.

After primary vaccination the seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody as measured by single radial haemolysis (SRH) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

SRH Assay	**18 – 59 years 21 Days After**		**60 years and above 21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroprotection rate*	55.5%	65.4%	57.9%	67.7%
Seroconversion rate**	51.3%	62.1%	52.4%	62.4%
Seroconversion factor***	3.7	4.8	3.6	4.6

* SRH area > 25 mm^2

** either SRH area ≥ 25 mm^2 if baseline sample negative or 50% increase in SRH area if baseline sample > 4 mm^2

*** geometric mean increase

After primary vaccination the rate of subjects with neutralizing antibody titres > 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

Microneutralisation assay	**18 – 59 years**		**60 years and above**	
	21 Days After		**21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroneutralisation rate*	49.4%	73.0%	54.4%	74.1%
Seroconversion rate**	39.1%	61.9%	14.3%	26.7%
Seroconversion factor***	3.4	4.7	2.1	2.8

* MN titre > 20
** > 4-fold increase in MN titre
*** geometric mean increase

Cross-reactive Immune Response Against Related H5N1 Strains

In the phase 3 study in adults (N = 265) and elderly subjects (N = 270) after vaccination with the A/Vietnam/1203/2004 strain vaccine the rate of subjects with cross-neutralising antibodies as measured by MN (titre > 20) was as follows:

	18 – 59 years		**60 years and above**	
	Day 42[a]	**Day 180**	**Day 42[a]**	**Day 180**
Tested against	**Strain A/Indonesia/05/2005**			
Seroneutralisation rate*	35.1%	14.4%	54.8%	28.0%

* MN titre > 20
a 21 days after 2nd dose

In a dose-finding study in adults aged 18 - 45 years investigating various dose levels of adjuvanted and non-adjuvanted formulations of the A/Vietnam/1203/2004 strain vaccine the rates of subjects with neutralising antibody titres > 20, seroconversion rates and seroconversion factor for cross-neutralising antibodies as measured by MN in subjects who received the 7.5µg non-adjuvanted formulation (N = 42) were as follows:

Tested against	**Strain A/Indonesia/05/2005**	
	Day 42[a]	**Day 180**
Seroneutralisation rate*	45.2%	33.3%
Seroconversion rate**	31.0%	21.4%
Seroconversion factor***	3.2	2.5

* MN titre > 20
** > 4-fold increase in MN titre
*** geometric mean increase
a 21 days after 2nd dose

Antibody Persistence and Booster Vaccination with Homologous and Heterologous Vaccine Strains

Antibody persistence after vaccination with the 7.5µg non-adjuvanted formulation of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (strain A/Vietnam/1203/2004) has been evaluated in two clinical studies in adults aged 18 - 59 years (N = 285) and in one clinical study in elderly subjects aged 60 years and above (N = 258) up to 6 months after the start of the primary vaccination series. The results indicate an overall decline in antibody levels over time. Data on later time points (months 12 and 24) are not yet available.

Seroprotection*/ Seroneutralisation rate**	**18 – 59 years**		**60 years and above**	
	SRH Assay	**MN Assay**	**SRH Assay**	**MN Assay**
Month 6	28.1%	37.9%	26.7%	40.5%

* SRH area > 25 mm²
** MN titre > 20

To date a booster vaccination with homologous and heterologous vaccine strains has been administered in the phase 3 study 6 months after primary vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine. Two dose levels (3.75µg and 7.5µg) of both the A/Vietnam/1203/2004 and A/Indonesia/05/2005 strain vaccines were investigated for the booster vaccination.

Seroprotective titres as determined by SRH assay against the homologous vaccine strain (A/Vietnam/1203/2004) were observed in 65.5% of subjects aged 18 - 59 years and in 59.4% of subjects aged 60 years and older at 21 days after a booster vaccination with the 7.5µg dose of the A/Vietnam strain vaccine. Twenty-one days after a booster vaccination with the 7.5µg dose of the A/Indonesia/05/2005 strain vaccine a cross reactive response against the A/Vietnam strain was obtained in 69.0% of subjects aged 18 - 59 years and in 40.6% of subjects aged 60 years and older.

Antibody responses as measured by MN 21 days after the booster vaccination were generally slightly higher with the A/Indonesia/05/2005 than with the A/Vietnam/1203/2004 strain vaccine. Seroneutralisation rates (MN titre > 20) at 21 days after a booster vaccination with the 7.5µg dose of the A/Vietnam and A/Indonesia vaccines, tested against both the homologous and heterologous strains were as follows:

6-Month Booster	**18 - 59 years**		**60 years and above**	
	Vaccination with 7.5µg strain A/Vietnam			
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
Seroneutralisation rate*	86.2%	65.5%	64.5%	54.8%
	Vaccination with 7.5µg strain A/Indonesia			
Seroneutralisation rate*	86.2%	93.1%	65.6%	71.9%

* MN titer > 1:20

Another study investigated a booster vaccination with 7.5µg of the heterologous A/Indonesia/05/2005 vaccine strain administered 12 - 15 months after an initial 2-dose priming with various dose levels of adjuvanted and non-adjuvanted formulations of the A/Vietnam/1203/2004 strain vaccine in subjects aged 18 - 45 years. In subjects who received the 7.5µg non-adjuvanted formulation for primary vaccination (N = 12) seroprotection rates as measured by SRH 21 days after the booster vaccination were 66.7% and 83.3%, and 100% and 91.7% of subjects achieved neutralising antibody titres > 20 when tested against the homologous A/Indonesia and the heterologous A/Vietnam strain, respectively.

No clinical data have been generated in subjects below 18 years of age.

Information from non-clinical studies

The protective efficacy of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER against morbidity and mortality induced by the infection with lethal doses of highly pathogenic avian Influenza H5N1 virus was assessed non-clinically in a ferret challenge model. Two studies have been performed using either the H5N1 A/Vietnam/1203/2004 or the A/Indonesia/05/2005 vaccine.

In one study, sixteen ferrets were divided into two cohorts and were vaccinated on days 0 and 21 with 7.5µg of the A/Vietnam/1203/2004 vaccine or were sham vaccinated. All ferrets were challenged intranasally on day 35 with a high dose of the highly virulent H5N1 virus strain A/Vietnam/1203/2004 and monitored for 14 days. Ferrets vaccinated with the 7.5µg dose of the A/Vietnam/1203/2004 vaccine demonstrated a high rate of seroconversion. The A/Vietnam/1203/2004 vaccine afforded protection against homologous challenge as evidenced by full survivorship, reduced weight loss, a less pronounced and shorter increase in temperature, a less marked reduction in lymphocyte counts and in reduction of inflammation and necrosis in brain and olfactory bulb in the vaccinated cohorts as compared to control animals. All controls animals succumbed to the infection.

In a second study, sixty-six ferrets were divided into 6 cohorts of 11 ferrets and were immunized on days 0 and 21 with 3.75µg or 7.5µg of the Indonesia vaccine or were sham vaccinated. The ferrets were challenged intranasally on day 35 with a high dose of either the clade 2 H5N1 virus A/Indonesia/05/2005 or the clade 1 H5N1 virus A/Vietnam/1203/2004 and monitored for 14 days. The A/lndonesia/05/2005 vaccine was shown to be efficacious with 100% survival, reduced incidence of fever, reduced weight loss, reduced virus burden, and reduced haematological (leukopenia and lymphopenia) changes in the vaccinated cohorts following homologous challenge. Similarly, the A/lndonesia/05/2005 vaccine was efficacious against a heterologous challenge, showing a vaccine dose dependent survivorship in the vaccinated cohorts as compared to the control cohort. Similar to the homologous challenge, vaccination against a heterologous challenge

reduced virus burden, and reduced haematological (leucopenia) changes associated with highly pathogenic avian influenza infection.

Pharmacokinetic properties

Not applicable.

Preclinical safety data

Non-clinical data reveal no special hazard for humans. Repeat dose toxicity studies in rats demonstrated alterations in liver enzymes and calcium levels. Such alterations in liver function have not been seen to date in human clinical studies. Alterations in calcium metabolism have not been examined in human clinical studies.

Animal reproductive toxicology studies do not indicate harmful effects in regard to female fertility, embryo-fetal and pre- and post-natal toxicity.

PHARMACEUTICAL PARTICULARS

List of excipients

Trometamol

Sodium chloride

Water for injections

Polysorbate 80

Incompatibilities

Compatibility with other medicinal products has not been examined.

Shelf-life

24 months.

After first opening, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original package in order to protect from light.

Nature and contents of the container

One pack of 20 multidose vials (type I glass) of 5mL suspension (10 x 0.5mL doses) with a stopper (bromobutyl rubber)

Instructions for Use Handling and Disposal

The vaccine should be allowed to reach room temperature before use. Shake before use.

Each vaccine dose of 0.5mL is withdrawn into a syringe for injection.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

NAME AND ADDRESS

Manufacturer

Baxter AG
Industriestrasse 67
A-1221 Vienna
Austria

Distributor

Baxter Healthcare Ltd
PO Box 14-062
Panmure
Auckland 1741

MEDICINE CLASSIFICATION

Prescription Only Medicine.

DATE OF PREPARATION

20 July 2010

Baxter and PANDEMIC INFLUENZA VACCINE H5N1 BAXTER are trademarks of Baxter International Inc.

Based on ccds20620090804.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Whole virion, Vero cell derived, inactivated

Suspension for injection

QUALITATIVE & QUANTITATIVE COMPOSITION

Whole virion influenza vaccine, inactivated, containing antigen of pandemic strain*:

A/Vietnam/1203/2004 (H5N1) 7.5 micrograms** per 0.5mL dose.

* propagated in Vero cells (continuous cell line of mammalian origin)
** expressed in micrograms haemagglutinin.

This vaccine complies with the WHO recommendation and EU decision for the pandemic.

This is a multidose container, *see Nature and Contents of the Container* for the number of doses per vial.

PHARMACEUTICAL FORM

Suspension for injection.

The vaccine is an off-white, opalescent, translucent suspension.

CLINICAL PARTICULARS

Therapeutic Indications

Prophylaxis of influenza in an officially declared pandemic situation. PANDEMIC INFLUENZA VACCINE H5N1 BAXTER should be used in accordance with official guidance *see Dosage and Method of Administration and Pharmacodynamic Properties*.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been evaluated in adults 18 - 59 years of age and in elderly 60 years of age and above.

Dosage and Method of Administration

Adults

First dose of 0.5mL at an elected date.

A second dose of vaccine should be given after an interval of at least 3 weeks.

Individuals with hypersensitivity to egg and/or chicken proteins can be vaccinated with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER since the vaccine does not contain either egg or chicken proteins.

There is no data on PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccination dose and schedule for subjects under 18 years old and for subjects with co-morbidities (e.g. immunosuppressed subjects). In a pandemic situation administration of the vaccine in those populations shall follow national recommendations.

For further information, *see Pharmacodynamic Properties*.

Immunization should be carried out by intramuscular injection into the deltoid muscle, *see Special Warnings and Precautions for Use*.

Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (e.g. formaldehyde, benzonase, sucrose) of this vaccine. If vaccination is considered necessary, facilities for resuscitation should be immediately available in case of need *see Special Warnings and Precautions for Use*.

Special Warnings and Precautions for Use

As with all vaccines administered by injection, allergic reactions, including severe anaphylactic reactions (such as anaphylactic shock), may occur after administration of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

Immediate emergency treatment for anaphylaxis should be available.

Hypersensitivity reactions, including anaphylaxis, have been reported following use of a similar whole virion, Vero cell derived H1N1 influenza vaccine administered during a pandemic period. Such reactions have occurred both in patients with a history of multiple allergies and in patients with no known allergy.

If the pandemic situation allows, immunisation shall be postponed in patients with severe febrile illness or acute infection.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER must not be administered intravascularly.

There are no data with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleeding.

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

A protective response may not be induced in all individuals receiving the vaccine, *see Pharmacodynamic Properties*.

Special Populations

Pediatric use

No data are available with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in subjects below 18 years of age. Therefore health care providers need to assess and take account of official guidance.

Although no pediatric information is available with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER, the following information was derived from clinical studies from a similar strain (inactivated H1N1 A/California/07/2009 strain).

Children and adolescents 3 to 17 years of age

In an ongoing clinical trial 51 children and adolescents aged 9 to 17 years and 51 children aged 3 to 8 years were administered the 7.5mcg dose of H1N1 A/California/07/2009 strain. The incidence and nature of symptoms after the first and second vaccination were similar to that observed in the adult and elderly population using inactivated H1N1 A/California/07/2009 strain.

Injection site pain was reported at a higher rate (very common) and headache and fatigue were reported at a lower rate (common) than in adults. Fever (≥ 38°C) was reported at a frequency of 7.8% and 9.8% after the first and second vaccination in children aged 3 to 8 years. No fever was reported in children and adolescents aged 9 to 17 years.

Children aged 6 to 35 months

In an ongoing clinical trial the 7.5mcg dose of inactivated H1N1 A/California/07/2009 strain was administered to 52 infants and young children aged 6 to 35 months. Sleep disorder was reported as very common, and additional symptoms reported at a common frequency in this age group were anorexia, crying, irritability and somnolence. Fever (≥ 38°C) was reported at a frequency of 13.4% and 11.5% after the first and second vaccination.

Pandemic Observational Study

Preliminary safety data from 240 children, adolescents and adults (above 5 years of age) showed that within 7 days after the first vaccination 37.5% of subjects reported systemic Issued and reactions and 25.0% reported injection site reactions. In 53 children aged 6 months to 5 years, systemic reactions were reported in 30.2% and injection site reactions occurred in 20.8% of subjects. After the second dose, adverse reactions occurred at a lower frequency.

Very common reactions reported in children, adolescents and adults above 5 years of age
Injection site reaction, Fatigue, Headache, Myalgia, Gastrointestinal symptoms

Very common reactions reported in children aged 6 months to 5 years
Injection site reaction, Drowsiness, Irritability, Loss of appetite

Interactions with other Medicinal Products and other forms of Interaction

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER should not be given at the same time as other vaccines as it has not been studied. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs.

Immunoglobulin is not to be given with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER unless it is necessary during a medical emergency to provide immediate protection. If necessary, PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may be given at the same time as normal or specific immunoglobulin into separate limbs.

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

Pregnancy and Lactation

The safety of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in pregnancy and lactation has not been assessed in clinical trials. Animal studies with H5N1 strain vaccines (A/Vietnam/1203/2004 and A/Indonesia/05/2005) do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development *see Preclinical Safety Data*. Health care providers should carefully consider the potential risks and benefits for each specific patient before prescribing PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

Effects on Ability to Drive and Use Machines

There is no information of the effects of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER on the ability to drive or operate an automobile or other heavy machinery.

Adverse Reactions

Adverse Reactions from Clinical Trials

Clinical trials were conducted with the PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccine (*see Section Pharmacological Properties/Pharmacodynamic Properties* for more information on the H5N1 vaccine) in approximately 3500 subjects (ranging in age from 18 to 60 years and above) and special risk groups of approximately 300 subjects each, consisting of immune-compromised and patients with chronic disease conditions. The safety profile in immune-compromised subjects and patients with chronic disease conditions is similar to the safety profile in healthy subjects. The adverse reactions observed are shown in the table below.

Clinical Trial Adverse Reactions			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Adults/Elderly**	
		Frequency Category	**Frequency Percentage[1]**
INFECTIONS AND INFESTATIONS	Nasopharyngitis	Common	3.8%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy	Uncommon	0.2%
PSYCHIATRIC DISORDERS	Insomnia	Uncommon	0.3%
NERVOUS SYSTEM DISORDERS	Headache	Very Common	16.2%
	Sensory abnormalities: • Paresthesia • Dysesthesia • Hypoesthesia • Oral dysesthesia • Burning sensation • Dysgeusia	Common	1.1%
	Dizziness	Uncommon	0.8%
	Somnolence	Uncommon	0.3%
EYE DISORDERS	Conjunctivitis	Uncommon	0.5%
	Eye irritation	Uncommon	0.7%
EAR AND LABYRINTH DISORDERS	Vertigo	Common	1.0%
	Sudden hearing loss	Uncommon	0.3%*
	Ear pain	Uncommon	0.1%
VASCULAR DISORDERS	Hypotension	Uncommon	0.5%
	Syncope	Uncommon	0.2%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Oropharyngeal pain	Common	2.4%
	Nasal congestion	Uncommon	0.3%
	Cough	Common	1.4%
	Dyspnoea	Uncommon	0.3%
	Rhinorrhoea	Uncommon	0.8%

Clinical Trial Adverse Reactions			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Adults/Elderly**	
		Frequency Category	**Frequency Percentage[1]**
	Dry throat	Uncommon	0.2%
GASTROINTESTINAL DISORDERS	Vomiting	Uncommon	0.3%
	Diarrhoea	Common	1.0%
	Abdominal pain	Uncommon	0.6%
	Nausea	Uncommon	0.6%
	Dyspepsia	Uncommon	0.5%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash	Uncommon	0.5%
	Pruritis	Common	1.3%
	Hyperhidrosis	Common	5.5%
	Urticaria	Uncommon	0.3%*
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Myalgia	Common	5.6%
	Arthralgia	Common	5.7%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Injection site reactions		
	Injection site pain	Very Common	11.4%
	Injection site induration	Common	1.3%
	Injection site erythema	Common	1.5%
	Injection site swelling	Common	1.0%
	Injection site haemorrhage	Common	2.0%
	Injection site irritation	Uncommon	0.3%
	Injection site pruritus	Uncommon	0.1%
	Injection site movement impairment	Uncommon	0.1%
	Fatigue	Very common	10.3%
	Pyrexia	Common	2.2%
	Malaise	Common	7.5%
	Chills	Common	5.6%
	Chest discomfort	Uncommon	0.1%
	Influenza like illness	Uncommon	0.9%

Legend: ADR frequency is based upon the following scale: Very Common (≥ 1/10); Common (≥ 1/100 - < 1/10), Uncommon (≥ 1/1,000 - < 1/100), Rare (≥ 1/10,000 - < 1/1,000), Very Rare (< 1/10,000)

* Only reported in the healthy elderly study population (aged 60 years and above, n = 400)

[1] Percentage represents the highest frequency observed either in the healthy adult (18 – 59 years, n = 3056) or healthy elderly study population (60 years and older, n = 400).

Post-marketing Adverse Reactions

There are no post-marketing data available for PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

Class effects

From post-marketing surveillance with a whole virion, Vero cell derived, H1N1 vaccine, the following adverse reactions have been reported:

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction, Hypersensitivity
NERVOUS SYSTEM DISORDERS: Convulsion
SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Angioedema
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Pain in extremity
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Influenza-like illness

Overdose

No symptoms of overdose are known for PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This section describes the clinical experience with the PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccine.

Pandemic and Pre-Pandemic 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 and pre-pandemic vaccines will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with H5N1 vaccines are relevant for the pandemic and pre-pandemic vaccines.

Immune response against the vaccine strain contained in PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (A/Vietnam/1203/2004)

The immunogenicity of the 7.5mcg non-adjuvanted formulation of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (strain A/Vietnam/1203/2004) has been evaluated in two clinical studies in adults aged 18 - 59 years (N = 312) and one clinical study in elderly subjects aged 60

years and older (N = 272) following a 0, 21 day schedule in support of licensure of a pandemic vaccine (ie mock-up license). The immunogenicity of the 7.5mcg non-adjuvanted formulation of the A/Vietnam/1203/2004 strain vaccine has been evaluated further in an additional Phase 3 study in adults aged 18 to 59 years (N = 649), in subjects aged 60 years and older (N =119) and specified risk groups of immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123) following a 0, 21 day schedule to expand the database in support of licensure of a pre-pandemic vaccine (i.e., pre-pandemic license).

Clinical studies in adults aged 18 to 59 years (N = 312) and in subjects aged 60 years and older (N = 272) in support of mock-up license

After vaccination the seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody as measured by single radial haemolysis (SRH) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

SRH Assay	**18 – 59 years 21 Days After**		**60 years and above 21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroprotection rate*	55.5%	65.4%	57.9%	67.7%
Seroconversion rate**	51.3%	62.1%	52.4%	62.4%
Seroconversion factor***	3.7	4.8	3.6	4.6

* SRH area ≥ 25mm²

** either SRH area ≥ 25mm² if baseline sample negative or 50% increase in SRH area if baseline sample > 4mm²

*** geometric mean increase

After vaccination the rate of subjects with neutralizing antibody titres ≥ 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

Microneutralisation assay	**18 – 59 years 21 Days After**		**60 years and above 21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroneutralisation rate*	49.4%	73.0%	54.4%	74.1%
Seroconversion rate**	39.1%	61.9%	14.3%	26.7%
Seroconversion factor***	3.4	4.7	2.1	2.8

* MN titre ≥ 20

** ≥ 4-fold increase in MN titre

*** geometric mean increase

Phase 3 clinical study in adults aged 18 to 59 years (N = 649), in subjects aged 60 years and older (N = 119), in immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123)

After vaccination, the seroprotection rate, seroconversion rate, and seroconversion factor for anti-HA antibody as measured by SRH in adults aged 18 to 59 years and in subjects aged 60 years and above were as follows:

SRH assay	**18 – 59 years 21 Days After**		**60 years and above 21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroneutralisation rate*	52.2%	67.5%	24.4%	39.5%
Seroconversion rate**	34.3%	49.5%	16.0%	26.9%
Seroconversion factor***	2.0	2.8	1.5	1.9

* SRH area ≥ 25mm^2

** either SRH area ≥ 25mm^2 if baseline sample negative or 50% increase in SRH area if baseline sample > 4mm^2

*** geometric mean increase

After vaccination, the seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody as measured by SRH in immunocompromised subjects and patients with chronic disease conditions were as follows:

SRH assay	**Immunocompromised subjects 21 Days After**		**Patients with chronic disease conditions 21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroneutralisation rate*	37.2%	53.4%	28.7%	42.3%
Seroconversion rate**	19.8%	35.6%	20.5%	33.3%
Seroconversion factor***	1.4	1.9	1.5	20.

* SRH area ≥ 25mm^2

** either SRH area ≥ 25mm^2 if baseline sample negative or 50% increase in SRH area if baseline sample > 4mm^2

*** geometric mean increase

After vaccination the rate of subjects with neutralizing antibody titers ≥ 20, seroconversion rate and seroconversion factor as measured by MN assay in adults aged 18 to 59 years and in subjects aged 60 years and above were as follows:

Microneutralisation assay	18 – 59 years 21 Days After		60 years and above 21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	42.0%	68.1%	46.2%	58.0%
Seroconversion rate**	29.6%	53.1%	10.9%	17.6%
Seroconversion factor***	2.9	4.4	1.7	2.1

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

After vaccination the rate of subjects with neutralizing antibody titers ≥ 20, seroconversion rate and seroconversion factor as measured by MN assay in immunocompromised subjects and patients with chronic disease conditions were as follows:

Microneutralisation assay	Immunocompromised subjects 21 Days After		Patients with chronic disease conditions 21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	24.8%	41.5%	44.3%	64.2%
Seroconversion rate**	9.1%	32.2%	17.2%	35.0%
Seroconversion factor***	1.6	2.5	2.3	3.0

* MN titre ≥ 20
** > 4-fold increase in MN titre
*** geometric mean increase

Cross-reactive Immune Response Against Related H5N1 Strains

In a clinical study in adults aged 18 to 59 years (N = 270) and subjects aged 60 years and above (N = 272) after vaccination with the 7.5mcg non-adjuvanted formulation of the A/Vietnam/1203/2004 strain vaccine, the rate of subjects with cross-neutralising antibodies as measured by MN (titre ≥ 20) was as follows:

Tested against	18 – 59 years Day 42[a]	18 – 59 years Day 180	60 years and above Day 42[a]	60 years and above Day 180
	Strain A/Indonesia/05/2005			
Seroneutralisation rate*	35.1%	14.4%	54.8%	28.0%

* MN titre ≥ 20
a 21 days after 2nd dose

In a dose-finding study in adults aged 18 - 45 years investigating various dose levels of adjuvanted and non-adjuvanted formulations of the A/Vietnam/1203/2004 strain vaccine the rates of subjects with neutralising antibody titres > 20, seroconversion rates and seroconversion factor for cross-neutralising antibodies as measured by MN in subjects who received the 7.5mcg non-adjuvanted formulation (N = 42) were as follows:

Tested against	**Strain A/Indonesia/05/2005**	
	Day 42[a]	**Day 180**
Seroneutralisation rate*	45.2%	33.3%
Seroconversion rate**	31.0%	21.4%
Seroconversion factor***	3.2	2.5

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase
a 21 days after 2nd dose

Antibody Persistence and Booster Vaccination with Homologous and Heterologous Vaccine Strains

In a clinical study in adults aged 18 - 59 years and subjects aged 60 years and above antibody persistence after vaccination with the 7.5mcg non-adjuvanted formulation of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (A/Vietnam/120/2004) at 6 months, 12 to 15 months and 24 months after the start of the priming vaccination series was as follows:

Seroprotection*/ Seroneutralisation rate**	**18 – 59 years**		**60 years and above**	
	SRH Assay	**MN Assay**	**SRH Assay**	**MN Assay**
Month 6	23.9 %	35.0%	26.7%	40.5%
Months 12 – 15	20.7%	34.2%	18.9%	36.2%
Month 24	22.4%	18.4%	12.3%	22.8%

* SRH area ≥ 25mm²
** MN titre ≥ 20

To date, a booster vaccination with homologous and heterologous vaccine strains has been administered in a clinical study in adults aged 18 to 59 years and in subjects aged 60 years and above at 6 months, 12 to 15 months, and 24 months after a two-dose priming vaccination with the 7.5mcg non-adjuvanted formulation of the A/Vietnam/1203/2004 strain vaccine. Both the A/Vietnam/1203/2004 and A/Indonesia/05/2005 strain vaccine (7.5mcg) were investigated for the booster vaccination and the A/Indonesia/05/2005 strain vaccine was investigated for the 12 to 15 month and 24 month booster vaccination.

Seroprotection rates (SRH area ≥ 25mm^2) at 21 days after a booster vaccination with the 7.5mcg dose of the A/Vietnam/1203/2004 and A/Indonesia/05/2005 strain vaccines, tested against both the homologous and heterologous strains were as follows:

Seroprotection rate*	**18 - 59 years**		**60 years and above**	
	Booster Vaccination with 7.5µg strain A/Vietnam			
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
6 – Month Booster	65.5%	41.4%	59.4%	34.3%

Seroprotection rate*	**18 - 59 years**		**60 years and above**	
	Booster Vaccination with 7.5µg strain A/Vietnam			
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
6 – Month Booster	69.0%	55.2%	40.6%	40.6%
12 - 15 Month Booster	75.9%	69.0%	64.5%	77.4%
24 – Month Booster	86.4%	77.3%	75.0%	70.8%

* SRH area ≥ 25mm²

Seroneutralization rates (MN titer ≥ 20) at 21 days after a booster vaccination with the 7.5mcg dose of the A/Vietnam/1203/2004 and A/Indonesia/05/2005 strain vaccines, tested against both the homologous and heterologous strains were as follows:

Seroneutralisation rate*	**18 - 59 years**		**60 years and above**	
	Booster Vaccination with 7.5µg strain A/Vietnam			
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
6 – Month Booster	86.2%	65.5%	64.5%	54.8%

Seroprotection rate*	**18 - 59 years**		**60 years and above**	
	Booster Vaccination with 7.5µg strain A/Vietnam			
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
6 – Month Booster	86.2%	93.1%	65.6%	71.9%
12 - 15 Month Booster	96.6%	93.1%	83.9%	83.9%
24 – Month Booster	100%	95.5%	91.7%	83.3%

* MN titer ≥ 20

In another study, a booster vaccination with 7.5mcg of the heterologous A/Indonesia/05/2005 vaccine strain (non-adjuvanted) was administered 12 - 17 months after an initial two-dose priming vaccination with various dose levels of adjuvanted and non-adjuvanted formulations of the A/Vietnam/1203/2004 strain vaccine in subjects aged 18 - 45 years. In subjects who received the 7.5mcg non-adjuvanted formulation for primary vaccination (N = 12), 100% and 91.7% achieved neutralising antibody titres > 20 (21 days after the booster vaccination) when tested against the homologous A/Indonesia/05/2005 and the heterologous A/Vietnam/1203/2004 strain, respectively.

No clinical data have been generated in subjects below 18 years of age.

Information from non-clinical studies

The protective efficacy of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER against morbidity and mortality induced by the infection with lethal doses of highly pathogenic avian Influenza H5N1 virus was assessed non-clinically in a ferret challenge model. Two studies have been performed using either the H5N1 A/Vietnam/1203/2004 or the A/Indonesia/05/2005 vaccine.

In one study, sixteen (16) ferrets were divided into two cohorts and were vaccinated on days 0 and 21 with 7.5mcg of the A/Vietnam/1203/2004 vaccine or were sham vaccinated. All ferrets were challenged intranasally on day 35 with a high dose of the highly virulent H5N1 virus strain A/Vietnam/1203/2004 and monitored for 14 days. Ferrets vaccinated with the 7.5mcg dose of the A/Vietnam/1203/2004 vaccine demonstrated a high rate of seroconversion. The A/Vietnam/1203/2004 vaccine afforded protection against homologous challenge as evidenced by full survival, reduced weight loss, a less pronounced and shorter increase in temperature, a less marked reduction in lymphocyte count and in reduction of inflammation and necrosis in brain and olfactory bulb in the vaccinated cohorts as compared to control animals. All controls animals succumbed to the infection.

In a second study, sixty-six (66) ferrets were divided into 6 cohorts of 11 ferrets and were immunized on days 0 and 21 with 3.75mcg or 7.5mcg of the Indonesia vaccine or were sham vaccinated. The ferrets were challenged intranasally on day 35 with a high dose of either the clade 2 H5N1 virus A/Indonesia/05/2005 or the clade 1 H5N1 virus A/Vietnam/1203/2004 and monitored for 14 days. The A/Indonesia/05/2005 vaccine was shown to be efficacious with 100% survival, reduced incidence of fever, reduced weight loss, reduced virus burden, and reduced haematological (leukopenia and lymphopenia) changes in the vaccinated cohorts following homologous challenge. Similarly, the A/Indonesia/05/2005 vaccine was efficacious against a heterologous challenge, showing a vaccine dose dependent survival in the vaccinated cohorts as compared to the control cohort. Similar to the homologous challenge, vaccination against a heterologous challenge reduced virus burden, and reduced haematological (leucopenia) changes associated with highly pathogenic avian influenza infection.

Pharmacokinetic properties

Not applicable.

Preclinical safety data

Non-clinical data reveal no special hazard for humans. Repeat dose toxicity studies in rats demonstrated alterations in liver enzymes and calcium levels. Such alterations in liver function have not been seen to date in human clinical studies. Alterations in calcium metabolism have not been examined in human clinical studies.

Animal reproductive toxicology studies do not indicate harmful effects in regard to female fertility, embryo-foetal and pre- and post-natal toxicity.

PHARMACEUTICAL PARTICULARS

List of excipients

Trometamol

Sodium chloride

Water for injections

Polysorbate 80

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be combined or mixed with other medicinal products.

Shelf-life

36 months.

After first opening, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Store in the original package in order to protect from light.

Nature and contents of the container

One pack of 20 multi-dose vials (type I glass) of 5mL suspension (10 x 0.5mL doses) with a stopper (bromobutyl rubber)

Instructions for Use Handling and Disposal

The vaccine should be allowed to reach room temperature before use. Shake before use.

Each vaccine dose of 0.5mL is withdrawn into a syringe for injection.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

NAME AND ADDRESS

Manufacturer

Baxter AG
Industriestrasse 67
A-1221 Vienna
Austria

Distributor

Baxter Healthcare Ltd
PO Box 14-062
Panmure
Auckland 1741

MEDICINE CLASSIFICATION

Prescription Only Medicine.

DATE OF PREPARATION

15 December 2011

Based on ccds20620101105

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Whole virion, Vero cell derived, inactivated,

Suspension for injection

QUALITATIVE & QUANTITATIVE COMPOSITION

Suspension for injection.

One dose of 0.5mL contains:

Whole virion, non-adjuvanted influenza vaccine, inactivated, containing antigen† of strain:

A/Vietnam/1203/2004 (H5N1) 7.5 micrograms*.

† propagated in Vero cells (continuous cell line of mammalian origin)
* expressed in micrograms haemagglutinin.

This vaccine complies with the WHO recommendation and EU decision for the pandemic.

This vaccine is available in a multidose container, *see Pharmaceutical Particulars/Nature and Contents of the Container* for the number of doses per vial.

For a full list of excipients, see *Pharmaceutical Particulars/List of Excipients.*

PHARMACEUTICAL FORM

Suspension for injection. The H5N1 vaccine is a clear to opalescent, translucent suspension.

CLINICAL PARTICULARS

Therapeutic Indications

Prophylaxis of influenza in an officially declared pandemic situation.

The vaccine may only be marketed or distributed in accordance with the directives contained in the current version of the New Zealand Influenza Pandemic Action Plan.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been evaluated in adults 18 - 59 years of age and in elderly 60 years of age and above.

Dosage and Method of Administration

Adults (18 years and older)

First dose of 0.5mL at an elected date.

A second dose of vaccine should be given after an interval of at least 3 weeks.

Immunization should be carried out by intramuscular injection into the deltoid muscle, *see Clinical Particulars/Special Warnings and Precautions for Use*.

There is no data available on PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccination dose and schedule for subjects under 18 years old and for subjects with co-morbidities (e.g. immunosuppressed subjects). In a pandemic situation administration of the vaccine in those populations shall follow national recommendations.

Individuals with hypersensitivity to egg and/or chicken proteins can be vaccinated with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER since the vaccine does not contain either egg or chicken proteins.

Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

For pregnant women, see *Clinical Particulars/Pregnancy, Lactation and Fertility*.

Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (e.g. formaldehyde, benzonase, sucrose, trypsin) of this vaccine. If vaccination is considered necessary, facilities for resuscitation should be immediately available in case of need *see Clinical Particulars/Special Warnings and Precautions for Use*.

Special Warnings and Precautions for Use

As with all vaccines administered by injection, allergic reactions, including severe anaphylactic reactions (such as anaphylactic shock), may occur after administration of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER. Immediate emergency treatment for anaphylaxis should be available.

Hypersensitivity reactions, including anaphylaxis, have been reported following use of a similar whole virion, Vero cell derived H1N1 influenza vaccine administered during a pandemic period, and have been observed both in patients with a history of multiple allergies and in patients with no known allergy.

If the situation allows, immunisation is recommended to be postponed in patients with severe febrile illness or acute infection.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER must not be administered intravascularly.

There are limited data with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER using the subcutaneous route see *Clinical Particulars/Adverse Reactions*. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleeding.

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

A protective immune response may not be induced in all individuals receiving the vaccine, *see Pharmacological Properties/Pharmacodynamic Properties*.

Special Populations

Pediatric use

No data are available with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in subjects below 18 years of age. Healthcare providers need to assess and take account of official guidance. (For adverse reactions with a similar vaccine used in children see *Clinical Particulars/Class Reactions*).

Although no pediatric information is available with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER, the following information was derived from clinical studies from a similar strain (inactivated H1N1 A/California/07/2009 strain).

Children and adolescents 3 to 17 years of age

In an ongoing clinical trial 51 children and adolescents aged 9 to 17 years and 51 children aged 3 to 8 years were administered the 7.5mcg dose of H1N1 A/California/07/2009 strain. The incidence and nature of symptoms after the first and second vaccination were similar to that observed in the adult and elderly population using inactivated H1N1 A/California/07/2009 strain.

Injection site pain was reported at a higher rate (very common) and headache and fatigue were reported at a lower rate (common) than in adults. Fever (≥ 38°C) was reported at a frequency of 7.8% and 9.8% after the first and second vaccination in children aged 3 to 8 years. No fever was reported in children and adolescents aged 9 to 17 years.

Children aged 6 to 35 months

In an ongoing clinical trial the 7.5mcg dose of inactivated H1N1 A/California/07/2009 strain was administered to 52 infants and young children aged 6 to 35 months. Sleep disorder was reported as

very common, and additional symptoms reported at a common frequency in this age group were anorexia, crying, irritability and somnolence. Fever (≥ 38°C) was reported at a frequency of 13.4% and 11.5% after the first and second vaccination.

Pandemic Observational Study

Preliminary safety data from 240 children, adolescents and adults (above 5 years of age) showed that within 7 days after the first vaccination 37.5% of subjects reported systemic Issued and reactions and 25.0% reported injection site reactions. In 53 children aged 6 months to 5 years, systemic reactions were reported in 30.2% and injection site reactions occurred in 20.8% of subjects. After the second dose, adverse reactions occurred at a lower frequency.

Very common reactions reported in children, adolescents and adults above 5 years of age
Injection site reaction, Fatigue, Headache, Myalgia, Gastrointestinal symptoms

Very common reactions reported in children aged 6 months to 5 years
Injection site reaction, Drowsiness, Irritability, Loss of appetite

Interactions with other Medicinal Products and other forms of Interaction

There are no data on co-administration of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER with other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs.

Immunoglobulin is not to be given with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER unless it is necessary during a medical emergency to provide immediate protection. If necessary, PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may be given at the same time as normal or specific immunoglobulin into separate limbs.

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

Following seasonal influenza vaccination, false positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus, and especially, HTLV-1. In such cases, the western blot method is negative. These transitory false-positive results may be due to IgM production in response to the vaccine.

Pregnancy, Lactation and Fertility

The safety of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in pregnancy and lactation has not been assessed in clinical trials. Animal studies with H5N1 strain vaccines (A/Vietnam/1203/2004 and A/Indonesia/05/2005) do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development. Healthcare providers should balance the potential risks and only prescribe PANDEMIC INFLUENZA VACCINE H5N1 BAXTER if clearly needed.

Effects on Ability to Drive and Use Machines

There is no information of the effects of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER on the ability to drive or operate an automobile or other heavy machinery.

Adverse Reactions

Adverse Reactions from Clinical Trials

Clinical trials were conducted with the PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccine (*see Section Pharmacological Properties/Pharmacodynamic Properties* for more information on the H5N1 vaccine) in approximately 3700 subjects (ranging in age from 18 to 60 years and above) and special risk groups of approximately 300 subjects each, consisting of immunocompromised subjects and patients with chronic disease conditions. The safety profile in immunocompromised subjects and patients with chronic disease conditions is similar to the safety profile in healthy subjects. The adverse reactions observed are shown in the table below.

Clinical Trial Adverse Reactions			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency Category**	**Frequency Percentage[1]**
INFECTIONS AND INFESTATIONS	Nasopharyngitis	Common	3.8%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy	Uncommon	0.2%
PSYCHIATRIC DISORDERS	Insomnia	Uncommon	0.3%
NERVOUS SYSTEM DISORDERS	Headache	Very Common	16.2%
	Dizziness	Uncommon	0.8%
	Somnolence	Uncommon	0.3%
	Sensory abnormalities: Paresthesia Dysesthesia Hypoesthesia Oral dysesthesia Burning sensation Dysgeusia	Common	1.1%
	Syncope	Uncommon	0.2%
EYE DISORDERS	Conjunctivitis	Uncommon	0.5%
	Eye irritation	Uncommon	0.7%
EAR AND LABYRINTH DISORDERS	Vertigo	Common	1.0%
	Sudden hearing loss	Uncommon	0.3%*
	Ear pain	Uncommon	0.1%
VASCULAR DISORDERS	Hypotension	Uncommon	0.5%

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Oropharyngeal pain	Common	2.4%
	Cough	Common	1.4%
	Dyspnoea	Uncommon	0.3%
	Nasal congestion	Uncommon	0.3%
	Rhinorrhoea	Uncommon	0.8%
	Dry throat	Uncommon	0.2%
GASTROINTESTINAL DISORDERS	Diarrhoea	Common	1.0%
	Vomiting	Uncommon	0.3%
	Nausea	Uncommon	0.6%
	Abdominal pain	Uncommon	0.6%
	Dyspepsia	Uncommon	0.5%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis	Common	5.5%
	Pruritis	Common	1.3%
	Rash	Uncommon	0.5%
	Urticaria	Uncommon	0.3%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia	Common	5.7%
	Myalgia	Common	5.6%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue	Very common	10.3%
	Pyrexia	Common	2.2%
	Chills	Common	5.6%
	Malaise	Common	7.5%
	Influenza like illness	Uncommon	0.9%
	Chest discomfort	Uncommon	0.1%
	Injection site reactions		
	Injection site pain	Very Common	11.4%
	Injection site induration	Common	1.3%
	Injection site erythema	Common	1.5%
	Injection site swelling	Common	1.0%
	Injection site haemorrhage	Common	2.0%
	Injection site irritation	Uncommon	0.3%
	Injection site pruritus	Uncommon	0.3%
	Injection site movement impairment	Uncommon	0.1%

Legend: ADR frequency is based upon the following scale: Very Common (≥ 1/10); Common (≥ 1/100 - < 1/10), Uncommon (≥ 1/1,000 - < 1/100), Rare (≥ 1/10,000 - < 1/1,000), Very Rare (< 1/10,000)

* The frequency 'uncommon' (0.3%) represents a single report in the elderly population (N = 400)

[1] Percentage represents the highest frequency (independent of investigator causality) observed either in the healthy adult (18 – 59 years, n = 3056) or healthy elderly study population (60 years and older, n = 400).

Adverse reactions reported with subcutaneous injection

In a study evaluating effectiveness and safety of subcutaneous administration of a different H5N1 strain (A/Indonesia/05/2005 strain) in Japanese subjects (N = 84), the following adverse reactions were reported:

Very common:	Injection site pain
Common:	Headache, Myalgia, Fatigue, Malaise, Hyperhydrosis, Oropharyngeal pain, Pruritus, Sedation, Dizziness, Chills, Asthma, Face swelling, Injection site erythema, Injection site haemorrhage, Injection site swelling, Injection site induration, Injection site paresthesia

Post-marketing Adverse Reactions

There are no post-marketing data available for PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

Class Reactions

Post-marketing experience with a whole virion, Vero cell derived, H1N1 vaccine:

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction, Hypersensitivity

NERVOUS SYSTEM DISORDERS: (Febrile) convulsion

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Angioedema

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Pain in extremity

Post-marketing experience with egg-derived interpandemic trivalent vaccines:

The following serious adverse reactions have been reported:

Uncommon:	Generalized skin reactions
Rare:	Neuralgia, Transient thrombocytopoenia. Allergic reactions (including shock)
Very rare:	Vasculitis with transient renal involvement. Neurological disorders, such as Encephalomyelitis, Neuritis, and Guillain Barré syndrome.

Overdose

No symptoms of overdose are known for PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This section describes the clinical experience with the PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccine.

Pandemic and Pre-Pandemic 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 H5N1 vaccines will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with H5N1 vaccines are relevant for the pandemic and pre-pandemic vaccines.

Immune response against (A/Vietnam/1203/2004)

The immunogenicity of the A/Vietnam/1203/2004 strain vaccine has been evaluated in three clinical studies in adults aged 18 - 59 years (N = 961) and in two clinical studies in subjects aged 60 years and older (N = 391) following a 0, 21 day schedule. In addition, the immunogenicity has also been evaluated in a Phase 3 study in specified risk groups of immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123) following a 0, 21 day schedule.

Immunogenicity in adults aged 18 to 59 years (N = 961) and in subjects aged 60 years and older (N = 391)

After vaccination, the seroprotection rate, seroconversion rate, and seroconversion factor for anti-HA antibody as measured by single radial haemolysis (SRH) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

SRH Assay	**18 – 59 years 21 Days After**		**60 years and above 21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroprotection rate*	53.2%	66.8%	47.7%	59.0%
Seroconversion rate**	39.8%	53.7%	41.9%	52.2%
Seroconversion factor***	2.5	3.4	2.7	3.5

* SRH area ≥ 25mm²

** either SRH area ≥ 25mm² if baseline sample negative or 50% increase in SRH area if baseline sample > 4mm²

*** geometric mean increase

After vaccination the rate of subjects with neutralizing antibody titres ≥ 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

MN assay	18 – 59 years 21 Days After		60 years and above 21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	44.4%	69.7%	51.9%	69.2%
Seroconversion rate**	32.7%	56.0%	13.3%	23.9%
Seroconversion factor***	3.0	4.5	2.0	2.6

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Immunogenicity in immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123)

After vaccination, the seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody, as measured by SRH, in immunocompromised subjects and patients with chronic disease conditions were as follows:

SRH assay	Immunocompromised subjects 21 Days After		Patients with chronic disease conditions 21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	37.2%	53.4%	28.7%	42.3%
Seroconversion rate**	19.8%	35.6%	20.5%	33.3%
Seroconversion factor***	1.4	1.9	1.5	2.0

* SRH area ≥ 25mm^2
** either SRH area ≥ 25mm^2 if baseline sample negative or 50% increase in SRH area if baseline sample > 4mm^2
*** geometric mean increase

After vaccination, the rate of subjects with neutralizing antibody titres ≥ 20, seroconversion rate and seroconversion factor, as measured by MN assay in immunocompromised subjects and patients with chronic disease conditions were as follows:

MN assay	Immunocompromised subjects		Patients with chronic disease conditions	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	24.8%	41.5%	44.3%	64.2%
Seroconversion rate**	9.1%	32.2%	17.3%	35.0%
Seroconversion factor***	1.6	2.5	2.3	3.0

* MN area ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Cross-reactive Immune Response Against Related H5N1 Strains

In a clinical study in adults aged 18 to 59 years (N = 265) and subjects aged 60 years and above (N = 270) after vaccination with the A/Vietnam/1203/2004 strain vaccine, the rate of subjects with cross-neutralising antibodies as measured by MN (titre ≥ 20) was as follows:

Tested against	18 – 59 years		60 years and above	
	Strain A/Indonesia/05/2005			
	Day 42[a]	Day 180	Day 42[a]	Day 180
Seroneutralisation rate*	35.1%	14.4%	54.8%	28.0%

* MN titre ≥ 20
a 21 days after 2nd dose

In a dose-finding study in adults aged 18 to 45 years investigating various dose levels of adjuvanted and non-adjuvanted formulations of the A/Vietnam/1203/2004 strain vaccine, the rates of subjects with neutralising antibody titres > 20, seroconversion rates and seroconversion factor for cross-neutralising antibodies, as measured by MN, in subjects who received the 7.5mcg non-adjuvanted formulation (N = 42) were as follows:

Tested against	Strain A/Indonesia/05/2005	
	Day 42[a]	Day 180
Seroneutralisation rate*	45.2%	33.3%
Seroconversion rate**	31.0%	21.4%
Seroconversion factor***	3.2	2.5

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase
a 21 days after 2nd dose

Heterologous Booster Vaccinations

A heterologous booster vaccination with a 7.5mcg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered in a time frame of 12 to 24 months after priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in three clinical studies in adults aged 18 to 59 years, adults aged 18 to 59 years (N = 177) and, in subjects aged 60 years (N = 146). A 12 to 24 months heterologous booster has also been administered in a Phase 3 study in immunocompromised subjects (N = 67) and patients with chronic disease conditions (N = 89).

Seroprotection rates (SRH area ≥ 25mm²) at 21 days after a 12 to 24 months booster vaccination with the 7.5mcg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains, were as follows:

Seroprotection rate*	**18 – 59 years**		**60 years and above**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	69.9%	57.5%	57.1%	47.3%

* SRH area ≥ 25mm²

Seroprotection rate*	**Immunocompromised subjects**		**Patients with chronic disease conditions**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	64.2%	41.8%	64.0%	50.6%

* SRH area ≥ 25mm²

Seroneutralization rates (MN titer ≥ 20) at 21 days after a booster vaccination with the 7.5mcg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains, were as follows:

Seroneutralization rate*	**18 – 59 years**		**60 years and above**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	85.8%	82.3%	80.2%	70.3%

* MN titre ≥ 20

Seroneutralization rate*	**Immunocompromised subjects**		**Patients with chronic disease conditions**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	71.6%	65.7%	77.5%	70.8%

* MN titre ≥ 20

A booster with a 7.5 mcg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine administered 12 months after a single dose priming vaccination with the A/Vietnam/1203/2004 strain vaccine was also evaluated in adults aged 18 to 59 years (N = 99).

Seroprotection/seroneutralization rates (SRH area ≥ 25mm^2; MN titre ≥ 20) at 21 days after a booster vaccination with the 7.5mcg dose of A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

Seroprotection rate*/ Seroneutralization rate**	**SRH Assay**		**MN Assay**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – Month Booster	79.8%	77.8%	85.9%	92.9%

* SRH area ≥ 25mm²
** MN titer ≥ 20

No clinical data have been generated in subjects below 18 years of age.

Information from non-clinical studies

The protective efficacy of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER against morbidity and mortality induced by the infection with lethal doses of highly pathogenic avian Influenza H5N1 virus was assessed non-clinically in a ferret challenge model. Two studies have been performed using either the H5N1 A/Vietnam/1203/2004 or the A/Indonesia/05/2005 vaccine.

In one study, sixteen (16) ferrets were divided into two cohorts and were vaccinated on days 0 and 21 with 7.5mcg of the A/Vietnam/1203/2004 vaccine or were sham vaccinated. All ferrets were challenged intranasally on day 35 with a high dose of the highly virulent H5N1 virus strain A/Vietnam/1203/2004 and monitored for 14 days. Ferrets vaccinated with the 7.5mcg dose of the A/Vietnam/1203/2004 vaccine demonstrated a high rate of seroconversion. The A/Vietnam/1203/2004 vaccine afforded protection against homologous challenge as evidenced by full survival, reduced weight loss, a less pronounced and shorter increase in temperature, a less marked reduction in lymphocyte count and in reduction of inflammation and necrosis in brain and olfactory bulb in the vaccinated cohorts as compared to control animals. All controls animals succumbed to the infection.

In a second study, sixty-six ferrets were divided into 6 cohorts of 11 ferrets and were immunized on days 0 and 21 with 3.75mcg or 7.5mcg of the Indonesia vaccine or were sham vaccinated. The ferrets were challenged intranasally on day 35 with a high dose of either the clade 2 H5N1 virus A/Indonesia/05/2005 or the clade 1 H5N1 virus A/Vietnam/1203/2004 and monitored for 14 days. The A/Indonesia/05/2005 vaccine was shown to be efficacious with 100% survival, reduced incidence of fever, reduced weight loss, reduced virus burden, and reduced haematological (leukopenia and lymphopenia) changes in the vaccinated cohorts following homologous challenge. Similarly, the A/Indonesia/05/2005 vaccine was efficacious against a heterologous challenge, showing a vaccine dose dependent survival in the vaccinated cohorts as compared to the control cohort. Similar to the homologous challenge, vaccination against a heterologous challenge reduced

virus burden, and reduced haematological (leucopenia) changes associated with highly pathogenic avian influenza infection.

Pharmacokinetic Properties

Not applicable.

Preclinical Safety Data

Non-clinical data reveal no special hazard for humans. Non-clinical studies demonstrated minor alterations in liver enzymes and calcium levels in a repeat dose toxicity study in rats. Clinically significant alterations in liver enzymes and calcium levels have not been seen to date in human clinical studies.

Animal reproductive and developmental toxicology studies do not indicate harmful effects in regard to female fertility, embryo-foetal and pre- and post-natal toxicity.

PHARMACEUTICAL PARTICULARS

List of Excipients

Trometamol

Sodium chloride

Water for injections

Polysorbate 80

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be combined or mixed with other medicinal products.

Shelf-Life

36 months.

After first opening, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

Special Precautions for Storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Store in the original package in order to protect from light.

Nature and Contents of the Container

One pack of 20 multi-dose vials (type I glass) of 5mL suspension (10 x 0.5mL doses) with a stopper (bromobutyl rubber)

Instructions for Use Handling and Disposal

The vaccine should be allowed to reach room temperature before use. Shake before use.

Each vaccine dose of 0.5mL is withdrawn into a syringe for injection. After first opening, the H5N1 vaccine should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

NAME AND ADDRESS

Manufacturer

Baxter AG
Industriestrasse 67
A-1221 Vienna
Austria

Distributor

Baxter Healthcare Ltd
PO Box 14-062
Panmure
Auckland 1741

MEDICINE CLASSIFICATION

Prescription Only Medicine.

DATE OF PREPARATION

16 July 2012

Based on ccds20620120508

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Whole virion, Vero cell derived, inactivated,

Suspension for injection

QUALITATIVE & QUANTITATIVE COMPOSITION

Suspension for injection.

One dose of 0.5mL contains:

Whole virion, non-adjuvanted influenza vaccine, inactivated, containing antigen† of strain:

A/Vietnam/1203/2004 (H5N1) 7.5 micrograms*.

† propagated in Vero cells (continuous cell line of mammalian origin)
* expressed in micrograms haemagglutinin.

This vaccine complies with the WHO recommendation and EU decision for the pandemic.

This vaccine is either available in a single dose pre-filled syringe or in a multidose container, *see Pharmaceutical Particulars/Nature and Contents of the Container* for the number of doses per vial.

For a full list of excipients, see *Pharmaceutical Particulars/List of Excipients.*

PHARMACEUTICAL FORM

Suspension for injection. The H5N1 vaccine is a clear to opalescent, translucent suspension.

CLINICAL PARTICULARS

Therapeutic Indications

Prophylaxis of influenza in an officially declared pandemic situation.

The vaccine may only be marketed or distributed in accordance with the directives contained in the current version of the New Zealand Influenza Pandemic Action Plan.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been evaluated in adults 18 - 59 years of age and in elderly 60 years of age and above.

Dosage and Method of Administration

Adults (18 years and older)

First dose of 0.5mL at an elected date.

A second dose of vaccine should be given after an interval of at least 3 weeks.

Immunization should be carried out by intramuscular injection into the deltoid muscle, *see Clinical Particulars/Special Warnings and Precautions for Use*.

There is no data available on PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccination dose and schedule for subjects under 18 years old and for subjects with co-morbidities (e.g. immunosuppressed subjects). In a pandemic situation administration of the vaccine in those populations shall follow national recommendations.

Individuals with hypersensitivity to egg and/or chicken proteins can be vaccinated with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER since the vaccine does not contain either egg or chicken proteins.

Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

For pregnant women, see *Clinical Particulars/Pregnancy, Lactation and Fertility*.

Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (e.g. formaldehyde, benzonase, sucrose, trypsin) of this vaccine. If vaccination is considered necessary, facilities for resuscitation should be immediately available in case of need *see Clinical Particulars/Special Warnings and Precautions for Use*.

Special Warnings and Precautions for Use

As with all vaccines administered by injection, allergic reactions, including severe anaphylactic reactions (such as anaphylactic shock), may occur after administration of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER. Immediate emergency treatment for anaphylaxis should be available.

Hypersensitivity reactions, including anaphylaxis, have been reported following use of a similar whole virion, Vero cell derived H1N1 influenza vaccine administered during a pandemic period, and have been observed both in patients with a history of multiple allergies and in patients with no known allergy.

If the situation allows, immunisation is recommended to be postponed in patients with severe febrile illness or acute infection.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER must not be administered intravascularly.

There are limited data with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER using the subcutaneous route see *Clinical Particulars/Adverse Reactions*. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleeding.

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

A protective immune response may not be induced in all individuals receiving the vaccine, *see Pharmacological Properties/Pharmacodynamic Properties*.

Special Populations

Pediatric use

No data are available with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in subjects below 18 years of age. Healthcare providers need to assess and take account of official guidance. (For adverse reactions with a similar vaccine used in children see *Clinical Particulars/Class Reactions*).

Although no pediatric information is available with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER, the following information was derived from clinical studies from a similar strain (inactivated H1N1 A/California/07/2009 strain).

Children and adolescents 3 to 17 years of age

In an ongoing clinical trial 51 children and adolescents aged 9 to 17 years and 51 children aged 3 to 8 years were administered the 7.5mcg dose of H1N1 A/California/07/2009 strain. The incidence and nature of symptoms after the first and second vaccination were similar to that observed in the adult and elderly population using inactivated H1N1 A/California/07/2009 strain.

Injection site pain was reported at a higher rate (very common) and headache and fatigue were reported at a lower rate (common) than in adults. Fever (≥ 38°C) was reported at a frequency of 7.8% and 9.8% after the first and second vaccination in children aged 3 to 8 years. No fever was reported in children and adolescents aged 9 to 17 years.

Children aged 6 to 35 months

In an ongoing clinical trial the 7.5mcg dose of inactivated H1N1 A/California/07/2009 strain was administered to 52 infants and young children aged 6 to 35 months. Sleep disorder was reported as

very common, and additional symptoms reported at a common frequency in this age group were anorexia, crying, irritability and somnolence. Fever (≥ 38°C) was reported at a frequency of 13.4% and 11.5% after the first and second vaccination.

Pandemic Observational Study

Preliminary safety data from 240 children, adolescents and adults (above 5 years of age) showed that within 7 days after the first vaccination 37.5% of subjects reported systemic Issued and reactions and 25.0% reported injection site reactions. In 53 children aged 6 months to 5 years, systemic reactions were reported in 30.2% and injection site reactions occurred in 20.8% of subjects. After the second dose, adverse reactions occurred at a lower frequency.

Very common reactions reported in children, adolescents and adults above 5 years of age
Injection site reaction, Fatigue, Headache, Myalgia, Gastrointestinal symptoms

Very common reactions reported in children aged 6 months to 5 years
Injection site reaction, Drowsiness, Irritability, Loss of appetite

Interactions with other Medicinal Products and other forms of Interaction

There are no data on co-administration of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER with other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs.

Immunoglobulin is not to be given with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER unless it is necessary during a medical emergency to provide immediate protection. If necessary, PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may be given at the same time as normal or specific immunoglobulin into separate limbs.

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

Following seasonal influenza vaccination, false positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus, and especially, HTLV-1. In such cases, the western blot method is negative. These transitory false-positive results may be due to IgM production in response to the vaccine.

Pregnancy, Lactation and Fertility

The safety of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in pregnancy and lactation has not been assessed in clinical trials. Animal studies with H5N1 strain vaccines (A/Vietnam/1203/2004 and A/Indonesia/05/2005) do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development. Healthcare providers should balance the potential risks and only prescribe PANDEMIC INFLUENZA VACCINE H5N1 BAXTER if clearly needed.

Effects on Ability to Drive and Use Machines

There is no information of the effects of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER on the ability to drive or operate an automobile or other heavy machinery.

Adverse Reactions

Adverse Reactions from Clinical Trials

Clinical trials were conducted with the PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccine (*see Section Pharmacological Properties/Pharmacodynamic Properties* for more information on the H5N1 vaccine) in approximately 3700 subjects (ranging in age from 18 to 60 years and above) and special risk groups of approximately 300 subjects each, consisting of immunocompromised subjects and patients with chronic disease conditions. The safety profile in immunocompromised subjects and patients with chronic disease conditions is similar to the safety profile in healthy subjects. The adverse reactions observed are shown in the table below.

Clinical Trial Adverse Reactions			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency Category**	**Frequency Percentage[1]**
INFECTIONS AND INFESTATIONS	Nasopharyngitis	Common	3.8%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy	Uncommon	0.2%
PSYCHIATRIC DISORDERS	Insomnia	Uncommon	0.3%
NERVOUS SYSTEM DISORDERS	Headache	Very Common	16.2%
	Dizziness	Uncommon	0.8%
	Somnolence	Uncommon	0.3%
	Sensory abnormalities: Paresthesia Dysesthesia Hypoesthesia Oral dysesthesia Burning sensation Dysgeusia	Common	1.1%
	Syncope	Uncommon	0.2%
EYE DISORDERS	Conjunctivitis	Uncommon	0.5%
	Eye irritation	Uncommon	0.7%
EAR AND LABYRINTH DISORDERS	Vertigo	Common	1.0%
	Sudden hearing loss	Uncommon	0.3%*
	Ear pain	Uncommon	0.1%
VASCULAR DISORDERS	Hypotension	Uncommon	0.5%

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Oropharyngeal pain	Common	2.4%
	Cough	Common	1.4%
	Dyspnoea	Uncommon	0.3%
	Nasal congestion	Uncommon	0.3%
	Rhinorrhoea	Uncommon	0.8%
	Dry throat	Uncommon	0.2%
GASTROINTESTINAL DISORDERS	Diarrhoea	Common	1.0%
	Vomiting	Uncommon	0.3%
	Nausea	Uncommon	0.6%
	Abdominal pain	Uncommon	0.6%
	Dyspepsia	Uncommon	0.5%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis	Common	5.5%
	Pruritis	Common	1.3%
	Rash	Uncommon	0.5%
	Urticaria	Uncommon	0.3%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia	Common	5.7%
	Myalgia	Common	5.6%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue	Very common	10.3%
	Pyrexia	Common	2.2%
	Chills	Common	5.6%
	Malaise	Common	7.5%
	Influenza like illness	Uncommon	0.9%
	Chest discomfort	Uncommon	0.1%
	Injection site reactions		
	Injection site pain	Very Common	11.4%
	Injection site induration	Common	1.3%
	Injection site erythema	Common	1.5%
	Injection site swelling	Common	1.0%
	Injection site haemorrhage	Common	2.0%
	Injection site irritation	Uncommon	0.3%
	Injection site pruritus	Uncommon	0.3%
	Injection site movement impairment	Uncommon	0.1%

Legend: ADR frequency is based upon the following scale: Very Common (≥ 1/10); Common (≥ 1/100 - < 1/10), Uncommon (≥ 1/1,000 - < 1/100), Rare (≥ 1/10,000 - < 1/1,000), Very Rare (< 1/10,000)

* The frequency 'uncommon' (0.3%) represents a single report in the elderly population (N = 400)

[1] Percentage represents the highest frequency (independent of investigator causality) observed either in the healthy adult (18 – 59 years, n = 3056) or healthy elderly study population (60 years and older, n = 400).

Adverse reactions reported with subcutaneous injection

In a study evaluating effectiveness and safety of subcutaneous administration of a different H5N1 strain (A/Indonesia/05/2005 strain) in Japanese subjects (N = 84), the following adverse reactions were reported:

Very common:	Injection site pain
Common:	Headache, Myalgia, Fatigue, Malaise, Hyperhydrosis, Oropharyngeal pain, Pruritus, Sedation, Dizziness, Chills, Asthma, Face swelling, Injection site erythema, Injection site haemorrhage, Injection site swelling, Injection site induration, Injection site paresthesia

Post-marketing Adverse Reactions

There are no post-marketing data available for PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

Class Reactions

Post-marketing experience with a whole virion, Vero cell derived, H1N1 vaccine:

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction, Hypersensitivity

NERVOUS SYSTEM DISORDERS: (Febrile) convulsion

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Angioedema

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Pain in extremity

Post-marketing experience with egg-derived interpandemic trivalent vaccines:

The following serious adverse reactions have been reported:

Uncommon:	Generalized skin reactions
Rare:	Neuralgia, Transient thrombocytopoenia. Allergic reactions (including shock)
Very rare:	Vasculitis with transient renal involvement. Neurological disorders, such as Encephalomyelitis, Neuritis, and Guillain Barré syndrome.

Overdose

No symptoms of overdose are known for PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This section describes the clinical experience with the PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccine.

Pandemic and Pre-Pandemic 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 H5N1 vaccines will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with H5N1 vaccines are relevant for the pandemic and pre-pandemic vaccines.

Immune response against (A/Vietnam/1203/2004)

The immunogenicity of the A/Vietnam/1203/2004 strain vaccine has been evaluated in three clinical studies in adults aged 18 - 59 years (N = 961) and in two clinical studies in subjects aged 60 years and older (N = 391) following a 0, 21 day schedule. In addition, the immunogenicity has also been evaluated in a Phase 3 study in specified risk groups of immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123) following a 0, 21 day schedule.

Immunogenicity in adults aged 18 to 59 years (N = 961) and in subjects aged 60 years and older (N = 391)

After vaccination, the seroprotection rate, seroconversion rate, and seroconversion factor for anti-HA antibody as measured by single radial haemolysis (SRH) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

SRH Assay	**18 – 59 years 21 Days After**		**60 years and above 21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroprotection rate*	53.2%	66.8%	47.7%	59.0%
Seroconversion rate**	39.8%	53.7%	41.9%	52.2%
Seroconversion factor***	2.5	3.4	2.7	3.5

* SRH area ≥ 25mm²

** either SRH area ≥ 25mm² if baseline sample negative or 50% increase in SRH area if baseline sample > 4mm²

*** geometric mean increase

After vaccination the rate of subjects with neutralizing antibody titres ≥ 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

MN assay	18 – 59 years 21 Days After		60 years and above 21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	44.4%	69.7%	51.9%	69.2%
Seroconversion rate**	32.7%	56.0%	13.3%	23.9%
Seroconversion factor***	3.0	4.5	2.0	2.6

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Immunogenicity in immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123)

After vaccination, the seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody, as measured by SRH, in immunocompromised subjects and patients with chronic disease conditions were as follows:

SRH assay	Immunocompromised subjects 21 Days After		Patients with chronic disease conditions 21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	37.2%	53.4%	28.7%	42.3%
Seroconversion rate**	19.8%	35.6%	20.5%	33.3%
Seroconversion factor***	1.4	1.9	1.5	2.0

* SRH area ≥ 25mm^2
** either SRH area ≥ 25mm^2 if baseline sample negative or 50% increase in SRH area if baseline sample > 4mm^2
*** geometric mean increase

After vaccination, the rate of subjects with neutralizing antibody titres ≥ 20, seroconversion rate and seroconversion factor, as measured by MN assay in immunocompromised subjects and patients with chronic disease conditions were as follows:

MN assay	Immunocompromised subjects		Patients with chronic disease conditions	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	24.8%	41.5%	44.3%	64.2%
Seroconversion rate**	9.1%	32.2%	17.3%	35.0%
Seroconversion factor***	1.6	2.5	2.3	3.0

* MN area ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Cross-reactive Immune Response Against Related H5N1 Strains

In a clinical study in adults aged 18 to 59 years (N = 265) and subjects aged 60 years and above (N = 270) after vaccination with the A/Vietnam/1203/2004 strain vaccine, the rate of subjects with cross-neutralising antibodies as measured by MN (titre ≥ 20) was as follows:

Tested against	18 – 59 years		60 years and above	
	Strain A/Indonesia/05/2005			
	Day 42[a]	Day 180	Day 42[a]	Day 180
Seroneutralisation rate*	35.1%	14.4%	54.8%	28.0%

* MN titre ≥ 20
a 21 days after 2nd dose

In a dose-finding study in adults aged 18 to 45 years investigating various dose levels of adjuvanted and non-adjuvanted formulations of the A/Vietnam/1203/2004 strain vaccine, the rates of subjects with neutralising antibody titres > 20, seroconversion rates and seroconversion factor for cross-neutralising antibodies, as measured by MN, in subjects who received the 7.5mcg non-adjuvanted formulation (N = 42) were as follows:

Tested against	Strain A/Indonesia/05/2005	
	Day 42[a]	Day 180
Seroneutralisation rate*	45.2%	33.3%
Seroconversion rate**	31.0%	21.4%
Seroconversion factor***	3.2	2.5

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase
a 21 days after 2nd dose

Heterologous Booster Vaccinations

A heterologous booster vaccination with a 7.5mcg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered in a time frame of 12 to 24 months after priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in three clinical studies in adults aged 18 to 59 years, adults aged 18 to 59 years (N = 177) and, in subjects aged 60 years (N = 146). A 12 to 24 months heterologous booster has also been administered in a Phase 3 study in immunocompromised subjects (N = 67) and patients with chronic disease conditions (N = 89).

Seroprotection rates (SRH area ≥ 25mm²) at 21 days after a 12 to 24 months booster vaccination with the 7.5mcg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains, were as follows:

Seroprotection rate*	**18 – 59 years**		**60 years and above**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	69.9%	57.5%	57.1%	47.3%

* SRH area ≥ 25mm²

Seroprotection rate*	**Immunocompromised subjects**		**Patients with chronic disease conditions**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	64.2%	41.8%	64.0%	50.6%

* SRH area ≥ 25mm²

Seroneutralization rates (MN titer ≥ 20) at 21 days after a booster vaccination with the 7.5mcg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains, were as follows:

Seroneutralization rate*	**18 – 59 years**		**60 years and above**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	85.8%	82.3%	80.2%	70.3%

* MN titre ≥ 20

Seroneutralization rate*	**Immunocompromised subjects**		**Patients with chronic disease conditions**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	71.6%	65.7%	77.5%	70.8%

* MN titre ≥ 20

A booster with a 7.5 mcg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine administered 12 months after a single dose priming vaccination with the A/Vietnam/1203/2004 strain vaccine was also evaluated in adults aged 18 to 59 years (N = 99).

Seroprotection/seroneutralization rates (SRH area ≥ 25mm^2; MN titre ≥ 20) at 21 days after a booster vaccination with the 7.5mcg dose of A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

Seroprotection rate*/ Seroneutralization rate**	**SRH Assay**		**MN Assay**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – Month Booster	79.8%	77.8%	85.9%	92.9%

* SRH area ≥ 25mm²
** MN titer ≥ 20

No clinical data have been generated in subjects below 18 years of age.

Information from non-clinical studies

The protective efficacy of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER against morbidity and mortality induced by the infection with lethal doses of highly pathogenic avian Influenza H5N1 virus was assessed non-clinically in a ferret challenge model. Two studies have been performed using either the H5N1 A/Vietnam/1203/2004 or the A/Indonesia/05/2005 vaccine.

In one study, sixteen (16) ferrets were divided into two cohorts and were vaccinated on days 0 and 21 with 7.5mcg of the A/Vietnam/1203/2004 vaccine or were sham vaccinated. All ferrets were challenged intranasally on day 35 with a high dose of the highly virulent H5N1 virus strain A/Vietnam/1203/2004 and monitored for 14 days. Ferrets vaccinated with the 7.5mcg dose of the A/Vietnam/1203/2004 vaccine demonstrated a high rate of seroconversion. The A/Vietnam/1203/2004 vaccine afforded protection against homologous challenge as evidenced by full survival, reduced weight loss, a less pronounced and shorter increase in temperature, a less marked reduction in lymphocyte count and in reduction of inflammation and necrosis in brain and olfactory bulb in the vaccinated cohorts as compared to control animals. All controls animals succumbed to the infection.

In a second study, sixty-six ferrets were divided into 6 cohorts of 11 ferrets and were immunized on days 0 and 21 with 3.75mcg or 7.5mcg of the Indonesia vaccine or were sham vaccinated. The ferrets were challenged intranasally on day 35 with a high dose of either the clade 2 H5N1 virus A/Indonesia/05/2005 or the clade 1 H5N1 virus A/Vietnam/1203/2004 and monitored for 14 days. The A/Indonesia/05/2005 vaccine was shown to be efficacious with 100% survival, reduced incidence of fever, reduced weight loss, reduced virus burden, and reduced haematological (leukopenia and lymphopenia) changes in the vaccinated cohorts following homologous challenge. Similarly, the A/Indonesia/05/2005 vaccine was efficacious against a heterologous challenge, showing a vaccine dose dependent survival in the vaccinated cohorts as compared to the control cohort. Similar to the homologous challenge, vaccination against a heterologous challenge reduced

virus burden, and reduced haematological (leucopenia) changes associated with highly pathogenic avian influenza infection.

Pharmacokinetic Properties

Not applicable.

Preclinical Safety Data

Non-clinical data reveal no special hazard for humans. Non-clinical studies demonstrated minor alterations in liver enzymes and calcium levels in a repeat dose toxicity study in rats. Clinically significant alterations in liver enzymes and calcium levels have not been seen to date in human clinical studies.

Animal reproductive and developmental toxicology studies do not indicate harmful effects in regard to female fertility, embryo-foetal and pre- and post-natal toxicity.

PHARMACEUTICAL PARTICULARS

List of Excipients

Trometamol

Sodium chloride

Water for injections

Polysorbate 80

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be combined or mixed with other medicinal products.

Shelf-Life

36 months.

After first opening, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

Special Precautions for Storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Store in the original package in order to protect from light.

Nature and Contents of the Container

One pack of 20 multi-dose vials (type I glass) of 5mL suspension (10 x 0.5mL doses) with a stopper (bromobutyl rubber).

One pack of 1 single dose pre-filled syringe (type I glass) containing 0.5 mL suspension for injection, with a latex free plunger stopper (halogeno butyl rubber) with or without needles.

Not all pack sizes may be marketed.

Instructions for Use Handling and Disposal

The vaccine should be allowed to reach room temperature before use. Shake before use.

Multi-dose vial: Each vaccine dose of 0.5mL is withdrawn into a syringe for injection. After first opening, the H5N1 vaccine should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

Pre-filled syringe: After removing the syringe cap, attach the needle immediately and remove the needle shield prior to administration. Once the needle is attached, the vaccine must be administered immediately.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

FURTHER INFORMATION

This medicine has been granted provisional consent for distribution under section 23 of the Medicines Act 1981.

The product may only be marketed or distributed in accordance with the directives contained in the current version of the National Health Emergency Plan.

NAME AND ADDRESS

Manufacturer

Baxter AG
Industriestrasse 67
A-1221 Vienna
Austria

Distributor

Baxter Healthcare Ltd
PO Box 14-062
Panmure
Auckland 1741

MEDICINE CLASSIFICATION

Prescription Only Medicine.

DATE OF PREPARATION

14 August 2012

Based on ccds20620120508

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

Baxter and PANDEMIC INFLUENZA VACCINE H5N1 BAXTER are trademarks of Baxter International Inc.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Whole virion, Vero cell derived, inactivated,

Suspension for injection

QUALITATIVE & QUANTITATIVE COMPOSITION

Suspension for injection.

One dose of 0.5mL contains:

Whole virion, non-adjuvanted influenza vaccine, inactivated, containing antigen† of strain:

A/Vietnam/1203/2004 (H5N1) 7.5 micrograms*.

† propagated in Vero cells (continuous cell line of mammalian origin)
* expressed in micrograms haemagglutinin.

This vaccine complies with the WHO recommendation and EU decision for the pandemic.

This vaccine is either available in a single dose pre-filled syringe or in a multi-dose container, *see PHARMACEUTICAL PARTICULARS/Nature and Contents of the Container* for the number of doses per vial.

For a full list of excipients, see *PHARMACEUTICAL PARTICULARS/List of Excipients.*

PHARMACEUTICAL FORM

Suspension for injection. The H5N1 vaccine is a clear to opalescent, translucent suspension.

CLINICAL PARTICULARS

Therapeutic Indications

Prophylaxis of influenza in an officially declared pandemic situation.

The vaccine may only be marketed or distributed in accordance with the directives contained in the current version of the New Zealand Influenza Pandemic Action Plan.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been evaluated in adults 18 - 59 years of age and in elderly 60 years of age and above.

Dosage and Method of Administration

Adults (18 years and older): first dose of 0.5mL at an elected date.

A second dose of vaccine should be given after an interval of at least 3 weeks.

Immunization should be carried out by intramuscular injection into the deltoid muscle, *see CLINICAL PARTICULARS/Special Warnings and Precautions for Use*.

There is no data available on PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccination dose and schedule for subjects under 18 years old and for subjects with co-morbidities (e.g. immunosuppressed subjects). In a pandemic situation administration of the vaccine in those populations shall follow national recommendations.

Individuals with hypersensitivity to egg and/or chicken proteins can be vaccinated with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER since egg and chicken proteins are not used in the manufacturing process.

Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

For pregnant women, see *CLINICAL PARTICULARS/Pregnancy, Lactation and Fertility*.

Contraindications

History of an anaphylactic reaction to any of the constituents or trace residues of this vaccine (formaldehyde, benzonase, sucrose, trypsin, or Vero Host Cell Protein). If vaccination is considered necessary, facilities for resuscitation should be immediately available in case of need *see CLINICAL PARTICULARS/Special Warnings and Precautions for Use*.

Special Warnings and Precautions for Use

As with all vaccines administered by injection, allergic reactions, including severe anaphylactic reactions (such as anaphylactic shock), may occur after administration of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER. Immediate emergency treatment for anaphylaxis should be available.

Hypersensitivity reactions, including anaphylaxis, have been reported following use of a similar whole virion, Vero cell derived H1N1 influenza vaccine administered during a pandemic period, and have been observed both in patients with a history of multiple allergies and in patients with no known allergy.

If the situation allows, immunisation is recommended to be postponed in patients with severe febrile illness or acute infection.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER must not be administered intravascularly.

There are limited data with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER using the subcutaneous route see *CLINICAL PARTICULARS/Adverse Reactions*. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleeding.

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

A protective immune response may not be induced in all individuals receiving the vaccine, *see PHARMACOLOGICAL PROPERTIES/Pharmacodynamic Properties*.

Interactions with other Medicinal Products and other forms of Interaction

There are no data on co-administration of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER with other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs.

Immunoglobulin is not to be given with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER unless it is necessary during a medical emergency to provide immediate protection. If necessary, PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may be given at the same time as normal or specific immunoglobulin into separate limbs.

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

Following seasonal influenza vaccination, false positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus, and especially, HTLV-1. In such cases, the western blot method is negative. These transitory false-positive results may be due to IgM production in response to the vaccine.

Pregnancy, Lactation and Fertility

There are no data from the use of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in pregnant or lactating women. Healthcare providers should balance the potential risks and only prescribe PANDEMIC INFLUENZA VACCINE H5N1 BAXTER if clearly needed.

Animal studies with H5N1 strain vaccines (A/Vietnam/1203/2004 and A/Indonesia/05/2005) do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

The effects of **PANDEMIC INFLUENZA VACCINE H5N1 BAXTER** on fertility have not been established.

Effects on Ability to Drive and Use Machines

There is no information of the effects of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER on the ability to drive or operate an automobile or other heavy machinery.

Special Populations

Pediatric use

No data are available with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in subjects below 18 years of age. Healthcare providers need to assess and take account of official guidance. (For adverse reactions with a similar vaccine used in children see *CLINICAL PARTICULARS/Class Reactions*).

Although no pediatric information is available with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER, the following information was derived from clinical studies from a similar strain (inactivated H1N1 A/California/07/2009 strain).

Children and adolescents 3 to 17 years of age

In an ongoing clinical trial 51 children and adolescents aged 9 to 17 years and 51 children aged 3 to 8 years were administered the 7.5mcg dose of H1N1 A/California/07/2009 strain. The incidence and nature of symptoms after the first and second vaccination were similar to that observed in the adult and elderly population using inactivated H1N1 A/California/07/2009 strain.

Injection site pain was reported at a higher rate (very common) and headache and fatigue were reported at a lower rate (common) than in adults. Fever (≥ 38°C) was reported at a frequency of 7.8% and 9.8% after the first and second vaccination in children aged 3 to 8 years. No fever was reported in children and adolescents aged 9 to 17 years.

Children aged 6 to 35 months

In an ongoing clinical trial the 7.5mcg dose of inactivated H1N1 A/California/07/2009 strain was administered to 52 infants and young children aged 6 to 35 months. Sleep disorder was reported as very common, and additional symptoms reported at a common frequency in this age group were anorexia, crying, irritability and somnolence. Fever (≥ 38°C) was reported at a frequency of 13.4% and 11.5% after the first and second vaccination.

Pandemic Observational Study

Preliminary safety data from 240 children, adolescents and adults (above 5 years of age) showed that within 7 days after the first vaccination 37.5% of subjects reported systemic Issued and

reactions and 25.0% reported injection site reactions. In 53 children aged 6 months to 5 years, systemic reactions were reported in 30.2% and injection site reactions occurred in 20.8% of subjects. After the second dose, adverse reactions occurred at a lower frequency.

Very common reactions reported in children, adolescents and adults above 5 years of age
Injection site reaction, Fatigue, Headache, Myalgia, Gastrointestinal symptoms

Very common reactions reported in children aged 6 months to 5 years
Injection site reaction, Drowsiness, Irritability, Loss of appetite

Adverse Reactions

Adverse reactions from clinical trials

Clinical trials were conducted with the PANDEMIC INFLUENZA VACCINE H5N1 BAXTER vaccine (*see Section Pharmacological Properties/Pharmacodynamic Properties* for more information on the H5N1 vaccine) in approximately 3700 subjects (ranging in age from 18 to 59 years and 60 years and above) and special risk groups of approximately 300 subjects each, consisting of immunocompromised subjects and patients with chronic disease conditions. The safety profile in immunocompromised subjects and patients with chronic disease conditions is similar to the safety profile in healthy adults and elderly subjects. The adverse reactions observed are shown in the table below.

Clinical Trial Adverse Reactions			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**	**Frequency Percentage or Ratio[1]**
INFECTIONS AND INFESTATIONS	Nasopharyngitis	Common	3.8%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy	Uncommon	0.2%
PSYCHIATRIC DISORDERS	Insomnia	Uncommon	0.3%
NERVOUS SYSTEM DISORDERS	Headache	Very Common	16.2%
	Dizziness	Uncommon	0.8%
	Somnolence	Uncommon	0.3%
	Sensory disturbance: Paresthesia Dysesthesia Hypoesthesia Oral dysesthesia Burning sensation Dysgeusia	Common	1.1%
	Syncope	Uncommon	0.2%

EYE DISORDERS	**Conjunctivitis**	Uncommon	0.5%
	Eye irritation	Uncommon	0.7%
EAR AND LABYRINTH DISORDERS	Vertigo	Common	1.0%
	Sudden hearing loss	Uncommon	0.3%*
	Ear pain	Uncommon	0.1%
VASCULAR DISORDERS	Hypotension	Uncommon	0.5%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Oropharyngeal pain	Common	2.4%
	Cough	Common	1.4%
	Dyspnoea	Uncommon	0.3%
	Nasal congestion	Uncommon	0.3%
	Rhinorrhoea	Uncommon	0.8%
	Dry throat	Uncommon	0.2%
GASTROINTESTINAL DISORDERS	Diarrhoea	Common	1.0%
	Vomiting	Uncommon	0.3%
	Nausea	Uncommon	0.6%
	Abdominal pain	Uncommon	0.6%
	Dyspepsia	Uncommon	0.5%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis	Common	5.5%
	Pruritis	Common	1.3%
	Rash	Uncommon	0.5%
	Urticaria	Uncommon	0.3%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia	Common	5.7%
	Myalgia	Common	5.6%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue	Very common	10.3%
	Pyrexia	Common	2.2%
	Chills	Common	5.6%
	Malaise	Common	7.5%
	Influenza like illness	Uncommon	0.9%
	Chest discomfort	Uncommon	0.1%
	Injection site reactions:		
	Injection site pain	Very Common	11.4%
	Injection site induration	Common	1.3%
	Injection site erythema	Common	1.5%
	Injection site swelling	Common	1.0%
	Injection site haemorrhage	Common	2.0%
	Injection site irritation	Uncommon	0.3%
	Injection site pruritus	Uncommon	0.3%
	Injection site movement impairment	Uncommon	0.1%

Legend: ADR frequency is based upon the following scale: Very Common (≥ 1/10); Common (≥ 1/100 - < 1/10), Uncommon (≥ 1/1,000 - < 1/100), Rare (≥ 1/10,000 - < 1/1,000), Very Rare (< 1/10,000)
* The frequency 'uncommon' (0.3%) represents a single report in the elderly population (N = 400)
[1] Percentage represents the highest frequency (independent of investigator causality) observed either in the healthy adult (18 – 59 years, n = 3056) or healthy elderly study population (60 years and older, n = 400) after the first or second vaccination.

Adverse reactions reported with subcutaneous injection

In a clinical trial evaluating effectiveness and safety of subcutaneous administration of a different H5N1 strain (A/Indonesia/05/2005 strain) in Japanese subjects (N = 84), the following adverse reactions were reported:

Very common: Injection site pain
Common: Headache, Myalgia, Fatigue, Malaise, Hyperhydrosis, Oropharyngeal pain, Pruritus, Sedation, Dizziness, Chills, Asthma, Face swelling, Injection site erythema, Injection site haemorrhage, Injection site swelling, Injection site induration, Injection site paresthesia

Post-marketing adverse reactions

There are no post-marketing data available for PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

Class reactions

In addition to the adverse reactions observed with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in clinical trials (see *ADVERSE REACTIONS/Adverse Reactions from Clinical Trials*) the following adverse reactions were observed in the post-marketing experience with a whole virion, Vero cell derived, H1N1 vaccine:

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction, Hypersensitivity

NERVOUS SYSTEM DISORDERS: (Febrile) convulsion

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Angioedema

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Pain in extremity

Post-marketing experience with egg-derived interpandemic trivalent vaccines:

The following serious adverse reactions have been reported:

Uncommon: Generalized skin reactions
Rare: Neuralgia, Transient thrombocytopoenia. Allergic reactions (including shock)
Very rare: Vasculitis with transient renal involvement. Neurological disorders, such as Encephalomyelitis, Neuritis, and Guillain Barré syndrome.

Overdose

No symptoms of overdose are known for PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This section describes the clinical experience with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

Pandemic and Pre-Pandemic 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 H5N1 vaccines will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with H5N1 vaccines are relevant for the pandemic and pre-pandemic vaccines.

Immune response against (A/Vietnam/1203/2004) (H5N1)

The immunogenicity of the A/Vietnam/1203/2004 strain vaccine has been evaluated in three clinical studies in adults aged 18 - 59 years (N = 961) and in two clinical studies in subjects aged 60 years and older (N = 391) following a 0, 21 day schedule. In addition, the immunogenicity has also been evaluated in a Phase 3 study in specified risk groups of immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123) following a 0, 21 day schedule.

Immunogenicity in adults aged 18 - 59 years (N = 961) & subjects aged 60 years & older (N = 391)

After vaccination, the seroprotection rate, seroconversion rate, and seroconversion factor for anti-HA antibody as measured by single radial haemolysis (SRH) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

SRH Assay	**18 – 59 years 21 Days After**		**60 years and above 21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroprotection rate*	53.2%	66.8%	47.7%	59.0%
Seroconversion rate**	39.8%	53.7%	41.9%	52.2%
Seroconversion factor***	2.5	3.4	2.7	3.5

* SRH area ≥ 25mm²

** either SRH area ≥ 25mm² if baseline sample negative or 50% increase in SRH area if baseline sample > 4mm²

*** geometric mean increase

After vaccination the rate of subjects with neutralizing antibody titres ≥ 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above were as follows:

MN assay	**18 – 59 years 21 Days After**		**60 years and above 21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroneutralisation rate*	44.4%	69.7%	51.9%	69.2%
Seroconversion rate**	32.7%	56.0%	13.3%	23.9%
Seroconversion factor***	3.0	4.5	2.0	2.6

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Immunogenicity in immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123)

After vaccination, the seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody, as measured by SRH, in immunocompromised subjects and patients with chronic disease conditions were as follows:

SRH assay	**Immunocompromised subjects 21 Days After**		**Patients with chronic disease conditions 21 Days After**	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Seroneutralisation rate*	37.2%	53.4%	28.7%	42.3%
Seroconversion rate**	19.8%	35.6%	20.5%	33.3%
Seroconversion factor***	1.4	1.9	1.5	2.0

* SRH area ≥ 25mm^2
** either SRH area ≥ 25mm^2 if baseline sample negative or 50% increase in SRH area if baseline sample > 4mm^2
*** geometric mean increase

After vaccination, the rate of subjects with neutralizing antibody titres ≥ 20, seroconversion rate and seroconversion factor, as measured by MN assay in immunocompromised subjects and patients with chronic disease conditions were as follows:

MN assay	Immunocompromised subjects		Patients with chronic disease conditions	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	24.8%	41.5%	44.3%	64.2%
Seroconversion rate**	9.1%	32.2%	17.2%	35.0%
Seroconversion factor***	1.6	2.5	2.3	3.0

* MN area ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Cross-reactive Immune Response Against Related H5N1 Strains

In a clinical trial in adults aged 18 to 59 years (N = 265) and subjects aged 60 years and above (N = 270) after vaccination with the A/Vietnam/1203/2004 strain vaccine, the rate of subjects with cross-neutralising antibodies as measured by MN (titre ≥ 20) was as follows:

Tested against	18 – 59 years		60 years and above	
	Strain A/Indonesia/05/2005			
	Day 42[a]	Day 180	Day 42[a]	Day 180
Seroneutralisation rate*	35.1%	14.4%	54.8%	28.0%

* MN titre ≥ 20
a 21 days after 2nd dose

In a dose-finding study in adults aged 18 to 45 years investigating various dose levels of adjuvanted and non-adjuvanted formulations of the A/Vietnam/1203/2004 strain vaccine, the rates of subjects with neutralising antibody titres > 20, seroconversion rates and seroconversion factor for cross-neutralising antibodies, as measured by MN, in subjects who received the 7.5mcg non-adjuvanted formulation (N = 42) were as follows:

Tested against	Strain A/Indonesia/05/2005	
	Day 42[a]	Day 180
Seroneutralisation rate*	45.2%	33.3%
Seroconversion rate**	31.0%	21.4%
Seroconversion factor***	3.2	2.5

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase
a 21 days after 2nd dose

Heterologous Booster Vaccinations

A heterologous booster vaccination with a 7.5mcg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered in a time frame of 12 to 24 months after priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in three clinical studies in adults aged 18 to 59 years, adults aged 18 to 59 years (N = 177) and, in subjects aged 60 years (N = 146). A 12 to 24 months heterologous booster has also been administered in a Phase 3 study in immunocompromised subjects (N = 67) and patients with chronic disease conditions (N = 89).

Seroprotection rates (SRH area ≥ 25mm²) at 21 days after a 12 to 24 months booster vaccination with the 7.5mcg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains, were as follows:

Seroprotection rate*	**18 – 59 years**		**60 years and above**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	73.9%	62.5%	61.6%	57.5%

* SRH area ≥ 25mm²

Seroprotection rate*	**Immunocompromised subjects**		**Patients with chronic disease conditions**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	64.2%	41.8%	64.0%	50.6%

* SRH area ≥ 25mm²

Seroneutralization rates (MN titer ≥ 20) at 21 days after a booster vaccination with the 7.5mcg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains, were as follows:

Seroneutralization rate*	**18 – 59 years**		**60 years and above**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	89.8%	86.9%	82.9%	75.3%

* MN titre ≥ 20

Seroneutralization rate*	**Immunocompromised subjects**		**Patients with chronic disease conditions**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – 24 Month Booster	71.6%	65.7%	77.5%	70.8%

* MN titre ≥ 20

A booster with a 7.5 mcg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine administered 12 months after a single dose priming vaccination with the A/Vietnam/1203/2004 strain vaccine was also evaluated in adults aged 18 to 59 years (N = 99).

Seroprotection/seroneutralization rates (SRH area ≥ 25mm^2; MN titre ≥ 20) at 21 days after a booster vaccination with the 7.5mcg dose of A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

Seroprotection rate*/ Seroneutralization rate**	**SRH Assay**		**MN Assay**	
Tested against	**A/Vietnam**	**A/Indonesia**	**A/Vietnam**	**A/Indonesia**
12 – Month Booster	79.8%	77.8%	85.9%	92.9%

* SRH area ≥ 25mm²
** MN titer ≥ 20

Information from non-clinical studies

The protective efficacy of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER against morbidity and mortality induced by the infection with lethal doses of highly pathogenic avian Influenza H5N1 virus was assessed non-clinically in a ferret challenge model. Two studies have been performed using either the H5N1 A/Vietnam/1203/2004 or the A/Indonesia/05/2005 vaccine.

In one study, 16 ferrets were divided into two cohorts and were vaccinated on days 0 and 21 with 7.5mcg of the A/Vietnam/1203/2004 vaccine or were sham vaccinated. All ferrets were challenged intranasally on day 35 with a high dose of the highly virulent H5N1 virus strain A/Vietnam/1203/2004 and monitored for 14 days. Ferrets vaccinated with the 7.5mcg dose of the A/Vietnam/1203/2004 vaccine demonstrated a high rate of seroconversion. The A/Vietnam/1203/2004 vaccine afforded protection against homologous challenge as evidenced by full survival, reduced weight loss, a less pronounced and shorter increase in temperature, a less marked reduction in lymphocyte count and in reduction of inflammation and necrosis in brain and olfactory bulb in the vaccinated cohorts as compared to control animals. All controls animals succumbed to the infection.

In a second study, sixty-six ferrets were divided into 6 cohorts of 11 ferrets and were immunized on days 0 and 21 with 3.75mcg or 7.5mcg of the Indonesia vaccine or were sham vaccinated. The ferrets were challenged intranasally on day 35 with a high dose of either the clade 2 H5N1 virus A/Indonesia/05/2005 or the clade 1 H5N1 virus A/Vietnam/1203/2004 and monitored for 14 days. The A/Indonesia/05/2005 vaccine was shown to be efficacious with 100% survival, reduced incidence of fever, reduced weight loss, reduced virus burden, and reduced haematological (leukopenia and lymphopenia) changes in the vaccinated cohorts following homologous challenge. Similarly, the A/Indonesia/05/2005 vaccine was efficacious against a heterologous challenge, showing a vaccine dose dependent survival in the vaccinated cohorts as compared to the control cohort. Similar to the homologous challenge, vaccination against a heterologous challenge reduced

virus burden, and reduced haematological (leucopenia) changes associated with highly pathogenic avian influenza infection.

Pharmacokinetic Properties

Not applicable.

Preclinical Safety Data

Non-clinical data reveal no special hazard for humans. Non-clinical studies demonstrated minor alterations in liver enzymes and calcium levels in a repeat dose toxicity study in rats. Clinically significant alterations in liver enzymes and calcium levels have not been seen to date in human clinical studies.

Animal reproductive and developmental toxicology studies do not indicate harmful effects in regard to female fertility, embryo-foetal and pre- and post-natal toxicity.

PHARMACEUTICAL PARTICULARS

List of Excipients

Trometamol

Sodium chloride

Water for injections

Polysorbate 80

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be combined or mixed with other medicinal products.

Shelf Life

36 months.

After first opening, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

Special Precautions for Storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Store in the original package in order to protect from light.

Nature and Contents of the Container

One pack of 20 multi-dose vials (type I glass) of 5mL suspension (10 x 0.5mL doses) with a stopper (bromobutyl rubber).

One pack of 1 single dose pre-filled syringe (type I glass) containing 0.5 mL suspension for injection, with a latex free plunger stopper (halogeno butyl rubber) with or without needles.

Not all pack sizes may be marketed.

Instructions for Use Handling and Disposal

The vaccine should be allowed to reach room temperature before use. Shake before use.

Multi-dose vial: Each vaccine dose of 0.5mL is withdrawn into a syringe for injection. After first opening, the H5N1 vaccine should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

Pre-filled syringe: After removing the syringe cap, attach the needle immediately and remove the needle shield prior to administration. Once the needle is attached, the vaccine must be administered immediately.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

FURTHER INFORMATION

This medicine has been granted provisional consent for distribution under section 23 of the Medicines Act 1981.

This vaccine may only be marketed or distributed in accordance with the directives contained in the current version of the New Zealand Influenza Pandemic Action Plan.

NAME AND ADDRESS

Manufacturer

Baxter AG
Industriestrasse 67
A-1221 Vienna
Austria

Distributor

Baxter Healthcare Ltd
PO Box 14-062
Panmure
Auckland 1741

MEDICINE CLASSIFICATION

Prescription Only Medicine.

DATE OF PREPARATION

28 May 2014

Based on ccds20620131210

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

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DATA SHEET

PANDEMRIX™

Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted)

NAME OF THE MEDICINE

PANDEMRIX, emulsion and suspension for emulsion for injection.

Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted).

DESCRIPTION

The antigen composition will be determined depending on the strain for the pandemic influenza that will be recommended by the World Health Organisation (WHO).

Each 0.5mL vaccine dose contains 3.75 micrograms[1] of antigen[2] of the recommended strain and is adjuvanted with AS03[3].

[1]haemagglutinin

[2]propagated in eggs

[3]The GlaxoSmithKline proprietary AS03 adjuvant system is composed of squalene (10.68 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.85 milligrams)

Each 0.5mL vaccine dose also contains the excipients Polysorbate 80, Octoxinol 10, Thiomersal, Sodium Chloride, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Potassium Chloride and Magnesium chloride. The vaccine may also contain the following residues: egg residues including ovalbumin, gentamicin sulfate, formaldehyde, sucrose and sodium deoxycholate.

CLINICAL PHARMACOLOGY

Clinical Trials

This section describes the clinical experience with the mock-up vaccines following a two-dose administration.

Mock-up 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 mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical efficacy and safety data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Two clinical studies have evaluated the immunogenicity of the monovalent pandemic influenza A vaccine (H5N1).

A dose finding study tested different haemagglutinin dosages of the vaccine in a vaccine volume of 1 ml, which is twice the vaccine volume of the final formulation. In this study, approximately 200 unprimed subjects aged 18-60 years received the adjuvanted vaccine following a 0, 21 days schedule. Fifty out of these 200 subjects received 3.75 µg HA/AS03, which is the haemagglutinin dosage of the final formulation.

In a consistency study, more than 900 unprimed subjects aged 18-60 years received 3.75 µg HA/AS03 per 0.5 ml, which is the final formulation of the vaccine following a 0, 21 days schedule.

Immune response against vaccine strain:

Twenty-one days after the first and second dose of the vaccine, the seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody in the subjects who had received the final formulation of the vaccine were as follows:

anti-HA antibody	21 days after 1st dose	21 days after 2nd dose
Seroprotection rate*†	44.5%	94.3%
Seroconversion rate†	42.5%	93.7%
Seroconversion factor†	4.1	39.8

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty-one days after administration of the second dose, 96.0% of subjects had a 4-fold increase in serum neutralising antibody titers.

The ability of the vaccine to induce protection against the vaccine strain was assessed non-clinically using a ferret challenge model. Four groups of 6 ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing 15, 5, 1.7 or 0.6 µg of HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). The two control groups included ferrets immunized with adjuvant alone or phosphate buffered saline solution. Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of H5N1/A/Vietnam/1194/04. Of the animals receiving adjuvanted vaccine, 87 % were protected against the lethal challenge. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

Cross-reactivity:

In both studies, the candidate vaccine showed the ability to induce a cross-reactive immune response against variants of the vaccine strain.

In the dose finding study, the seroprotection rate, seroconversion rate and seroconversion factor against H5N1 drift variants 21 days after the second dose in a subset of subjects were as follows:

anti-HA antibody	A/Indonesia/5/2005 N = 50	A/Anhui/01/2005 N = 20	A/Turkey/Turkey/1/2005 N = 20
Seroprotection rate*†	20.0%	35.0%	60.0%
Seroconversion rate†	20.0%	35.0%	60.0%
Seroconversion factor†	2.0	3.4	4.7

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty one days after the second dose, a 4-fold increase in serum neutralising antibody titers was obtained in 77.1% of subjects against the A/Indonesia/5/2005 strain, in 75.0% of subjects against A/Anhui/01/2005 and in 85.0% of subjects against A/Turkey/Turkey/1/2005.

The consistency study confirmed that the candidate vaccine induces a cross-reactive immune response against A/Indonesia/5/2005. Twenty-one days after the second dose, seroconversion and seroprotection rates against this strain variant were both 50.2% with a seroconversion factor of 4.9. A 4-fold increase in serum neutralising antibody titers was obtained in 91.4% of subjects.

The ability of the vaccine to induce cross-reactivity and cross-protection against a variant of the vaccine strain was assessed non-clinically using a ferret challenge model. Four groups of 6 ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing 15, 7.5, 3.8 or 1.7 µg of HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). The two control groups included ferrets immunized with adjuvant alone or non-adjuvanted vaccine (15 µg HA). Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of heterologous H5N1/A/Indonesia/5/05. Of the animals receiving adjuvanted vaccine, 96% were protected against the lethal challenge. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

INDICATIONS

Prophylaxis of influenza in an officially declared pandemic situation. The vaccine may only be marketed, distributed or supplied in accordance with the directives contained in the New Zealand National Health Emergency Plan; New Zealand Influenza Pandemic Action Plan.

CONTRAINDICATIONS

History of an anaphylactic reaction (i.e. life-threatening) to any of the constituents or trace residues of this vaccine. (Also see Precautions section).

PRECAUTIONS

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients and to residues.

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.

If the pandemic situation allows, immunisation should be postponed in patients with severe febrile illness or acute infection.

PANDEMRIX should under no circumstances be administered intravascularly or intradermally.

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

A protective immune response may not be elicited in all vaccinees.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Use in Pregnancy (Category B2):
No data have been generated in pregnant women with *PANDEMRIX* and with the AS03 adjuvant contained in the vaccine. Data from vaccinations with intrapandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine.

Animal studies do not indicate direct of indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

Healthcare providers need to assess the benefits and potential risks of administering the vaccine to pregnant women.

Use in Lactation:
No data have been generated in breast-feeding women.

Interactions
No data are available on the concomitant administration of *PANDEMRIX* with other vaccines.

Therefore, *PANDEMRIX* is not intended to be given at the same time as other vaccines.

However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

False positive ELISA serologic tests for HIV-1, Hepatitis C, and especially HTLV-1 may occur following influenza vaccination. These transient false-positive results may be due to cross-reactive IgM elicited by the vaccine. For this reason, a definitive diagnosis of HIV-1, Hepatitis C, or HTLV-1

infection requires a positive result from a virus-specific confirmatory test (e.g,Western Blot or immunoblot).

ADVERSE REACTIONS

Clinical Trial Experience

Adverse reactions from clinical trials with the mock-up vaccine are listed here below (see „Clinical Trials" section for more information on mock-up vaccines).

The incidence of symptoms has been evaluated in more than 5,000 subjects 18 years old and above who received formulations containing at least 3.8 µg HA.

Undesirable effects reported are listed within body systems and categorised by frequency according to the following definitions:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders: *Common:* lymphadenopathy
Nervous system disorders: *Very common:* headache; *Uncommon:* dizziness, somnolence, paraesthesia
Psychiatric disorders: *Uncommon*: insomnia
Gastrointestinal disorders: *Uncommon*: gastro-intestinal symptoms (such as nausea, diarrhoea, vomiting, abdominal pain)
Skin and subcutaneous tissue disorders: *Common*: eccymosis at the injection site, increased sweating; *Uncommon*: pruritus, rash
Musculoskeletal and connective tissue disorders: *Very common*: myalgia, arthralgia
General disorders and administration site conditions: *Very common*: pain, redness, swelling and induration at the injection site, fatigue, fever; *Common*: injection site reactions (such as warmth, pruritus), shivering, influenza like illness; *Uncommon*: malaise

Post-marketing data

No post-marketing surveillance data are available following *PANDEMRIX*.

From Post-marketing surveillance with interpandemic trivalent vaccines, the following adverse events have been reported:

Blood and lymphatic system disorders: Transient thrombocytopenia.
Immune system disorders: Allergic reactions, in rare cases leading to shock.
Nervous system disorders: Neuralgia, convulsions. Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.
Vascular disorders: Vasculitis with transient renal involvement.
Skin and subcutaneous tissue disorders: Generalised skin reactions including urticaria

DOSAGE AND ADMINISTRATION

Dosage

Adults from the age of 18 to 60 years will receive two doses of *PANDEMRIX*, the first administered at an elected date, the second at least three weeks after the first dose for maximum efficacy.
Vaccination should be carried out by intramuscular injection.

Populations

Children and Elderly

No data have been generated below 18 years and above 60 years of age. The immunogenicity and reactogenicity profile of *PANDEMRIX* in this population is therefore unknown.
In a pandemic situation, administration of the vaccine in those populations shall follow national recommendations.

Method of Administration

PANDEMRIX H5N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The suspension is a colourless light opalescent liquid. The emulsion is a whitish to yellowish (milky) homogeneous liquid.
Prior to administration, the two components should be mixed.

Instructions for mixing and administration of the vaccine:

1. Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should be allowed to reach room temperature; each vial should be shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.

2. The vaccine is mixed by withdrawing the contents of the vial containing the adjuvant by means of a syringe and by adding it to the vial containing the antigen.

3. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish to yellowish (milky) homogeneous emulsion. In the event of other variation being observed, discard the vaccine.

4. The volume of *PANDEMRIX H5N1* vial after mixing is at least 5 mL. The vaccine should be administered in accordance with the recommended posology (see Dosage and Administration).

5. The vial should be shaken prior to each administration and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.

6. Each vaccine dose of 0.5 mL is withdrawn into a syringe for injection and administered intramuscularly.

7. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2ºC - 8ºC) or at room temperature not exceeding 25ºC. If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature before each withdrawal.

Any unused product or waste material should be disposed of in accordance with local requirements.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

OVERDOSAGE

Insufficient data are available.

For advice on management of over dosage, please contact the Poisons Information Centre on 131126

STORAGE

PANDEMRIX must be stored in a refrigerator between +2°C and +8°C and be protected from light. DO NOT FREEZE.

The expiry date of the vaccine is indicated on the label and packaging. The shelf life of *PANDEMRIX* is 3 years from the date of manufacture if stored between temperatures of +2°C and +8°C.

After mixing, the vaccine should be used within one working day.

PRESENTATIONS

2.5 ml suspension in a vial (type I glass) for 10 doses with a stopper. Pack size of 50.

2.5 ml emulsion in a vial (type I glass) for 10 doses with a stopper. Pack size of 25 X 2.

MANUFACTURER:

GlaxoSmithKline Biologicals SA

Rue de l'Institut 89

1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY:

GlaxoSmithKline Australia Pty Ltd,

1061 Mountain Hwy

Boronia VIC 3155

DISTRIBUTED IN NEW ZEALAND BY:

GlaxoSmithKline NZ Ltd
Private Bag 106600
Downtown Auckland 1143
New Zealand

Phone: (09) 367 2900
Facsimile (09) 367 2910

Date of Preparation
28 October 2011

PANDEMRIX™ is a trade mark of the GlaxoSmithKline group of companies.

Version 2.0

NEW ZEALAND DATA SHEET

PANDEMRIX®

Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted)

NAME OF THE MEDICINE

PANDEMRIX, emulsion and suspension for emulsion for injection.

Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted).

DESCRIPTION

The antigen composition will be determined depending on the strain for the pandemic influenza that will be recommended by the World Health Organisation (WHO).

Each 0.5mL vaccine dose contains 3.75 micrograms[1] of antigen[2] of the recommended strain and is adjuvanted with AS03[3].

[1]haemagglutinin

[2]propagated in eggs

[3]The GlaxoSmithKline proprietary AS03 adjuvant system is composed of squalene (10.68 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.85 milligrams)

Each 0.5mL vaccine dose also contains the excipients Polysorbate 80, Octoxinol 10, Thiomersal, Sodium Chloride, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Potassium Chloride, Magnesium chloride, Alpha-tocopherol, Monobasic potassium phosphate, Squalene, Dibasic sodium phosphate dodecahydrate, Monobasic potassium phosphate, and water for injections. The vaccine may also contain the following residues: egg residues including ovalbumin, gentamicin sulfate, formaldehyde, sucrose and sodium deoxycholate.

This medicine has been granted provisional consent under section 23 of the Medicines Act 1981.

CLINICAL PHARMACOLOGY

Clinical Trials

This section describes the clinical experience with the mock-up vaccines following a two-dose administration.

Mock-up 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 mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical efficacy and safety data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Two clinical studies have evaluated the immunogenicity of the monovalent pandemic influenza A vaccine (H5N1).

A dose finding study tested different haemagglutinin dosages of the vaccine in a vaccine volume of 1 ml, which is twice the vaccine volume of the final formulation. In this study, approximately 200 unprimed subjects aged 18-60 years received the adjuvanted vaccine following a 0, 21 days schedule. Fifty out of these 200 subjects received 3.75 µg HA/AS03, which is the haemagglutinin dosage of the final formulation.

In a consistency study, more than 900 unprimed subjects aged 18-60 years received 3.75 µg HA/AS03 per 0.5 ml, which is the final formulation of the vaccine following a 0, 21 days schedule.

Immune response against vaccine strain:

Twenty-one days after the first and second dose of the vaccine, the seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody in the subjects who had received the final formulation of the vaccine were as follows:

anti-HA antibody	21 days after 1st dose	21 days after 2nd dose
Seroprotection rate*†	44.5%	94.3%
Seroconversion rate†	42.5%	93.7%
Seroconversion factor†	4.1	39.8

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty-one days after administration of the second dose, 96.0% of subjects had a 4-fold increase in serum neutralising antibody titers.

The ability of the vaccine to induce protection against the vaccine strain was assessed non-clinically using a ferret challenge model. Four groups of 6 ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing 15, 5, 1.7 or 0.6 µg of HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). The two control groups included ferrets immunized with adjuvant alone or phosphate buffered saline solution. Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of H5N1/A/Vietnam/1194/04. Of the animals receiving adjuvanted vaccine, 87 % were protected against the lethal challenge. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to

controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

Cross-reactivity:

In both studies, the candidate vaccine showed the ability to induce a cross-reactive immune response against variants of the vaccine strain.

In the dose finding study, the seroprotection rate, seroconversion rate and seroconversion factor against H5N1 drift variants 21 days after the second dose in a subset of subjects were as follows:

anti-HA antibody	A/Indonesia/5/2005 N = 50	A/Anhui/01/2005 N = 20	A/Turkey/Turkey/1/2005 N = 20
Seroprotection rate*†	20.0%	35.0%	60.0%
Seroconversion rate†	20.0%	35.0%	60.0%
Seroconversion factor†	2.0	3.4	4.7

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty one days after the second dose, a 4-fold increase in serum neutralising antibody titers was obtained in 77.1% of subjects against the A/Indonesia/5/2005 strain, in 75.0% of subjects against A/Anhui/01/2005 and in 85.0% of subjects against A/Turkey/Turkey/1/2005.

The consistency study confirmed that the candidate vaccine induces a cross-reactive immune response against A/Indonesia/5/2005. Twenty-one days after the second dose, seroconversion and seroprotection rates against this strain variant were both 50.2% with a seroconversion factor of 4.9. A 4-fold increase in serum neutralising antibody titers was obtained in 91.4% of subjects.

The ability of the vaccine to induce cross-reactivity and cross-protection against a variant of the vaccine strain was assessed non-clinically using a ferret challenge model. Four groups of 6 ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing 15, 7.5, 3.8 or 1.7 µg of HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). The two control groups included ferrets immunized with adjuvant alone or non-adjuvanted vaccine (15 µg HA). Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of heterologous H5N1/A/Indonesia/5/05. Of the animals receiving adjuvanted vaccine, 96% were protected against the lethal challenge. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

INDICATIONS

Prophylaxis of influenza in an officially declared pandemic situation.

The vaccine may only be marketed, or distributed in accordance with the directives contained in the current version of the New Zealand Influenza Pandemic Action Plan.

CONTRAINDICATIONS

History of an anaphylactic reaction (i.e. life-threatening) to any of the constituents or trace residues of this vaccine. (Also see Precautions section).

PRECAUTIONS

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients and to residues.

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

If the pandemic situation allows, immunisation should be postponed in patients with severe febrile illness or acute infection.

PANDEMRIX should under no circumstances be administered intravascularly or intradermally.

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

A protective immune response may not be elicited in all vaccinees.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Epidemiological studies in several countries have reported an association between another pandemic influenza vaccine (Pandemrix H1N1 manufactured in Dresden, Germany) and narcolepsy with or without cataplexy. These studies have described an absolute risk increase of narcolepsy of approximately 1.4 to 8 additional cases per 100,000 vaccinated children/adolescents and approximately 1 additional case per 100,000 vaccinated adults compared to background rates of 0.12 to 0.79 per 100,000 children/adolescents per year and 0.67 to 1.10 per 100,000 adults per year. Further research is needed to investigate the observed association between Pandemrix and narcolepsy.

Use in Pregnancy (Category B2):

No data have been generated in pregnant women with *PANDEMRIX* and with the AS03 adjuvant contained in the vaccine. Data from vaccinations with intrapandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine.

Animal studies do not indicate direct of indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

Healthcare providers need to assess the benefits and potential risks of administering the vaccine to pregnant women.

Use in Lactation:

No data have been generated in breast-feeding women.

Interactions

No data are available on the concomitant administration of *PANDEMRIX* with other vaccines.

Therefore, *PANDEMRIX* is not intended to be given at the same time as other vaccines.

However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

False positive ELISA serologic tests for HIV-1, Hepatitis C, and especially HTLV-1 may occur following influenza vaccination. These transient false-positive results may be due to cross-reactive IgM elicited by the vaccine. For this reason, a definitive diagnosis of HIV-1, Hepatitis C, or HTLV-1 infection requires a positive result from a virus-specific confirmatory test (e.g,Western Blot or immunoblot).

ADVERSE REACTIONS

Clinical Trial Experience

Adverse reactions from clinical trials with the mock-up vaccine are listed here below (see 'Clinical Trials' section for more information on mock-up vaccines).

The incidence of symptoms has been evaluated in more than 5,000 subjects 18 years old and above who received formulations containing at least 3.8 µg HA.

Adverse Reactions reported are listed within body systems and categorised by frequency according to the following definitions:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

Blood and lymphatic system disorders: *Common:* lymphadenopathy
Nervous system disorders: *Very common:* headache; *Uncommon:* dizziness, somnolence, paraesthesia
Psychiatric disorders: *Uncommon*: insomnia
Gastrointestinal disorders: *Uncommon*: gastro-intestinal symptoms (such as nausea, diarrhoea, vomiting, abdominal pain)
Skin and subcutaneous tissue disorders: *Common*: eccymosis at the injection site, increased sweating; *Uncommon*: pruritus, rash
Musculoskeletal and connective tissue disorders: *Very common*: myalgia, arthralgia

General disorders and administration site conditions: *Very common*: pain, redness, swelling and induration at the injection site, fatigue, fever; *Common*: injection site reactions (such as warmth, pruritus), shivering, influenza like illness; *Uncommon*: malaise

Post-marketing data

No post-marketing surveillance data are available following *PANDEMRIX*.

From Post-marketing surveillance with interpandemic trivalent vaccines, the following adverse events have been reported:

Blood and lymphatic system disorders: Transient thrombocytopenia.
Immune system disorders: Allergic reactions, in rare cases leading to shock.
Nervous system disorders: Neuralgia, convulsions. Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.
Vascular disorders: Vasculitis with transient renal involvement.
Skin and subcutaneous tissue disorders: Generalised skin reactions including urticaria

DOSAGE AND ADMINISTRATION

Dosage

Adults from the age of 18 to 60 years will receive two doses of *PANDEMRIX*, the first administered at an elected date, the second at least three weeks after the first dose for maximum efficacy. Vaccination should be carried out by intramuscular injection.

Populations

Children and Elderly

No data have been generated below 18 years and above 60 years of age. The immunogenicity and reactogenicity profile of *PANDEMRIX* in this population is therefore unknown.
In a pandemic situation, administration of the vaccine in those populations shall follow national recommendations.

Method of Administration

PANDEMRIX H5N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The suspension is a colourless light opalescent liquid. The emulsion is a whitish to yellowish homogeneous milky liquid. Prior to administration, the two components should be mixed.

Instructions for mixing and administration of the vaccine:

1. Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should be allowed to reach room temperature (allow a minimum of 15 minutes); each vial should be shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.

2. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a 5 mL syringe and by adding it to the vial containing the antigen. The use of a 23-G needle is recommended. However, in the case this needle size would not be available, the use of a 21-G needle is recommended. The vial containing the adjuvant should be maintained in upside down position to facilitate the withdrawal of the full content.

3. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish to yellowish homogeneous milky liquid emulsion. In the event of other variation being observed, discard the vaccine.

4. The volume of *PANDEMRIX H5N1* vial after mixing is at least 5 mL. The vaccine should be administered in accordance with the recommended posology (see Dosage and Administration).

5. The vial should be shaken prior to each administration and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.

6. Each vaccine dose of 0.5 mL is withdrawn into a 1 mL syringe for injection and administered intramuscularly. The use of a needle gauge not larger than 23 G is recommended.

7. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2ºC - 8ºC) or at room temperature not exceeding 25ºC. If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature (allow a minimum of 15 minutes) before each withdrawal.

Any unused product or waste material should be disposed of in accordance with local requirements.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

OVERDOSAGE

Insufficient data are available.

For advice on management of overdosage:

In Australia, please contact the Poisons Information Centre on 131126.

In New Zealand, call the New Zealand Poisons Centre on 0800 POISON or 0800 764 766.

STORAGE

PANDEMRIX must be stored in a refrigerator between +2°C and +8°C and be protected from light. DO NOT FREEZE.

The expiry date of the vaccine is indicated on the label and packaging. The shelf life of *PANDEMRIX* is 3 years from the date of manufacture if stored between temperatures of +2°C and +8°C.

After mixing, the vaccine should be used within 24 hours.

PRESENTATIONS

2.5 ml suspension in a vial (type I glass) for 10 doses with a stopper (butyl rubber). Pack size of 50.

2.5 ml emulsion in a vial (type I glass) for 10 doses with a stopper (butyl rubber). Pack size of 25 X 2.

MANUFACTURER:

GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
1330 Rixensart, Belgium.

DISTRIBUTED IN NEW ZEALAND BY:

GlaxoSmithKline NZ Ltd
Private Bag 106600
Downtown Auckland 1143
New Zealand

Phone: (09) 367 2900
Facsimile (09) 367 2910

Date of Preparation
13 March 2014

PANDEMRIX is a trade mark of the GlaxoSmithKline group of companies.

Version 3.0

NEW ZEALAND DATA SHEET

PANDEMRIX®

Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted)

NAME OF THE MEDICINE

PANDEMRIX, emulsion and suspension for emulsion for injection.

Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted).

DESCRIPTION

The antigen composition will be determined depending on the strain for the pandemic influenza that will be recommended by the World Health Organisation (WHO).

Each 0.5mL vaccine dose contains 3.75 micrograms[1] of antigen[2] of the recommended strain and is adjuvanted with AS03[3].

[1]haemagglutinin

[2]propagated in eggs

[3]The GlaxoSmithKline proprietary AS03 adjuvant system is composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)

Each 0.5mL vaccine dose also contains the excipients Polysorbate 80, Octoxinol 10, Thiomersal, Sodium Chloride, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Potassium Chloride, Magnesium chloride, Alpha-tocopherol, Monobasic potassium phosphate, Squalene, Dibasic sodium phosphate dodecahydrate, Monobasic potassium phosphate, and water for injections. The vaccine may also contain the following residues: egg residues including ovalbumin, gentamicin sulfate, formaldehyde, sucrose and sodium deoxycholate.

This medicine has been granted provisional consent under section 23 of the Medicines Act 1981.

CLINICAL PHARMACOLOGY

Clinical Trials

This section describes the clinical experience with the mock-up vaccines following a two-dose administration.

Mock-up 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 mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical efficacy and safety data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Two clinical studies have evaluated the immunogenicity of the monovalent pandemic influenza A vaccine (H5N1).

A dose finding study tested different haemagglutinin dosages of the vaccine in a vaccine volume of 1 ml, which is twice the vaccine volume of the final formulation. In this study, approximately 200 unprimed subjects aged 18-60 years received the adjuvanted vaccine following a 0, 21 days schedule. Fifty out of these 200 subjects received 3.75 µg HA/AS03, which is the haemagglutinin dosage of the final formulation.

In a consistency study, more than 900 unprimed subjects aged 18-60 years received 3.75 µg HA/AS03 per 0.5 ml, which is the final formulation of the vaccine following a 0, 21 days schedule.

Immune response against vaccine strain:

Twenty-one days after the first and second dose of the vaccine, the seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody in the subjects who had received the final formulation of the vaccine were as follows:

anti-HA antibody	21 days after 1st dose	21 days after 2nd dose
Seroprotection rate*†	44.5%	94.3%
Seroconversion rate†	42.5%	93.7%
Seroconversion factor†	4.1	39.8

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty-one days after administration of the second dose, 96.0% of subjects had a 4-fold increase in serum neutralising antibody titers.

The ability of the vaccine to induce protection against the vaccine strain was assessed non-clinically using a ferret challenge model. Four groups of 6 ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing 15, 5, 1.7 or 0.6 µg of HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). The two control groups included ferrets immunized with adjuvant alone or phosphate buffered saline solution. Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of H5N1/A/Vietnam/1194/04. Of the animals receiving adjuvanted vaccine, 87 % were protected against the lethal challenge. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to

controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

Cross-reactivity:

In both studies, the candidate vaccine showed the ability to induce a cross-reactive immune response against variants of the vaccine strain.

In the dose finding study, the seroprotection rate, seroconversion rate and seroconversion factor against H5N1 drift variants 21 days after the second dose in a subset of subjects were as follows:

anti-HA antibody	A/Indonesia/5/2005 N = 50	A/Anhui/01/2005 N = 20	A/Turkey/Turkey/1/2005 N = 20
Seroprotection rate*†	20.0%	35.0%	60.0%
Seroconversion rate†	20.0%	35.0%	60.0%
Seroconversion factor†	2.0	3.4	4.7

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty one days after the second dose, a 4-fold increase in serum neutralising antibody titers was obtained in 77.1% of subjects against the A/Indonesia/5/2005 strain, in 75.0% of subjects against A/Anhui/01/2005 and in 85.0% of subjects against A/Turkey/Turkey/1/2005.

The consistency study confirmed that the candidate vaccine induces a cross-reactive immune response against A/Indonesia/5/2005. Twenty-one days after the second dose, seroconversion and seroprotection rates against this strain variant were both 50.2% with a seroconversion factor of 4.9. A 4-fold increase in serum neutralising antibody titers was obtained in 91.4% of subjects.

The ability of the vaccine to induce cross-reactivity and cross-protection against a variant of the vaccine strain was assessed non-clinically using a ferret challenge model. Four groups of 6 ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing 15, 7.5, 3.8 or 1.7 µg of HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). The two control groups included ferrets immunized with adjuvant alone or non-adjuvanted vaccine (15 µg HA). Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of heterologous H5N1/A/Indonesia/5/05. Of the animals receiving adjuvanted vaccine, 96% were protected against the lethal challenge. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

INDICATIONS

Prophylaxis of influenza in an officially declared pandemic situation.

The vaccine may only be marketed, or distributed in accordance with the directives contained in the current version of the New Zealand Influenza Pandemic Action Plan.

CONTRAINDICATIONS

History of an anaphylactic reaction (i.e. life-threatening) to any of the constituents or trace residues of this vaccine. (Also see Precautions section).

PRECAUTIONS

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients and to residues.

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

If the pandemic situation allows, immunisation should be postponed in patients with severe febrile illness or acute infection.

PANDEMRIX should under no circumstances be administered intravascularly or intradermally.

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

A protective immune response may not be elicited in all vaccinees.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Epidemiological studies in several countries have reported an association between another pandemic influenza vaccine (Pandemrix H1N1 manufactured in Dresden, Germany) and narcolepsy with or without cataplexy. These studies have described an absolute risk increase of narcolepsy of approximately 1.4 to 8 additional cases per 100,000 vaccinated children/adolescents and approximately 1 additional case per 100,000 vaccinated adults compared to background rates of 0.12 to 0.79 per 100,000 children/adolescents per year and 0.67 to 1.10 per 100,000 adults per year. Further research is needed to investigate the observed association between Pandemrix and narcolepsy.

Use in Pregnancy (Category B2):
No data have been generated in pregnant women with *PANDEMRIX* and with the AS03 adjuvant contained in the vaccine. Data from vaccinations with intrapandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

Healthcare providers need to assess the benefits and potential risks of administering the vaccine to pregnant women.

Use in Lactation:
No data have been generated in breast-feeding women.

Interactions
No data are available on the concomitant administration of *PANDEMRIX* with other vaccines.

Therefore, *PANDEMRIX* is not intended to be given at the same time as other vaccines.

However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

False positive ELISA serologic tests for HIV-1, Hepatitis C, and especially HTLV-1 may occur following influenza vaccination. These transient false-positive results may be due to cross-reactive IgM elicited by the vaccine. For this reason, a definitive diagnosis of HIV-1, Hepatitis C, or HTLV-1 infection requires a positive result from a virus-specific confirmatory test (e.g,Western Blot or immunoblot).

ADVERSE REACTIONS

Clinical Trial Experience

Adverse reactions from clinical trials with the mock-up vaccine are listed here below (see 'Clinical Trials' section for more information on mock-up vaccines).

The incidence of symptoms has been evaluated in more than 5,000 subjects 18 years old and above who received formulations containing at least 3.8 µg HA.

Adverse Reactions reported are listed within body systems and categorised by frequency according to the following definitions:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

Blood and lymphatic system disorders: *Common:* lymphadenopathy
Nervous system disorders: *Very common:* headache; *Uncommon:* dizziness, somnolence, paraesthesia
Psychiatric disorders: *Uncommon*: insomnia
Gastrointestinal disorders: *Uncommon*: gastro-intestinal symptoms (such as nausea, diarrhoea, vomiting, abdominal pain)
Skin and subcutaneous tissue disorders: *Common*: eccymosis at the injection site, increased sweating; *Uncommon*: pruritus, rash
Musculoskeletal and connective tissue disorders: *Very common*: myalgia, arthralgia

General disorders and administration site conditions: *Very common*: pain, redness, swelling and induration at the injection site, fatigue, fever; *Common*: injection site reactions (such as warmth, pruritus), shivering, influenza like illness; *Uncommon*: malaise

Post-marketing data

No post-marketing surveillance data are available following *PANDEMRIX*.

From Post-marketing surveillance with interpandemic trivalent vaccines, the following adverse events have been reported:

Blood and lymphatic system disorders: Transient thrombocytopenia.

Immune system disorders: Allergic reactions, in rare cases leading to shock.

Nervous system disorders: Neuralgia, convulsions. Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

Vascular disorders: Vasculitis with transient renal involvement.

Skin and subcutaneous tissue disorders: Generalised skin reactions including urticaria

DOSAGE AND ADMINISTRATION

Dosage

Adults from the age of 18 to 60 years will receive two doses of *PANDEMRIX*, the first administered at an elected date, the second at least three weeks after the first dose for maximum efficacy. Vaccination should be carried out by intramuscular injection.

Populations

Children and Elderly

No data have been generated below 18 years and above 60 years of age. The immunogenicity and reactogenicity profile of *PANDEMRIX* in this population is therefore unknown.
In a pandemic situation, administration of the vaccine in those populations shall follow national recommendations.

Method of Administration

PANDEMRIX H5N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The suspension is a colourless light opalescent liquid. The emulsion is a whitish to yellowish homogeneous milky liquid. Prior to administration, the two components should be mixed.

Instructions for mixing and administration of the vaccine:

1. Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should be allowed to reach room temperature (allow a minimum of 15 minutes); each vial should be shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.

2. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a 5 mL syringe and by adding it to the vial containing the antigen. The use of a 23-G needle is recommended. However, in the case this needle size would not be available, the use of a 21-G needle is recommended. The vial containing the adjuvant should be maintained in upside down position to facilitate the withdrawal of the full content.

3. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish to yellowish homogeneous milky liquid emulsion. In the event of other variation being observed, discard the vaccine.

4. The volume of *PANDEMRIX H5N1* vial after mixing is at least 5 mL. The vaccine should be administered in accordance with the recommended posology (see Dosage and Administration).

5. The vial should be shaken prior to each administration and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.

6. Each vaccine dose of 0.5 mL is withdrawn into a 1 mL syringe for injection and administered intramuscularly. The use of a needle gauge not larger than 23 G is recommended.

7. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2ºC - 8ºC) or at room temperature not exceeding 25ºC. If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature (allow a minimum of 15 minutes) before each withdrawal.

Any unused product or waste material should be disposed of in accordance with local requirements.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

OVERDOSAGE

Insufficient data are available.

For advice on management of overdosage:

In Australia, please contact the Poisons Information Centre on 131126.
In New Zealand, call the New Zealand Poisons Centre on 0800 POISON or 0800 764 766.

STORAGE

PANDEMRIX must be stored in a refrigerator between +2°C and +8°C and be protected from light. DO NOT FREEZE.

The expiry date of the vaccine is indicated on the label and packaging. The shelf life of *PANDEMRIX* is 5 years from the date of manufacture if stored between temperatures of +2°C and +8°C.

After mixing, the vaccine should be used within 24 hours.

PRESENTATIONS

2.5 ml suspension in a vial (type I glass) for 10 doses with a stopper (butyl rubber). Pack size of 50.
2.5 ml emulsion in a vial (type I glass) for 10 doses with a stopper (butyl rubber). Pack size of 25 X 2.

MANUFACTURER:
GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
1330 Rixensart, Belgium.

DISTRIBUTED IN NEW ZEALAND BY:
GlaxoSmithKline NZ Ltd
Private Bag 106600
Downtown Auckland 1143
New Zealand

Phone: (09) 367 2900
Facsimile (09) 367 2910

Date of Preparation
26 March 2015

PANDEMRIX is a registered trade mark of the GlaxoSmithKline group of companies.

Version 4.0

NEW ZEALAND DATA SHEET

1. NAME OF THE MEDICINE

PANDEMRIX Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted) emulsion and suspension for emulsion for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The antigen composition will be determined depending on the strain for the pandemic influenza that will be recommended by the World Health Organisation (WHO).

Each 0.5 mL vaccine dose contains 3.75 micrograms[1] of antigen[2] of the recommended strain and is adjuvanted with AS03[3].

[1]haemagglutinin

[2]propagated in eggs

[3]The GlaxoSmithKline proprietary AS03 adjuvant system is composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Emulsion and suspension for emulsion for injection.

The suspension is a colourless light opalescent liquid. The emulsion is a whitish to yellowish homogeneous milky liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation.

The vaccine may only be marketed, or distributed in accordance with the directives contained in the current version of the New Zealand Influenza Pandemic Action Plan.

4.2 Dose and method of administration

Dose

Adults from the age of 18 to 60 years will receive two doses of PANDEMRIX, the first administered at an elected date, the second at least three weeks after the first dose for maximum efficacy.

Special populations

Paediatric and elderly populations

No data have been generated below 18 years and above 60 years of age. The immunogenicity and reactogenicity profile of PANDEMRIX in this population is therefore unknown.

In a pandemic situation, administration of the vaccine in those populations shall follow national recommendations.

Method of administration

Vaccination should be carried out by intramuscular injection.

4.3 Contraindications

History of an anaphylactic reaction (i.e. life-threatening) to any of the constituents or trace residues of this vaccine (see section 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients and to residues.

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

If the pandemic situation allows, immunisation should be postponed in patients with severe febrile illness or acute infection.

PANDEMRIX should under no circumstances be administered intravascularly or intradermally.

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

A protective immune response may not be elicited in all vaccinees.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Epidemiological studies in several countries have reported an association between another pandemic influenza vaccine (PANDEMRIX H1N1 manufactured in Dresden, Germany) and narcolepsy with or without cataplexy. These studies have described an absolute risk increase of narcolepsy of approximately 1.4 to 8 additional cases per 100,000 vaccinated children/adolescents and approximately 1 additional case per 100,000 vaccinated adults compared to background rates of 0.12 to 0.79 per 100,000 children/adolescents per year and 0.67 to 1.10 per 100,000 adults per year. Further research is needed to investigate the observed association between Pandemrix and narcolepsy.

4.5 Interaction with other medicines and other forms of interaction

No data are available on the concomitant administration of PANDEMRIX with other vaccines.

Therefore, PANDEMRIX is not intended to be given at the same time as other vaccines.

However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

False positive ELISA serologic tests for HIV-1, Hepatitis C, and especially HTLV-1 may occur following influenza vaccination. These transient false-positive results may be due to cross-reactive IgM elicited by the vaccine. For this reason, a definitive diagnosis of HIV-1, Hepatitis C, or HTLV-1 infection requires a positive result from a virus-specific confirmatory test (e.g,Western Blot or immunoblot).

4.6 Fertility, pregnancy and lactation

Pregnancy (Category B2)

No data have been generated in pregnant women with PANDEMRIX and with the AS03 adjuvant contained in the vaccine. Data from vaccinations with intrapandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

Healthcare providers need to assess the benefits and potential risks of administering the vaccine to pregnant women.

Breast-feeding

No data have been generated in breast-feeding women.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Tabulated list of adverse reactions

Clinical Trial Experience

Adverse reactions from clinical trials with the mock-up vaccine are listed here below (see section 5.1 Pharmacodynamic properties - Clinical efficacy and safety for more information on mock-up vaccines).

The incidence of symptoms has been evaluated in more than 5,000 subjects 18 years old and above who received formulations containing at least 3.8 µg HA.

Adverse reactions reported are listed within body systems and categorised by frequency according to the following definitions:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Blood and lymphatic system disorders: *Common:* lymphadenopathy

Nervous system disorders: *Very common:* headache; *Uncommon:* dizziness, somnolence, paraesthesia

Psychiatric disorders: *Uncommon*: insomnia

Gastrointestinal disorders: *Uncommon*: gastro-intestinal symptoms (such as nausea, diarrhoea, vomiting, abdominal pain)

Skin and subcutaneous tissue disorders: *Common*: eccymosis at the injection site, increased sweating; *Uncommon*: pruritus, rash

Musculoskeletal and connective tissue disorders: *Very common*: myalgia, arthralgia

General disorders and administration site conditions: *Very common*: pain, redness, swelling and induration at the injection site, fatigue, fever; *Common*: injection site reactions (such as warmth, pruritus), shivering, influenza like illness; *Uncommon*: malaise

Post-marketing data

No post-marketing surveillance data are available following PANDEMRIX.

From post-marketing surveillance with interpandemic trivalent vaccines, the following adverse events have been reported:

Blood and lymphatic system disorders: Transient thrombocytopenia.

Immune system disorders: Allergic reactions, in rare cases leading to shock.

Nervous system disorders: Neuralgia, convulsions. Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

Vascular disorders: Vasculitis with transient renal involvement.

Skin and subcutaneous tissue disorders: Generalised skin reactions including urticaria

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphvc.otago.ac.nz/reporting.

4.9 Overdose

Insufficient data are available.

For the advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. CLINICAL PHARMACOLOGY

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC code: J07BB02.

Clinical efficacy and safety

This section describes the clinical experience with the mock-up vaccines following a two-dose administration.

Mock-up 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 mock-up vaccine will support a vaccination strategy that is likely to be used for the

pandemic vaccine: clinical efficacy and safety data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Two clinical studies have evaluated the immunogenicity of the monovalent pandemic influenza A vaccine (H5N1).

A dose finding study tested different haemagglutinin dosages of the vaccine in a vaccine volume of 1 ml, which is twice the vaccine volume of the final formulation. In this study, approximately 200 unprimed subjects aged 18-60 years received the adjuvanted vaccine following a 0, 21 days schedule. Fifty out of these 200 subjects received 3.75 µg HA/AS03, which is the haemagglutinin dosage of the final formulation.

In a consistency study, more than 900 unprimed subjects aged 18-60 years received 3.75 µg HA/AS03 per 0.5 ml, which is the final formulation of the vaccine following a 0, 21 days schedule.

Immune response against vaccine strain:

Twenty-one days after the first and second dose of the vaccine, the seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody in the subjects who had received the final formulation of the vaccine were as follows:

anti-HA antibody	21 days after 1st dose	21 days after 2nd dose
Seroprotection rate*†	44.5%	94.3%
Seroconversion rate†	42.5%	93.7%
Seroconversion factor†	4.1	39.8

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty-one days after administration of the second dose, 96.0% of subjects had a 4-fold increase in serum neutralising antibody titers.

The ability of the vaccine to induce protection against the vaccine strain was assessed non-clinically using a ferret challenge model. Four groups of 6 ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing 15, 5, 1.7 or 0.6 µg of HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). The two control groups included ferrets immunized with adjuvant alone or phosphate buffered saline solution. Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of H5N1/A/Vietnam/1194/04. Of the animals receiving adjuvanted vaccine, 87 % were protected against the lethal challenge. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

Cross-reactivity:

In both studies, the candidate vaccine showed the ability to induce a cross-reactive immune response against variants of the vaccine strain.

In the dose finding study, the seroprotection rate, seroconversion rate and seroconversion factor against H5N1 drift variants 21 days after the second dose in a subset of subjects were as follows:

anti-HA antibody	A/Indonesia/5/2005 N = 50	A/Anhui/01/2005 N = 20	A/Turkey/Turkey/1/2005 N = 20
Seroprotection rate*†	20.0%	35.0%	60.0%
Seroconversion rate†	20.0%	35.0%	60.0%
Seroconversion factor†	2.0	3.4	4.7

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty one days after the second dose, a 4-fold increase in serum neutralising antibody titers was obtained in 77.1% of subjects against the A/Indonesia/5/2005 strain, in 75.0% of subjects against A/Anhui/01/2005 and in 85.0% of subjects against A/Turkey/Turkey/1/2005.

The consistency study confirmed that the candidate vaccine induces a cross-reactive immune response against A/Indonesia/5/2005. Twenty-one days after the second dose, seroconversion and seroprotection rates against this strain variant were both 50.2% with a seroconversion factor of 4.9. A 4-fold increase in serum neutralising antibody titers was obtained in 91.4% of subjects.

The ability of the vaccine to induce cross-reactivity and cross-protection against a variant of the vaccine strain was assessed non-clinically using a ferret challenge model. Four groups of 6 ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing 15, 7.5, 3.8 or 1.7 µg of HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). The two control groups included ferrets immunized with adjuvant alone or non-adjuvanted vaccine (15 µg HA). Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of heterologous H5N1/A/Indonesia/5/05. Of the animals receiving adjuvanted vaccine, 96% were protected against the lethal challenge. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

This medicine has been given a provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited or that there are specific conditions for use.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical data obtained with the mock-up vaccines using a H5N1 vaccine strain reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, fertility, embryo-foetal and postnatal toxicity (up to the end of the lactation period).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each 0.5 mL vaccine dose also contains the excipients polysorbate 80, octoxinol 10, thiomersal, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride, alpha-tocopherol, monobasic potassium phosphate, squalene, dibasic sodium phosphate dodecahydrate, monobasic potassium phosphate, and water for injections.

The vaccine may also contain the following residues: egg residues including ovalbumin, gentamicin sulfate, formaldehyde, sucrose and sodium deoxycholate.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The shelf life of PANDEMRIX is 5 years from the date of manufacture if stored between temperatures of +2°C and +8°C.

After mixing, the vaccine should be used within 24 hours.

The expiry date of the vaccine is indicated on the label and packaging.

6.4 Special precautions for storage

PANDEMRIX must be stored in a refrigerator between +2°C and +8°C and be protected from light. DO NOT FREEZE.

6.5 Nature and contents of container

2.5 mL suspension in a vial (type I glass) for 10 doses with a stopper (butyl rubber). Pack size of 50.

2.5 mL emulsion in a vial (type I glass) for 10 doses with a stopper (butyl rubber). Pack size of 25 X 2.

6.6 Special precautions for disposal

PANDEMRIX H5N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The suspension is a colourless light opalescent liquid. The emulsion is a whitish to yellowish homogeneous milky liquid.

Prior to administration, the two components should be mixed.

Instructions for mixing and administration of the vaccine:

1. Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should be allowed to reach room temperature (allow a minimum of 15 minutes); each vial should be shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.

2. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a 5 mL syringe and by adding it to the vial containing the antigen. The use of a 23-G needle is recommended. However, in the case this needle size would not be available, the use of a 21-G needle is recommended. The vial containing the adjuvant should be maintained in upside down position to facilitate the withdrawal of the full content.

3. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish to yellowish homogeneous milky liquid emulsion. In the event of other variation being observed, discard the vaccine.

4. The volume of *PANDEMRIX H5N1* vial after mixing is at least 5 mL. The vaccine should be administered in accordance with the recommended posology (see section 4.2 Dose and method of administration).

5. The vial should be shaken prior to each administration and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.

6. Each vaccine dose of 0.5 mL is withdrawn into a 1 mL syringe for injection and administered intramuscularly. The use of a needle gauge not larger than 23 G is recommended.

7. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2ºC - 8ºC) or at room temperature not exceeding 25ºC. If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature (allow a minimum of 15 minutes) before each withdrawal.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
NEW ZEALAND

Phone: (09) 367 2900

Facsimile (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 31 July 2014

10. DATE OF REVISION OF THE TEXT

16 May 2018

Summary table of changes:

Section changed	Summary of new information
All	Data Sheet re-format
3	Added pharmaceutical form
4.6	Added fertility section
4.7	Added effects on ability to drive and use machines section
4.8	Added information on reporting of suspected adverse reactions
4.9	Updated mandatory statement regarding overdose management
5.1	Added pharmacotherapeutic group and ATC code
5.2	Added pharmacokinetic properties section
5.3	Added preclinical safety data
7	Added medicine schedule
8	Removal of overseas manufacturer details
9	Added date of first approval
End of document	Updated trade mark and copyright statements
All	Minor editorial updates

Version 4.0

NAME OF THE MEDICINE

Panvax® vaccine

Pandemic influenza vaccine (split virion, inactivated and adjuvanted).

DESCRIPTION

Panvax® vaccine is a split virion, inactivated, adjuvanted influenza virus vaccine formulated to contain 30 micrograms of haemagglutinin (HA) per 0.5 mL dose from the pandemic influenza virus strain:

A/Official strain (H5N1)-like (A/H5N1 Official strain)

Each 0.5 mL dose also contains: sodium chloride 4.1 mg, sodium phosphate – dibasic anhydrous 3.0 mg, sodium phosphate – monobasic 80 µg, potassium chloride 20 µg, potassium phosphate – monobasic 20 µg, calcium chloride 1.5 µg, thiomersal 50 µg and aluminium (as aluminium phosphate adjuvant) 0.5 mg.

Each dose may also contain sodium taurodeoxycholate ≤ 5 µg, ovalbumin ≤ 1.0 µg, sucrose < 10 µg, neomycin ≤ 1 ng, polymyxin B sulfate ≤ 0.2 ng and beta-propiolactone ≤ 2 ng.

Panvax® vaccine is prepared from influenza virus propagated in the allantoic fluid of embryonated chicken eggs. The virus is harvested from the eggs, purified and inactivated with beta-propiolactone. The virus particles are then disrupted with sodium taurodeoxycholate to produce split virion particles which are further purified prior to formulation with aluminium phosphate adjuvant.

This vaccine complies with the Health Authorities' decision for the pandemic, taking into account the recommendation from the WHO.

PHARMACOLOGY

Prototype pandemic influenza vaccines contain influenza virus antigens that are different from those included in seasonal trivalent influenza vaccines and may also be substantially different from the virus which causes pandemic influenza. If a pandemic influenza virus emerges, the clinical efficacy and safety data obtained from clinical trials with prototype pandemic influenza vaccines is expected to be relevant for the pandemic vaccine made from the official pandemic influenza virus strain.

Clinical experience with prototype pandemic vaccines, following a two-dose primary vaccination course, has been derived from clinical trials in healthy adult and elderly adult populations. The efficacy of prototype pandemic vaccines is assessed by serum immunogenicity, since clinical protection is not able to be evaluated.

The immunogenicity of prototype vaccines has been assessed in clinical trials by two serum antibody assays, the haemagglutination inhibition (HI) assay and a viral microneutralisation (MN) assay. There are currently no defined levels of serum antibody responses known to correlate with clinical protection against infection with pandemic influenza viruses. Guidelines for assessment of the pandemic influenza vaccines are based on those for inter-pandemic influenza vaccines developed by the European

Medicines Agency (EMEA) *Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* (CPMP/BWP/214/96) and the EMEA guidance document for pandemic vaccines (CPMP/VEG/4717/03).

A ferret efficacy challenge study using the prototype A/Vietnam/1194/2004 (H5N1) pandemic influenza vaccine has demonstrated that seroconversion (as measured by both HI and MN immune responses) in ferrets vaccinated with the 30 µg HA per dose adjuvanted formulation was associated with 100% survival following lethal challenge and also prevented serious morbidity. This data provides support for the assessment of HI and MN immune responses as a surrogate measure of clinical efficacy in human clinical trials.

CLINICAL TRIALS

Three clinical trials have been conducted to assess the immunogenicity and safety of a prototype pandemic influenza vaccine in healthy adults aged 18 years and older. The immunogenicity of the vaccine was demonstrated in 2 double blind, randomised Phase II clinical studies conducted in adults aged 18 to 64 years, and elderly adults aged 65 years and older.

The safety of the vaccine was assessed in 3 clinical studies that were randomised Phase I or Phase II studies conducted in adults aged 18 years and older. The Phase I trial in 400 adults, 18 to 45 years of age, assessed vaccines formulated with lower HA antigen doses, with and without aluminium phosphate adjuvant. The data from this study demonstrated that higher antigen doses and an adjuvant were required and that two doses of the vaccine elicited modest levels of cross-reactive neutralising antibodies against antigenically distinct H5N1 strains. The immunogenicity data from this study is not presented, however the safety data has been included in the overall safety analysis for the vaccine.

The Healthy Adult Phase II study evaluated the immunogenicity of an inactivated, split virion, monovalent, aluminium phosphate adjuvanted prototype pandemic vaccine containing either 30 µg or 45 µg of influenza HA antigen per 0.5 mL dose from the A/Vietnam/1194/2004 (H5N1) influenza vaccine strain. The study enrolled 400 participants aged 18 to 64 years. Two doses of vaccine were administered 21 days apart, with HI and MN antibody assessment approximately 21 days after each dose. MN antibody assessment only was conducted 6 months after Dose 2.

Immunogenicity results for the 45 µg HA per dose vaccine were in general comparable with immune responses to the 30 µg HA per dose vaccine, so immunogenicity results for the higher HA dose level are not reported.

HI antibody immunogenicity results from the Healthy Adult Phase II study were as follows:

Serum HI antibody	**After Dose 1 n=200 (95% CI)**	**After Dose 2 n=197 (95% CI)**
Geometric Mean Titre (GMT)	12.2 (9.9,15.0)	29.4 (23.7,36.5)
Fold increase in GMT	2.8 (2.3,3.5)	6.8 (5.5,8.4)
Seroconversion or significant increase	22.0% (16.5,28.4)	48.2% (41.1,55.4)
Proportion with HI ≥ 40	23.0% (17.4,29.5)	49.7% (42.6,56.9)

MN antibody immunogenicity results from the Healthy Adult Phase II study were as follows:

Serum viral neutralising antibody (MN)	**After Dose 1 n=200 (95% CI)**	**After Dose 2 n=197 (95% CI)**	**6 months after Dose 2 n=192 (95% CI)**
Geometric Mean Titre (GMT)	17.8 (15.4,20.4)	43.3 (37.3,50.3)	34.8 (29.3,41.4)
Fold increase in GMT	1.8 (1.5,2.0)	4.3 (3.7,5.0)	3.4 (2.9,4.1)
Seroconversion or significant increase	18.5% (13.4,24.6)	53.8% (46.6,60.9)	40.4% (33.4,47.7)
Proportion seropositive (MN ≥ 20)	28.0% (21.9,34.8)	72.6% (65.8,78.7)	60.1% (52.8,67.1)
Proportion with MN ≥ 40	18.5% (13.4,24.6)	53.8% (46.6,60.9)	40.4% (33.4,47.7)

The Elderly Adult Phase II study evaluated the immunogenicity of an inactivated, split virion, monovalent, aluminium phosphate adjuvanted prototype pandemic vaccine containing either 30 µg or 45 µg of influenza HA antigen per 0.5 ml dose from the A/Vietnam/1194/2004 (H5N1) influenza vaccine strain. The study enrolled 201 participants 65 years of age and older. Two doses of vaccine were administered 21 days apart. Immunogenicity assessment was conducted by MN assay only, with assessments approximately 21 days after each dose and 6 months after Dose 2 to assess antibody persistence.

Immunogenicity results for the 45 µg HA per dose vaccine were in general comparable with immune responses to the 30 µg HA per dose vaccine, so immunogenicity results for the higher HA dose level are not reported.

MN antibody immunogenicity results from the Elderly Adult Phase II study were as follows:

Serum viral neutralising antibody (MN)	After Dose 1 n=100 (95% CI)	After Dose 2 n=101 (95% CI)	6 months after Dose 2 n=98 (95% CI)
Geometric Mean Titre (GMT)	22.6 (17.3,29.6)	45.1 (34.1,59.7)	30.3 (23.8,38.4)
Fold increase in GMT	2.1 (1.6,2.7)	4.2 (3.2,5.4)	2.8 (2.2,3.5)
Seroconversion or significant increase	22.0% (14.3,31.4)	47.5% (37.5,57.7)	38.8% (29.1,49.2)
Proportion seropositive (MN ≥ 20)	32.0% (23.0,42.1)	62.4% (52.2,71.8)	51.0% (40.7,61.3)
Proportion with MN ≥ 40	24.0% (16.0,33.6)	48.5% (38.4,58.7)	40.8% (31.0,51.2)

INDICATIONS

Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with New Zealand Health Authorities' recommendations, taking into account the recommendation of the World Health Organisation.

CONTRAINDICATIONS

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (e.g. eggs, chicken protein; see Description section) of this vaccine. However, in a pandemic situation, it may be appropriate to give the vaccine, provided that facilities for resuscitation are immediately available in case of need.

PRECAUTIONS

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients, to thiomersal and to residues e.g. eggs, chicken protein, neomycin or polymyxin B sulfate.

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.

If the pandemic situation allows, immunisation shall be postponed in patients with severe febrile illness or acute infection.

Panvax® vaccine should under no circumstances be administered intravascularly.

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

Use in pregnancy (Category B2)
The effects of Panvax® vaccine have not been studied in pregnant women. Therefore, health care providers should assess the risks and potential benefits of administering the vaccine to pregnant women on a case by case basis, taking into account New Zealand Health Authorities' recommendations. Data from vaccinations with inter-pandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. Animal embryofetal development studies have not been conducted with the vaccine.

Use in lactation
Panvax® vaccine may be used during lactation.

Paediatric use
No data have been generated in participants younger than 18 years. The immunogenicity and reactogenicity profile in children and adolescents are not known.

Interactions with other medicines
The vaccine should not be mixed with other injection fluids.

Panvax® vaccine should not be given at the same time as other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

Influenza vaccines may impair the metabolism of warfarin, theophylline, phenytoin, phenobarbitone and carbamazepine by the hepatic P450 system. Results from studies showed conflicting evidence or found no evidence of an interaction. Studies which found a positive association have been variable in the degree of interaction and time after vaccination for the interaction to take effect. The interaction may be idiosyncratic."

Effects on ability to drive and use machines
The vaccine is unlikely to produce an effect on the ability to drive and use machines.

ADVERSE EFFECTS
Clinical trials
Adverse reactions from the three clinical trials in adults 18 years and older with prototype pandemic vaccines (A/Vietnam/1194/2004; H5N1) are listed below (see Pharmacology for more information on the prototype vaccines). A total of 801 adult participants received the inactivated, split virion, monovalent, aluminium-adjuvanted vaccine with different influenza HA antigen doses of 7.5 µg, 15 µg, 30 µg and 45 µg.

The frequency of adverse reactions observed in participants ≥ 65 years was lower compared to those in the 18 to 64 year age group.

Adverse effects are listed according to the following frequency: Very Common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000)

Infections and Infestations
Common - nasopharyngitis, upper respiratory tract infection

Nervous System Disorders
Very Common - headache

Respiratory, Thoracic and Mediastinal Disorders
Common - cough, nasal congestion, pharyngolaryngeal pain, rhinorrhoea

Gastrointestinal Disorders
Very Common - nausea
Common - diarrhoea, toothache, vomiting

Skin and Subcutaneous Tissue Disorders
Common – hyperhidrosis

Musculoskeletal and Connective Tissue Disorders
Very Common - myalgia
Common - arthralgia, back pain

Reproductive System and Breast Disorders
Common - dysmenorrhoea

General Disorders and Administration Site Conditions
Very Common - fatigue, injection site erythema, injection site induration, injection site pain, injection site swelling
Common - chills, injection site haemorrhage, pyrexia

These reactions generally resolve within 3 days.

Post-marketing surveillance
Post-marketing information is not available for Panvax® vaccine, however similar adverse reactions to inter-pandemic trivalent influenza vaccines may be observed. From post marketing surveillance with inter-pandemic trivalent influenza vaccines, the following adverse reactions have been reported:

Uncommon(≥ 1/1,000 to < 1/100):
Generalised skin reactions including pruritus, urticaria or non-specific rash.

Rare (≥ 1/10,000 to < 1/1000):
Neuralgia, paraesthesia, convulsions, transient thrombocytopenia.
Allergic reactions, in rare cases leading to shock, have been reported.

Very rare (< 1/10,000):
Vasculitis with transient renal involvement.
Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

This medicinal product contains thiomersal (an organomercuric compound) as a preservative, and therefore, it is possible that sensitisation reactions may occur.

DOSAGE AND ADMINISTRATION

Dosage

Two 0.5 mL doses, 21 days apart.

Method of administration

Immunisation should be carried out by intramuscular injection.

The vaccine should be allowed to reach room temperature before use. Shake before use. The vaccine should appear as a homogeneous creamy/white opaque liquid suspension with no large clumps visible.

Once opened, the vaccine is to be used immediately and within the one vaccination session, with any remaining contents discarded in accordance with local requirements. No additions should be made to the contents of the vial. Please refer to the Ministry of Health *Immunisation Handbook* for recommendations regarding the appropriate vaccination technique and needle size.

OVERDOSAGE

There is no specific information on overdose of Panvax® vaccine.

For general advice on overdose management, contact the New Zealand Poisons Centre on 0800 POISON or 0800 764 766.

PRESENTATION AND STORAGE CONDITIONS

Panvax® vaccine is presented in a multi-dose glass vial. Each vial contains 10mL 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.

Pack size is 50 vials.

Storage

Panvax® vaccine should be stored in a refrigerator (2°C to 8°C). IT MUST NOT BE FROZEN. Store in the original package in order to protect from light.

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

Manufactured by:
CSL Limited ABN 99 051 588 348
45 Poplar Road, Parkville
VICTORIA 3052 AUSTRALIA

Distributed by:
CSL Biotherapies (New Zealand) Limited
Level 9, Building 5
666 Great South Road
Central Park Penrose
AUCKLAND
NEW ZEALAND

Date of preparation: 01 September 2008

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NAME OF THE MEDICINE

Panvax® vaccine

Pandemic influenza vaccine (split virion, inactivated and adjuvanted).

DESCRIPTION

Panvax® vaccine is a split virion, inactivated, adjuvanted influenza virus vaccine formulated to contain 30 micrograms of haemagglutinin (HA) per 0.5 mL dose from the pandemic influenza virus strain:

A/Official strain (H5N1)-like (A/H5N1 Official strain)

Each 0.5 mL dose also contains: sodium chloride 4.1 mg, sodium phosphate – dibasic anhydrous 3.0 mg, sodium phosphate – monobasic 80 µg, potassium chloride 20 µg, potassium phosphate – monobasic 20 µg, calcium chloride 1.5 µg, thiomersal 50 µg and aluminium (as aluminium phosphate adjuvant) 0.5 mg.

Each dose may also contain sodium taurodeoxycholate ≤ 5 µg, ovalbumin ≤ 1.0 µg, sucrose < 10 µg, neomycin ≤ 1 ng, polymyxin B sulfate ≤ 0.2 ng and beta-propiolactone ≤ 2 ng.

Panvax® vaccine is prepared from influenza virus propagated in the allantoic fluid of embryonated chicken eggs. The virus is harvested from the eggs, purified and inactivated with beta-propiolactone. The virus particles are then disrupted with sodium taurodeoxycholate to produce split virion particles which are further purified prior to formulation with aluminium phosphate adjuvant.

This vaccine complies with the Health Authorities' decision for the pandemic, taking into account the recommendation from the WHO.

PHARMACOLOGY

Prototype pandemic influenza vaccines contain influenza virus antigens that are different from those included in seasonal trivalent influenza vaccines and may also be substantially different from the virus which causes pandemic influenza. If a pandemic influenza virus emerges, the clinical efficacy and safety data obtained from clinical trials with prototype pandemic influenza vaccines is expected to be relevant for the pandemic vaccine made from the official pandemic influenza virus strain.

Clinical experience with prototype pandemic vaccines, following a two-dose primary vaccination course, has been derived from clinical trials in healthy adult, elderly and paediatric populations. The efficacy of prototype pandemic vaccines is assessed by serum immunogenicity, since clinical protection is not able to be evaluated.

The immunogenicity of prototype vaccines has been assessed in clinical trials by two serum antibody assays, the haemagglutination inhibition (HI) assay and a viral microneutralisation (MN) assay. There are currently no defined levels of serum antibody responses known to correlate with clinical protection against infection with pandemic influenza viruses. Guidelines for assessment of the pandemic influenza vaccines are based on those for inter-pandemic influenza vaccines developed by the European

Medicines Agency (EMEA) *Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* (CPMP/BWP/214/96) and the EMEA guidance document for pandemic vaccines (CPMP/VEG/4717/03).

A ferret efficacy challenge study using the prototype A/Vietnam/1194/2004 (H5N1) pandemic influenza vaccine has demonstrated that seroconversion (as measured by both HI and MN immune responses) in ferrets vaccinated with the 30 µg HA per dose adjuvanted formulation was associated with 100% survival following lethal challenge and also prevented serious morbidity. This data provides support for the assessment of HI and MN immune responses as a surrogate measure of clinical efficacy in human clinical trials.

CLINICAL TRIALS

Four clinical trials have been conducted to assess the immunogenicity and safety of a prototype pandemic influenza vaccine in healthy persons aged 6 months and older.

The safety of the vaccine was assessed in 4 randomised Phase I or Phase II studies conducted in persons aged 6 months and older. The Phase I trial in 400 adults, 18 to 45 years of age, assessed vaccines formulated with lower HA antigen doses, with and without aluminium phosphate adjuvant. The data from this study demonstrated that higher antigen doses and an adjuvant were required and that two doses of the vaccine elicited modest levels of cross-reactive neutralising antibodies against antigenically distinct H5N1 strains. The immunogenicity data from this study is not presented, however the safety data has been included in the overall safety analysis for the vaccine.

Three double blind, randomised Phase II clinical studies evaluated the immunogenicity of an inactivated, split virion, monovalent, aluminium phosphate-adjuvanted, prototype pandemic vaccine in adults aged 18 to 64 years, elderly adults aged 65 years and over, and children aged ≥ 6 months to < 9 years. Two doses were administered 21 days apart.

For the Adult Phase II study, immunogenicity was assessed by HI and MN approximately 21 days after each dose and by MN only, 6 months after the second dose to evaluate antibody persistence. For the Elderly Adult and Paediatric studies, immunogenicity was assessed by MN only approximately 21 days after each dose and 6 months after Dose 2.

The Adult Phase II study enrolled 400 participants, aged 18 to 64 years. Immunogenicity results for the 30 µg HA per dose vaccine are shown in Tables 1a-b.

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

Serum HI antibody	After Dose 1 n=200 (95% CI)	After Dose 2 n=197 (95% CI)
Fold increase in GMT[a]	2.8 (2.3,3.5)	6.8 (5.5,8.4)
Seroconversion or significant increase[b]	22.0% (16.5,28.4)	48.2% (41.1,55.4)
Proportion with HI ≥ 40	23.0% (17.4,29.5)	49.7% (42.6,56.9)

[a] Fold increase in GMT (geometric mean titre) is the fold increase in antibody titre over the pre-vaccination GMT. [b] 'Seroconversion or significant increase' is defined as at least a four fold increase over the pre-vaccination GMT, and with a post-vaccination titre value of at least 40.

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

Serum viral neutralising antibody (MN)	After Dose 1 n=200 (95% CI)	After Dose 2 n=197 (95% CI)	6 months after Dose 2 n=192 (95% CI)
Fold increase in GMT	1.8 (1.5,2.0)	4.3 (3.7,5.0)	3.4 (2.9,4.1)
Seroconversion or significant increase	18.5% (13.4,24.6)	53.8% (46.6,60.9)	40.4% (33.4,47.7)
Proportion seropositive (MN ≥ 20)	28.0% (21.9,34.8)	72.6% (65.8,78.7)	60.1% (52.8,67.1)
Proportion with MN ≥ 40	18.5% (13.4,24.6)	53.8% (46.6,60.9)	40.4% (33.4,47.7)

The Elderly Adult Phase II study enrolled 201 participants, 65 years of age and older. Immunogenicity results for the 30 µg HA per dose vaccine are shown in Table 2.

Table 2: Immunogenicity Results for Elderly Adult Population (MN)

Serum viral neutralising antibody (MN)	After Dose 1 n=100 (95% CI)	After Dose 2 n=101 (95% CI)	6 months after Dose 2 n=98 (95% CI)
Fold increase in GMT	2.1 (1.6,2.7)	4.2 (3.2,5.4)	2.8 (2.2,3.5)
Seroconversion or significant increase	22.0% (14.3,31.4)	47.5% (37.5,57.7)	38.8% (29.1,49.2)
Proportion seropositive (MN ≥ 20)	32.0% (23.0,42.1)	62.4% (52.2,71.8)	51.0% (40.7,61.3)
Proportion with MN ≥ 40	24.0% (16.0,33.6)	48.5% (38.4,58.7)	40.8% (31.0,51.2)

The Paediatric Phase II study enrolled 150 participants, aged ≥ 6 months to < 9 years. Participants within this study were further defined into two age groups: Group A, ≥ 6 months to < 3 years, and Group B, ≥ 3 years to < 9 years. Immunogenicity results were comparable across these age groups and are presented for the 30 µg HA per dose vaccine as combined results in Table 3.

Table 3: Immunogenicity Results for Paediatric Population (MN)

Serum viral neutralising antibody (MN)	After Dose 1 n=55 (95% CI)	After Dose 2 n=66 (95% CI)	6 months after Dose 2 n=67 (95% CI)
Fold increase in GMT [a, 1]	1.6 (1.2, 2.2)	40.2 (30.6, 52.8)	5.4 (4.3, 6.8)
Seroconversion or significant increase [b, 1]	12.7% (5.3, 24.5)	98.3% (91.1, 100.0)	66.7% (53.3, 78.3)
Proportion seropositive (MN ≥ 20)	25.5% (14.7, 39.0)	98.5% (91.8, 100.0)	85.1% (74.3, 92.6)
Proportion with MN ≥ 40	14.5% (6.5, 26.7)	98.5% (91.8, 100.0)	67.2% (54.6, 78.2)

[1] The number of participants assessed for Fold Increase in GMT and Seroconversion or significant increase, after Dose 2 and 6 months after Dose 2, was 60.

INDICATIONS

Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with New Zealand Health Authorities' recommendations, taking into account the recommendation of the World Health Organisation.

CONTRAINDICATIONS

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (e.g. eggs, chicken protein; see Description section) of this vaccine. However, in a pandemic situation, it may be appropriate to give the vaccine, provided that facilities for resuscitation are immediately available in case of need.

PRECAUTIONS

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients, to thiomersal and to residues e.g. eggs, chicken protein, neomycin or polymyxin B sulfate.

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.

If the pandemic situation allows, immunisation shall be postponed in patients with severe febrile illness or acute infection.

Panvax® vaccine should under no circumstances be administered intravascularly.

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

Use in pregnancy (Category B2)
The effects of Panvax® vaccine have not been studied in pregnant women. Therefore, health care providers should assess the risks and potential benefits of administering the vaccine to pregnant women on a case by case basis, taking into account New Zealand Health Authorities' recommendations. Data from vaccinations with inter-pandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. Animal embryofetal development studies have not been conducted with the vaccine.

Use in lactation
Panvax® vaccine may be used during lactation.

Paediatric use
Panvax® vaccine may be used in children from 6 months of age.

Interactions with other medicines
The vaccine should not be mixed with other injection fluids.

Panvax® vaccine should not be given at the same time as other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

Influenza vaccines may impair the metabolism of warfarin, theophylline, phenytoin, phenobarbitone and carbamazepine by the hepatic P450 system. Results from studies showed conflicting evidence or found no evidence of an interaction. Studies which found a positive association have been variable in the degree of interaction and time after vaccination for the interaction to take effect. The interaction may be idiosyncratic."

Effects on ability to drive and use machines
The vaccine is unlikely to produce an effect on the ability to drive and use machines.

ADVERSE EFFECTS
Clinical trials (Adults)
Adverse reactions from the three clinical trials in adults 18 years and older with prototype pandemic vaccines (A/Vietnam/1194/2004; H5N1) are listed below (see Pharmacology for more information on the prototype vaccines). A total of 801 adult participants received the inactivated, split virion, monovalent, aluminium-adjuvanted vaccine with different influenza HA antigen doses of 7.5 µg, 15 µg, 30 µg and 45 µg.

The frequency of adverse reactions observed in participants ≥ 65 years was lower compared to those in the 18 to 64 year age group.

Adverse effects are listed according to the following frequency: Very Common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000)

Infections and Infestations
Common - nasopharyngitis, upper respiratory tract infection

Nervous System Disorders
Very Common - headache

Respiratory, Thoracic and Mediastinal Disorders
Common - cough, nasal congestion, pharyngolaryngeal pain, rhinorrhoea

Gastrointestinal Disorders
Very Common - nausea
Common - diarrhoea, toothache, vomiting

Skin and Subcutaneous Tissue Disorders
Common – hyperhidrosis

Musculoskeletal and Connective Tissue Disorders
Very Common - myalgia
Common - arthralgia, back pain

Reproductive System and Breast Disorders
Common - dysmenorrhoea

General Disorders and Administration Site Conditions
Very Common - fatigue, injection site erythema, injection site induration, injection site pain, injection site swelling
Common - chills, injection site haemorrhage, pyrexia

These reactions generally resolve within 3 days.

Clinical trial (Paediatric)

Adverse reactions from the Paediatric clinical trial, in children aged 6 months to < 9 years, are listed below. The safety population consisted of a total of 149 participants who received the inactivated, split virion, monovalent, aluminium-adjuvanted vaccine with 30 µg or 45 µg HA influenza antigen per dose.

Infections and Infestations
Common - upper respiratory tract infection, gastroenteritis, otitis media

Metabolism and Nutritional Disorders
Very common – decreased appetite

Nervous System Disorders
Very Common – headache

Eye Disorders
Common – conjunctivitis

Ear and Labyrinth Disorders
Common – ear pain

Respiratory, Thoracic and Mediastinal Disorders
Very common – rhinorrhoea, wheezing
Common – asthma, cough, pharyngolaryngeal pain

Gastrointestinal Disorders
Very Common – diarrhoea, vomiting
Common – abdominal pain

Skin and Subcutaneous Tissue Disorders
Common – rash

Musculoskeletal and Connective Tissue Disorders
Very Common - myalgia

General Disorders and Administration Site Conditions
Very Common - injection site pain, injection site erythema, injection site induration, injection site haemorrhage, injection site swelling, irritability, pyrexia

These reactions generally resolve within 3 days.

Injection site reactions occurred slightly less frequently in Group A (≥ 6 months to < 3 years) compared to Group B (≥ 3 years to < 9 years). Headache and myalgia was reported less frequently in Group A, while fever, irritability, reduced appetite, diarrhoea, wheezing and vomiting occurred less frequently in the Group B population.

Post-marketing surveillance
Post-marketing information is not available for Panvax® vaccine, however similar adverse reactions to inter-pandemic trivalent influenza vaccines may be observed. From post marketing surveillance with inter-pandemic trivalent influenza vaccines, the following adverse reactions have been reported:

Uncommon(≥ 1/1,000 to < 1/100):
Generalised skin reactions including pruritus, urticaria or non-specific rash.

Rare (≥ 1/10,000 to < 1/1000):
Neuralgia, paraesthesia, convulsions, transient thrombocytopenia.
Allergic reactions, in rare cases leading to shock, have been reported.

Very rare (< 1/10,000):
Vasculitis with transient renal involvement.
Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.
This medicinal product contains thiomersal (an organomercuric compound) as a preservative, and therefore, it is possible that sensitisation reactions may occur.

DOSAGE AND ADMINISTRATION

Dosage

Two 0.5 mL doses, 21 days apart.

Method of administration

Immunisation should be carried out by intramuscular injection.

The vaccine should be allowed to reach room temperature before use. Shake before use. The vaccine should appear as a homogeneous creamy/white opaque liquid suspension with no large clumps visible.

Once opened, the vaccine is to be used immediately and within the one vaccination session, with any remaining contents discarded in accordance with local requirements. No additions should be made to the contents of the vial. Please refer to the Ministry of Health *Immunisation Handbook* for recommendations regarding the appropriate vaccination technique and needle size.

OVERDOSAGE

There is no specific information on overdose of Panvax® vaccine.

For general advice on overdose management, contact the New Zealand Poisons Centre on 0800 POISON or 0800 764 766.

FURTHER INFORMATION

This medicine has been granted provisional consent under section 23 of the Medicines Act 1981.

PRESENTATION AND STORAGE CONDITIONS

Panvax® vaccine is presented in a multi-dose glass vial. Each vial contains 10mL 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.

Pack size is 50 vials.

Storage

Panvax® vaccine should be stored in a refrigerator (2°C to 8°C). IT MUST NOT BE FROZEN. Store in the original package in order to protect from light.

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

Manufactured by:
CSL Limited ABN 99 051 588 348
45 Poplar Road, Parkville
VICTORIA 3052 AUSTRALIA

Distributed by:
CSL Biotherapies (New Zealand) Limited
Level 9, Building 5
666 Great South Road
Central Park Penrose
AUCKLAND
NEW ZEALAND

Date of preparation: 08 February 2011

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NAME OF THE MEDICINE

Panvax® vaccine

Pandemic influenza vaccine (split virion, inactivated and adjuvanted).

DESCRIPTION

Panvax® vaccine is a split virion, inactivated, adjuvanted influenza virus vaccine formulated to contain 30 micrograms of haemagglutinin (HA) per 0.5 mL dose from the pandemic influenza virus strain:

A/Official strain (H5N1)-like (A/H5N1 Official strain)

Each 0.5 mL dose also contains: sodium chloride 4.1 mg, sodium phosphate – dibasic anhydrous 3.0 mg, sodium phosphate – monobasic 80 µg, potassium chloride 20 µg, potassium phosphate – monobasic 20 µg, calcium chloride 1.5 µg, thiomersal 50 µg and aluminium (as aluminium phosphate adjuvant) 0.5 mg.

Each dose may also contain sodium taurodeoxycholate ≤ 5 µg, ovalbumin ≤ 1.0 µg, sucrose < 10 µg, neomycin ≤ 4.3 ng, polymyxin B sulfate ≤ 0.65 ng and beta-propiolactone ≤ 0.67 ng.

Panvax® vaccine is prepared from influenza virus propagated in the allantoic fluid of embryonated chicken eggs. The virus is harvested from the eggs, purified and inactivated with beta-propiolactone. The virus particles are then disrupted with sodium taurodeoxycholate to produce split virion particles which are further purified prior to formulation with aluminium phosphate adjuvant.

This vaccine complies with the Health Authorities' decision for the pandemic, taking into account the recommendation from the WHO.

PHARMACOLOGY

Prototype pandemic influenza vaccines contain influenza virus antigens that are different from those included in seasonal trivalent influenza vaccines and may also be substantially different from the virus which causes pandemic influenza. If a pandemic influenza virus emerges, the clinical efficacy and safety data obtained from clinical trials with prototype pandemic influenza vaccines is expected to be relevant for the pandemic vaccine made from the official pandemic influenza virus strain.

Clinical experience with prototype pandemic vaccines, following a two-dose primary vaccination course, has been derived from clinical trials in healthy adult, elderly and paediatric populations. The efficacy of prototype pandemic vaccines is assessed by serum immunogenicity, since clinical protection is not able to be evaluated.

The immunogenicity of prototype vaccines has been assessed in clinical trials by two serum antibody assays, the haemagglutination inhibition (HI) assay and a viral microneutralisation (MN) assay. There are currently no defined levels of serum antibody responses known to correlate with clinical protection against infection with pandemic influenza viruses. Guidelines for assessment of the pandemic influenza vaccines are based on those for inter-pandemic influenza vaccines developed by the European

Medicines Agency (EMEA) *Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* (CPMP/BWP/214/96) and the EMEA guidance document for pandemic vaccines (CPMP/VEG/4717/03).

A ferret efficacy challenge study using the prototype A/Vietnam/1194/2004 (H5N1) pandemic influenza vaccine has demonstrated that seroconversion (as measured by both HI and MN immune responses) in ferrets vaccinated with the 30 µg HA per dose adjuvanted formulation was associated with 100% survival following lethal challenge and also prevented serious morbidity. This data provides support for the assessment of HI and MN immune responses as a surrogate measure of clinical efficacy in human clinical trials.

CLINICAL TRIALS

Four clinical trials have been conducted to assess the immunogenicity and safety of a prototype pandemic influenza vaccine in healthy persons aged 6 months and older.

The safety of the vaccine was assessed in 4 randomised Phase I or Phase II studies conducted in persons aged 6 months and older. The Phase I trial in 400 adults, 18 to 45 years of age, assessed vaccines formulated with lower HA antigen doses, with and without aluminium phosphate adjuvant. The data from this study demonstrated that higher antigen doses and an adjuvant were required and that two doses of the vaccine elicited modest levels of cross-reactive neutralising antibodies against antigenically distinct H5N1 strains. The immunogenicity data from this study is not presented, however the safety data has been included in the overall safety analysis for the vaccine.

Three double blind, randomised Phase II clinical studies evaluated the immunogenicity of an inactivated, split virion, monovalent, aluminium phosphate-adjuvanted, prototype pandemic vaccine in adults aged 18 to 64 years, elderly adults aged 65 years and over, and children aged ≥ 6 months to < 9 years. Two doses were administered 21 days apart.

For the Adult Phase II study, immunogenicity was assessed by HI and MN approximately 21 days after each dose and by MN only, 6 months after the second dose to evaluate antibody persistence. For the Elderly Adult and Paediatric studies, immunogenicity was assessed by MN only approximately 21 days after each dose and 6 months after Dose 2.

The Adult Phase II study enrolled 400 participants, aged 18 to 64 years. Immunogenicity results for the 30 µg HA per dose vaccine are shown in Tables 1a-b.

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

Serum HI antibody	After Dose 1 n=200 (95% CI)	After Dose 2 n=197 (95% CI)
Fold increase in GMT[a]	2.8 (2.3,3.5)	6.8 (5.5,8.4)
Seroconversion or significant increase[b]	22.0% (16.5,28.4)	48.2% (41.1,55.4)
Proportion with HI ≥ 40	23.0% (17.4,29.5)	49.7% (42.6,56.9)

[a] Fold increase in GMT (geometric mean titre) is the fold increase in antibody titre over the pre-vaccination GMT. [b] 'Seroconversion or significant increase' is defined as at least a four fold increase over the pre-vaccination GMT, and with a post-vaccination titre value of at least 40.

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

Serum viral neutralising antibody (MN)	After Dose 1 n=200 (95% CI)	After Dose 2 n=197 (95% CI)	6 months after Dose 2 n=192 (95% CI)
Fold increase in GMT	1.8 (1.5,2.0)	4.3 (3.7,5.0)	3.4 (2.9,4.1)
Seroconversion or significant increase	18.5% (13.4,24.6)	53.8% (46.6,60.9)	40.4% (33.4,47.7)
Proportion seropositive (MN ≥ 20)	28.0% (21.9,34.8)	72.6% (65.8,78.7)	60.1% (52.8,67.1)
Proportion with MN ≥ 40	18.5% (13.4,24.6)	53.8% (46.6,60.9)	40.4% (33.4,47.7)

The Elderly Adult Phase II study enrolled 201 participants, 65 years of age and older. Immunogenicity results for the 30 µg HA per dose vaccine are shown in Table 2.

Table 2: Immunogenicity Results for Elderly Adult Population (MN)

Serum viral neutralising antibody (MN)	After Dose 1 n=100 (95% CI)	After Dose 2 n=101 (95% CI)	6 months after Dose 2 n=98 (95% CI)
Fold increase in GMT	2.1 (1.6,2.7)	4.2 (3.2,5.4)	2.8 (2.2,3.5)
Seroconversion or significant increase	22.0% (14.3,31.4)	47.5% (37.5,57.7)	38.8% (29.1,49.2)
Proportion seropositive (MN ≥ 20)	32.0% (23.0,42.1)	62.4% (52.2,71.8)	51.0% (40.7,61.3)
Proportion with MN ≥ 40	24.0% (16.0,33.6)	48.5% (38.4,58.7)	40.8% (31.0,51.2)

The Paediatric Phase II study enrolled 150 participants, aged ≥ 6 months to < 9 years. Participants within this study were further defined into two age groups: Group A, ≥ 6 months to < 3 years, and Group B, ≥ 3 years to < 9 years. Immunogenicity results were comparable across these age groups and are presented for the 30 µg HA per dose vaccine as combined results in Table 3.

Table 3: Immunogenicity Results for Paediatric Population (MN)

Serum viral neutralising antibody (MN)	After Dose 1 n=55 (95% CI)	After Dose 2 n=66 (95% CI)	6 months after Dose 2 n=67 (95% CI)
Fold increase in GMT [a, 1]	1.6 (1.2, 2.2)	40.2 (30.6, 52.8)	5.4 (4.3, 6.8)
Seroconversion or significant increase [b, 1]	12.7% (5.3, 24.5)	98.3% (91.1, 100.0)	66.7% (53.3, 78.3)
Proportion seropositive (MN ≥ 20)	25.5% (14.7, 39.0)	98.5% (91.8, 100.0)	85.1% (74.3, 92.6)
Proportion with MN ≥ 40	14.5% (6.5, 26.7)	98.5% (91.8, 100.0)	67.2% (54.6, 78.2)

[1] The number of participants assessed for Fold Increase in GMT and Seroconversion or significant increase, after Dose 2 and 6 months after Dose 2, was 60.

INDICATIONS

Prophylaxis of influenza in an officially declared pandemic situation. The vaccine may only be marketed or distributed in accordance with the directives contained in the current version of the New Zealand Influenza Pandemic Action Plan.

CONTRAINDICATIONS

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (e.g. eggs, chicken protein; see Description section) of this vaccine. However, in a pandemic situation, it may be appropriate to give the vaccine, provided that facilities for resuscitation are immediately available in case of need.

PRECAUTIONS

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients, to thiomersal and to residues e.g. eggs, chicken protein, neomycin or polymyxin B sulfate.

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.

If the pandemic situation allows, immunisation shall be postponed in patients with severe febrile illness or acute infection.

Panvax® vaccine should under no circumstances be administered intravascularly.

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

Use in pregnancy (Category B2)
The effects of Panvax® vaccine have not been studied in pregnant women. Therefore, health care providers should assess the risks and potential benefits of administering the vaccine to pregnant women on a case by case basis, taking into account New Zealand Health Authorities' recommendations. Data from vaccinations with inter-pandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. Animal embryofetal development studies have not been conducted with the vaccine.

Use in lactation
Panvax® vaccine may be used during lactation.

Paediatric use
Panvax® vaccine may be used in children from 6 months of age.

Interactions with other medicines
The vaccine should not be mixed with other injection fluids.

Panvax® vaccine should not be given at the same time as other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

Influenza vaccines may impair the metabolism of warfarin, theophylline, phenytoin, phenobarbitone and carbamazepine by the hepatic P450 system. Results from studies showed conflicting evidence or found no evidence of an interaction. Studies which found a positive association have been variable in the degree of interaction and time after vaccination for the interaction to take effect. The interaction may be idiosyncratic."

Effects on ability to drive and use machines
The vaccine is unlikely to produce an effect on the ability to drive and use machines.

ADVERSE EFFECTS
Clinical trials (Adults)
Adverse reactions from the three clinical trials in adults 18 years and older with prototype pandemic vaccines (A/Vietnam/1194/2004; H5N1) are listed below (see Pharmacology for more information on the prototype vaccines). A total of 801 adult participants received the inactivated, split virion, monovalent, aluminium-adjuvanted vaccine with different influenza HA antigen doses of 7.5 µg, 15 µg, 30 µg and 45 µg.

The frequency of adverse reactions observed in participants ≥ 65 years was lower compared to those in the 18 to 64 year age group.

Adverse effects are listed according to the following frequency: Very Common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000)

Infections and Infestations
Common - nasopharyngitis, upper respiratory tract infection

Nervous System Disorders
Very Common - headache

Respiratory, Thoracic and Mediastinal Disorders
Common - cough, nasal congestion, pharyngolaryngeal pain, rhinorrhoea

Gastrointestinal Disorders
Very Common - nausea
Common - diarrhoea, toothache, vomiting

Skin and Subcutaneous Tissue Disorders
Common – hyperhidrosis

Musculoskeletal and Connective Tissue Disorders
Very Common - myalgia
Common - arthralgia, back pain

Reproductive System and Breast Disorders
Common - dysmenorrhoea

General Disorders and Administration Site Conditions
Very Common - fatigue, injection site erythema, injection site induration, injection site pain, injection site swelling
Common - chills, injection site haemorrhage, pyrexia

These reactions generally resolve within 3 days.

Clinical trial (Paediatric)

Adverse reactions from the Paediatric clinical trial, in children aged 6 months to < 9 years, are listed below. The safety population consisted of a total of 149 participants who received the inactivated, split virion, monovalent, aluminium-adjuvanted vaccine with 30 µg or 45 µg HA influenza antigen per dose.

Infections and Infestations
Common - upper respiratory tract infection, gastroenteritis, otitis media

Metabolism and Nutritional Disorders
Very common – decreased appetite

Nervous System Disorders
Very Common – headache

Eye Disorders
Common – conjunctivitis

Ear and Labyrinth Disorders
Common – ear pain

Respiratory, Thoracic and Mediastinal Disorders
Very common – rhinorrhoea, wheezing
Common – asthma, cough, pharyngolaryngeal pain

Gastrointestinal Disorders
Very Common – diarrhoea, vomiting
Common – abdominal pain

Skin and Subcutaneous Tissue Disorders
Common – rash

Musculoskeletal and Connective Tissue Disorders
Very Common - myalgia

General Disorders and Administration Site Conditions
Very Common - injection site pain, injection site erythema, injection site induration, injection site haemorrhage, injection site swelling, irritability, pyrexia

These reactions generally resolve within 3 days.

Injection site reactions occurred slightly less frequently in Group A (≥ 6 months to < 3 years) compared to Group B (≥ 3 years to < 9 years). Headache and myalgia was reported less frequently in Group A, while fever, irritability, reduced appetite, diarrhoea, wheezing and vomiting occurred less frequently in the Group B population.

Post-marketing surveillance
Post-marketing information is not available for Panvax® vaccine, however similar adverse reactions to inter-pandemic trivalent influenza vaccines may be observed. From post marketing surveillance with inter-pandemic trivalent influenza vaccines, the following adverse reactions have been reported:

Uncommon(≥ 1/1,000 to < 1/100):
Generalised skin reactions including pruritus, urticaria or non-specific rash.

Rare (≥ 1/10,000 to < 1/1000):
Neuralgia, paraesthesia, convulsions, transient thrombocytopenia.
Allergic reactions, in rare cases leading to shock, have been reported.

Very rare (< 1/10,000):
Vasculitis with transient renal involvement.
Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.
This medicinal product contains thiomersal (an organomercuric compound) as a preservative, and therefore, it is possible that sensitisation reactions may occur.

DOSAGE AND ADMINISTRATION

Dosage
Two 0.5 mL doses, 21 days apart.

Method of administration
Immunisation should be carried out by intramuscular injection.

The vaccine should be allowed to reach room temperature before use. Shake before use. The vaccine should appear as a homogeneous creamy/white opaque liquid suspension with no large clumps visible.

Once opened, the vaccine is to be used immediately and within the one vaccination session, with any remaining contents discarded in accordance with local requirements. No additions should be made to the contents of the vial. Please refer to the Ministry of Health *Immunisation Handbook* for recommendations regarding the appropriate vaccination technique and needle size.

OVERDOSAGE
There is no specific information on overdose of Panvax® vaccine.

For general advice on overdose management, contact the New Zealand Poisons Centre on 0800 POISON or 0800 764 766.

FURTHER INFORMATION
This medicine has been granted provisional consent under section 23 of the Medicines Act 1981.

PRESENTATION AND STORAGE CONDITIONS
Panvax® vaccine is presented in a multi-dose glass vial. Each vial contains 10mL 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.

Pack size is 50 vials.

Storage
Panvax® vaccine should be stored in a refrigerator (2°C to 8°C). IT MUST NOT BE FROZEN. Store in the original package in order to protect from light.

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

Manufactured by:
CSL Limited ABN 99 051 588 348
45 Poplar Road, Parkville
VICTORIA 3052 AUSTRALIA

Distributed by:
bioCSL (New Zealand) Limited
Level 9, Building 5
666 Great South Road
Central Park Penrose

AUCKLAND
NEW ZEALAND

Date of preparation: 28 March 2014

® Registered trademark of CSL Limited

VEPACEL

Pre-Pandemic Influenza Vaccine (A/H5N1) (whole virion, Vero cell derived, inactivated)

Suspension for injection

QUALITATIVE & QUANTITATIVE COMPOSITION

One dose of 0.5mL contains:

Influenza Viruse (whole virion, inactivated), containing antigen of *:
A/Vietnam/1203/2004 (H5N1) 7.5 micrograms**.

* propagated in Vero cells (continuous cell line of mammalian origin)
** production target value expressed in micrograms Haemagglutinin (SRD).

This is a multi-dose container, see *Pharmaceutical Particulars/Nature and Contents of Container* for the number of doses per vial.

This vaccine may contain traces of formaldehyde, benzonase, sucrose, trypsin and Vero cell protein, which are used during the manufacturing process, see *Clinical Particulars/Contraindications and Special Warnings and Precautions for Use*.

For the full list of excipients see *Pharmaceutical Particulars/List of Excipients.*

PHARMACEUTICAL FORM

Suspension for injection. The vaccine is a clear to opalescent suspension.

CLINICAL PARTICULARS

Therapeutic Indications

Active immunization against H5N1 subtype of influenza A virus.

This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards as well as immunocompromised and chronically ill subjects following administration of two doses of vaccine prepared with H5N1 subtype strains, see *Pharmacological Properties/Pharmacodynamic Properties*.

VEPACEL may only be marketed or distributed in accordance with the directives contained in the current version of the New Zealand Influenza Pandemic Action Plan.

This medicine has been granted provisional consent under section 23 of the Medicines Act 1981.

Dosage and Method of Administration

Posology

Adults from the age of 18 years:
One dose of 0.5mL at an elected date. A second dose of 0.5mL should be given after an interval of at least 3 weeks.

Paediatric Population:
The safety and efficacy of VEPACEL in subjects under 18 years of age have not yet been established. No data are available for VEPACEL in this age group.

Method of administration

Immunization should be carried out by intramuscular injection into the deltoid muscle.

Contraindications

History of hypersensitivity to the active substance, or to any of the excipients listed in *Pharmaceutical Particulars/List of Excipients*, or trace residues (formaldehyde, benzonase, sucrose, trypsin, Vero cell protein). If vaccination is considered necessary, facilities for resuscitation should be immediately available in case of need. See *Clinical Particulars/Special Warnings and Precautions for Use*.

Special Warnings and Precautions for Use

This vaccine may contain traces of formaldehyde, benzonase, sucrose, trypsin and Vero cell protein, which are used during the manufacturing process. Therefore, hypersensitivity reactions may occur.

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

Hypersensitivity reactions, including anaphylaxis, have been reported following use of a similar whole virion, Vero cell derived H1N1 influenza vaccine administered during a pandemic period. Such reactions have occurred both in patients with a history of multiple allergies and in patients with no known allergy.

Immunisation shall be postponed in patients with severe febrile illness or acute infection.

VEPACEL must not be administered intravascularly.

There are no data with VEPACEL using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleeding.

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

A protective response may not be induced in all individuals receiving the vaccine, *see Pharmacological Properties/Pharmacodynamic Properties*.

Interaction with Other Medicinal Products and Other Forms of Interaction

There are no data on co-administration of VEPACEL with other vaccines. However, if co-administration with another vaccine is indicated, immunization should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

Immunoglobulin is not to be given with VEPACEL unless it is necessary during a medical emergency to provide immediate protection. If necessary, VEPACEL may be given at the same time as normal or specific immunoglobulin into separate limbs.

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

Following seasonal influenza vaccination, false positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus, and especially, HTLV-1. In such cases, the western blot method is negative. These transitory false-positive results may be due to IgM production in response to the vaccine.

Fertility, pregnancy and lactation

The safety of VEPACEL in pregnancy and lactation has not been assessed in clinical trials.

Animal studies with H5N1 strain vaccines (A/Vietnam/1203/2004 and A/Indonesia/05/2005) do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

Health care providers should carefully consider the potential risks and benefits for each specific patient before prescribing VEPACEL.

The use of VEPACEL during pregnancy and lactation may be considered in a prepandemic situation, taking into account official recommendations.

Effects on Ability to Drive and Use Machines

VEPACEL has minor influence on the ability to drive and use machines.

Undesirable Effects

Summary of safety profile

Clinical trials were conducted with the H5N1 vaccine (*see Pharmacological Properties/ Pharmacodynamic Properties* for more information on the H5N1 vaccines) in approximately 3700 subjects (ranging in age from 18 to 60 years and above) and special risk groups of approximately 300 subjects each, consisting of immunocompromised subjects and patients with chronic disease conditions. The safety profile in immunocompromised subjects and patients with chronic disease conditions. The adverse reactions observed are shown in the table below.

The safety profile in immunocompromised subjects and patients with chronic disease conditions is similar to the safety profile in healthy subjects.

Summary of adverse reactions

Adverse reactions are listed according to the following frequency:

Very Common (≥ 1/10)
Common (≥ 1/100 - < 1/10)
Uncommon (≥ 1/1,000 - < 1/100)
Rare (≥ 1/10,000 - < 1/1,000)
Very Rare (< 1/10,000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
INFECTIONS AND INFESTATIONS	Nasopharyngitis	Common
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy	Uncommon
PSYCHIATRIC DISORDERS	Insomnia	Uncommon
NERVOUS SYSTEM DISORDERS	Headache	Very Common
	Dizziness	Uncommon
	Somnolence	Uncommon
	Sensory abnormalities (paraesthesia, dysesthesia, oral dysesthesia, hypoesthesia, dysgeusia, and burning sensation)	Common
EYE DISORDERS	Conjunctivitis	Uncommon
	Eye irritation	Uncommon
EAR AND LABYRINTH DISORDERS	Vertigo	Common
	Ear pain	Uncommon
	Sudden hearing loss	Rare
VASCULAR DISORDERS	Hypotension	Uncommon
	Syncope	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Oropharyngeal pain	Common
	Cough	Common
	Dyspnoea	Uncommon
	Nasal congestion	Uncommon
	Rhinorrhoea	Uncommon
	Dry throat	Uncommon
GASTROINTESTINAL DISORDERS	Diarrhoea	Common
	Vomiting	Uncommon
	Nausea	Uncommon
	Abdominal pain	Uncommon
	Dyspepsia	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis	Common
	Pruritis	Common
	Rash	Uncommon
	Urticaria	Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia	Common
	Myalgia	Common

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue	Very common
	Pyrexia	Common
	Chills	Common
	Malaise	Common
	Influenza like illness	Uncommon
	Chest discomfort	Uncommon
	Injection site reactions • Injection site pain • Injection site induration • Injection site erythema • Injection site swelling • Injection site haemorrhage • Injection site irritation • Injection site pruritus • Injection site movement impairment	 Very Common Common Common Common Common Uncommon Uncommon Uncommon

Post-marketing surveillance

There are no post-marketing surveillance data available for VEPACEL.

Celvapan (H1N1)

From post-marketing surveillance with a whole virion, Vero cell derived, H1N1 vaccine, the following adverse reactions have been reported (the frequency of these adverse reactions is not known as it cannot be estimated from the available data):

Immune system disorders: anaphylactic reaction, hypersensitivity
Nervous system disorders: convulsion
Skin and subcutaneous tissue disorders: angioedema
Musculoskeletal and connective tissue disorders: pain in extremity.

Trivalent seasonal influenza vaccines

The following serious adverse reactions have been reported from post-marketing surveillance with egg-derived interpandemic trivalent vaccines:

Uncommon: Generalized skin reactions

Rare: Neuralgia, Transient thrombocytopenia. Allergic reactions, in rare cases leading to shock, have been reported.

Very rare: Vasculitis with transient renal involvement. Neurological disorders, such as encephalomyelitis, neuritis, and Guillain Barré syndrome.

Overdose

No case of overdose has been reported for VEPACEL.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This section describes the clinical experience with the H5N1 vaccine.

Pandemic and Pre-Pandemic 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 H5N1 vaccines will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with H5N1 vaccines are relevant for the pandemic and pre-pandemic vaccines.

Immune response against (A/Vietnam/1203/2004) (H5N1)

The immunogenicity of the A/Vietnam/1203/2004 strain vaccine has been evaluated in three clinical studies in adults aged 18 – 59 years (N = 961) and in two clinical studies in subjects aged 60 years and older (N = 391) following a 0, 21 day schedule. In addition, the immunogenicity has also been evaluated in a Phase 3 study in specified risk groups of immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123) following a 0, 21 day schedule.

Immunogenicity in adults aged 18 – 59 years (N = 961) and in subjects aged 60 years and older (N = 391)

After primary vaccination the rate of subjects with neutralizing antibody titres > 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 – 59 years and in elderly subjects aged 60 years and above were as follows:

	18 – 59 years 21 Days after		60 years and above 21 Days after	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	44.4%	69.7%	51.9%	69.2%
Seroconversion rate**	32.7%	56.0%	13.3%	23.9%
Seroconversion factor***	3.0	4.5	2.0	2.6

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Immunogenicity in immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123)

After vaccination the rate of subjects with neutralizing antibody titres ≥ 20, seroconversion rate and seroconversion factor as measured by MN assay in immunocompromised subjects and patients with chronic conditions were as follows:

	Immunocompromised subjects 21 Days After		Patients with chronic disease conditions 21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	24.8%	41.5%	44.3%	64.2%
Seroconversion rate**	9.1%	32.2%	17.2%	35.0%
Seroconversion factor***	1.6	2.5	2.3	3.0

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Cross-reactive immune response against related H5N1 strains

In a clinical study in adults aged 18 – 59 years (N = 265) and in elderly aged 60 years and above (N = 270) after vaccination with the A/Vietnam/1203/2004 strain vaccine, the rate of subjects with cross-neutralising antibodies as measured by MN (titre ≥ 20) was as follows:

	18 – 59 years Strain A/Indonesia/05/2005	60 years and above Strain A/Indonesia/05/2005
	21 Days after 2nd Dose	21 Days after 2nd Dose
Seroneutralisation rate*	35.1%	54.8%

* MN titre ≥ 20

Heterologous booster vaccinations

A heterologous booster vaccination with a 7.5µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered in a time frame of 12 – 24 months after priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in three clinical studies in adults aged 18 – 59 years and in elderly aged 60 years and above. A 12 – 24 months heterologous booster has also been administered in a Phase 3 study in immunocompromised subjects and patients with chronic disease conditions.

Seroneutralisation rates (MN titre ≥ 20) at 21 days after a 12 – 24 months booster vaccination with the 7.5mcg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

Seroneutralisation rate*	**18 – 59 years**		**60 years and above**	
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
12 – 24 months booster	89.8%	86.9%	82.9%	75.3%

* MN titre ≥ 20

Seroneutralisation rate*	**Immunocompromised subjects**		**Patients with chronic disease conditions**	
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
12 – 24 months booster	71.6%	65.7%	77.5%	70.8%

* MN titre ≥ 20

A booster with a 7.5µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine administered 12 months after a single dose priming vaccination with the A/Vietnam/ 1203/2004 strain vaccine was also evaluated in adults aged 18 – 59 years.

Seroneutralization rates (MN titer ≥ 20) at 21 days after a 12 months booster vaccination with the 7.5µg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

Seroneutralisation rate*	**18 – 59 years**	**60 years and above**
Tested against	A/Vietnam	A/Indonesia
12 months booster	85.9%	92.9%

* MN titre ≥ 20

Paediatric population

No data are available on VEPACEL for subjects under 18 years old.

The European Medicines Agency has deferred the obligation to submit the results of one study with *Vero Cell-Derived Whole Virus H5N1 Influenza Vaccine* in subjects of the paediatric population aged 6 months – 17 years in *"active immunization against H5N1 subtype of influenza A virus"*, see *Clinical Particulars/Posology and method of administration* for information on paediatric use.

Information from non-clinical studies

The protective efficacy of VEPACEL against morbidity and mortality induced by the infection with lethal doses of highly pathogenic avian influenza H5N1 virus was assessed non-clinically in a ferret challenge model.

Sixteen ferrets were divided into two cohorts and were vaccinated on days 0 and 21 with 7.5µg of the A/Vietnam/1203/2004 vaccine or were sham vaccinated. All ferrets were challenged intranasally on day 35 with a high dose of the highly virulent H5N1 virus strain A/Vietnam/1203/2004 and monitored for 14 days. Ferrets vaccinated with the 7.5µg dose of the A/Vietnam/1203/2004 vaccine demonstrated a high rate of seroconversion. The A/Vietnam/1203/2004 vaccine afforded protection against homologous challenge as evidenced by full survival, reduced weight loss, a less pronounced and shorter increase in temperature, a less marked reduction in lymphocyte counts and in reduction of inflammation and necrosis in brain and olfactory bulb in the vaccinated cohorts as compared to control animals. All control animals succumbed to the infection.

Pharmacokinetic properties

Not applicable.

Preclinical safety data

Non-clinical studies demonstrated minor alterations in liver enzymes and calcium levels in a repeat dose toxicity study in rats. Clinically significant alterations in liver enzymes and calcium levels have not been seen to date in human clinical studies.

Animal reproductive and developmental toxicology studies do not indicate harmful effects in regard to female fertility, embryo-foetal and pre- and post-natal toxicity.

PHARMACEUTICAL PARTICULARS

List of excipients

Trometamol
Sodium chloride
Water for injections
Polysorbate 80

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be combined or mixed with other medicinal products.

Shelf-life

36 months.

After first opening, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Store in the original package in order to protect from light.

Nature and contents of the container

5mL suspension (10 x 0.5mL doses) in a vial (type I glass) with a stopper (bromobutyl rubber).

Pack sizes of 20 vials.

Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use. Shake before use. Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

The vaccine contains 10 doses of 0.5mL.

Each dose of 0.5mL is withdrawn into a syringe for injection.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

NAME AND ADDRESS

Manufacturer

Baxter AG
Industriestrasse 67
A-1221 Vienna
Austria

Distributor

Baxter Healthcare Ltd
PO Box 14-062
Panmure
Auckland 1741

MEDICINE CLASSIFICATION

Prescription Only Medicine.

DATE OF PREPARATION

9 July 2013

This medicine has been granted provisional consent under section 23 of the Medicines Act 1981.

Based on Summary of Products Characteristics (EMA approved 17 February 2012)

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

DATA SHEET

1. VEPACEL

Pre-Pandemic Influenza Vaccine (A/H5N1) (whole virion, Vero cell derived, inactivated)

Suspension for injection

2. QUALITATIVE & QUANTITATIVE COMPOSITION

One dose of 0.5mL contains:

Influenza Viruse (whole virion, inactivated), containing antigen of *:
A/Vietnam/1203/2004 (H5N1) 7.5 micrograms**.

* propagated in Vero cells (continuous cell line of mammalian origin)
** production target value expressed in micrograms Haemagglutinin (SRD).

This is a multi-dose container, see *Pharmaceutical Particulars/Nature and Contents of Container* for the number of doses per vial.

This vaccine may contain traces of formaldehyde, benzonase, sucrose, trypsin and Vero cell protein, which are used during the manufacturing process, see *Clinical Particulars/Contraindications and Special Warnings and Precautions for Use*.

For the full list of excipients see *Pharmaceutical Particulars/List of Excipients.*

3. PHARMACEUTICAL FORM

Suspension for injection. The vaccine is a clear to opalescent suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Active immunization against H5N1 subtype of influenza A virus.

This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards as well as immunocompromised and chronically ill subjects following administration of two doses of vaccine prepared with H5N1 subtype strains, see *Pharmacological Properties/Pharmacodynamic Properties.*

VEPACEL may only be marketed or distributed in accordance with the directives contained in the current version of the New Zealand Influenza Pandemic Action Plan.

This medicine has been granted provisional consent under section 23 of the Medicines Act 1981.

4.2 Dosage and Method of Administration

Dose

Adults from the age of 18 years:
One dose of 0.5mL at an elected date. A second dose of 0.5mL should be given after an interval of at least 3 weeks.

Paediatric Population:
The safety and efficacy of VEPACEL in subjects under 18 years of age have not yet been established. No data are available for VEPACEL in this age group.

Method of administration

Immunization should be carried out by intramuscular injection into the deltoid muscle.

4.3 Contraindications

History of hypersensitivity to the active substance, or to any of the excipients listed in *Pharmaceutical Particulars/List of Excipients*, or trace residues (formaldehyde, benzonase, sucrose, trypsin, Vero cell protein). If vaccination is considered necessary, facilities for resuscitation should be immediately available in case of need. See *Clinical Particulars/Special Warnings and Precautions for Use*.

4.4 Special Warnings and Precautions for Use

This vaccine may contain traces of formaldehyde, benzonase, sucrose, trypsin and Vero cell protein, which are used during the manufacturing process. Therefore, hypersensitivity reactions may occur.

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

Hypersensitivity reactions, including anaphylaxis, have been reported following use of a similar whole virion, Vero cell derived H1N1 influenza vaccine administered during a pandemic period. Such reactions have occurred both in patients with a history of multiple allergies and in patients with no known allergy.

Immunisation shall be postponed in patients with severe febrile illness or acute infection.

VEPACEL must not be administered intravascularly.

There are no data with VEPACEL using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleeding.

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

A protective response may not be induced in all individuals receiving the vaccine, *see Pharmacological Properties/Pharmacodynamic Properties*.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

There are no data on co-administration of VEPACEL with other vaccines. However, if co-administration with another vaccine is indicated, immunization should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

Immunoglobulin is not to be given with VEPACEL unless it is necessary during a medical emergency to provide immediate protection. If necessary, VEPACEL may be given at the same time as normal or specific immunoglobulin into separate limbs.

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

Following seasonal influenza vaccination, false positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus, and especially, HTLV-1. In such cases, the western blot method is negative. These transitory false-positive results may be due to IgM production in response to the vaccine.

4.6 Fertility, pregnancy and lactation

The safety of VEPACEL in pregnancy and lactation has not been assessed in clinical trials.

Animal studies with H5N1 strain vaccines (A/Vietnam/1203/2004 and A/Indonesia/05/2005) do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

Health care providers should carefully consider the potential risks and benefits for each specific patient before prescribing VEPACEL.

The use of VEPACEL during pregnancy and lactation may be considered in a prepandemic situation, taking into account official recommendations.

4.7 Effects on Ability to Drive and Use Machines

VEPACEL has minor influence on the ability to drive and use machines.

4.8 Undesirable Effects

Summary of safety profile

Clinical trials were conducted with the H5N1 vaccine (*see Pharmacological Properties/ Pharmacodynamic Properties* for more information on the H5N1 vaccines) in approximately 3700 subjects (ranging in age from 18 to 60 years and above) and special risk groups of approximately 300 subjects each, consisting of immunocompromised subjects and patients with chronic disease conditions. The safety profile in immunocompromised subjects and patients with chronic disease conditions. The adverse reactions observed are shown in the table below.

The safety profile in immunocompromised subjects and patients with chronic disease conditions is similar to the safety profile in healthy subjects.

Summary of adverse reactions

Adverse reactions are listed according to the following frequency:

Very Common (≥ 1/10)
Common (≥ 1/100 - < 1/10)
Uncommon (≥ 1/1,000 - < 1/100)
Rare (≥ 1/10,000 - < 1/1,000)
Very Rare (< 1/10,000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
INFECTIONS AND INFESTATIONS	Nasopharyngitis	Common
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy	Uncommon
PSYCHIATRIC DISORDERS	Insomnia	Uncommon
NERVOUS SYSTEM DISORDERS	Headache	Very Common
	Dizziness	Uncommon
	Somnolence	Uncommon
	Sensory abnormalities (paraesthesia, dysesthesia, oral dysesthesia, hypoesthesia, dysgeusia, and burning sensation)	Common
EYE DISORDERS	Conjunctivitis	Uncommon
	Eye irritation	Uncommon
EAR AND LABYRINTH DISORDERS	Vertigo	Common
	Ear pain	Uncommon
	Sudden hearing loss	Rare
VASCULAR DISORDERS	Hypotension	Uncommon
	Syncope	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Oropharyngeal pain	Common
	Cough	Common
	Dyspnoea	Uncommon
	Nasal congestion	Uncommon
	Rhinorrhoea	Uncommon
	Dry throat	Uncommon
GASTROINTESTINAL DISORDERS	Diarrhoea	Common
	Vomiting	Uncommon
	Nausea	Uncommon
	Abdominal pain	Uncommon
	Dyspepsia	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis	Common
	Pruritis	Common
	Rash	Uncommon
	Urticaria	Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia	Common
	Myalgia	Common

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue	Very common
	Pyrexia	Common
	Chills	Common
	Malaise	Common
	Influenza like illness	Uncommon
	Chest discomfort	Uncommon
	Injection site reactions • Injection site pain • Injection site induration • Injection site erythema • Injection site swelling • Injection site haemorrhage • Injection site irritation • Injection site pruritus • Injection site movement impairment	 Very Common Common Common Common Common Uncommon Uncommon Uncommon

Post-marketing surveillance

There are no post-marketing surveillance data available for VEPACEL.

Celvapan (H1N1)

From post-marketing surveillance with a whole virion, Vero cell derived, H1N1 vaccine, the following adverse reactions have been reported (the frequency of these adverse reactions is not known as it cannot be estimated from the available data):

Immune system disorders: anaphylactic reaction, hypersensitivity
Nervous system disorders: convulsion
Skin and subcutaneous tissue disorders: angioedema
Musculoskeletal and connective tissue disorders: pain in extremity.

Trivalent seasonal influenza vaccines

The following serious adverse reactions have been reported from post-marketing surveillance with egg-derived interpandemic trivalent vaccines:

Uncommon: Generalized skin reactions

Rare: Neuralgia, Transient thrombocytopenia. Allergic reactions, in rare cases leading to shock, have been reported.

Very rare: Vasculitis with transient renal involvement. Neurological disorders, such as encephalomyelitis, neuritis, and Guillain Barré syndrome.

4.9 Overdose

No case of overdose has been reported for VEPACEL.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This section describes the clinical experience with the H5N1 vaccine.

Pandemic and Pre-Pandemic 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 H5N1 vaccines will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with H5N1 vaccines are relevant for the pandemic and pre-pandemic vaccines.

Immune response against (A/Vietnam/1203/2004) (H5N1)

The immunogenicity of the A/Vietnam/1203/2004 strain vaccine has been evaluated in three clinical studies in adults aged 18 – 59 years (N = 961) and in two clinical studies in subjects aged 60 years and older (N = 391) following a 0, 21 day schedule. In addition, the immunogenicity has also been evaluated in a Phase 3 study in specified risk groups of immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123) following a 0, 21 day schedule.

Immunogenicity in adults aged 18 – 59 years (N = 961) and in subjects aged 60 years and older (N = 391)

After primary vaccination the rate of subjects with neutralizing antibody titres > 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 – 59 years and in elderly subjects aged 60 years and above were as follows:

	18 – 59 years 21 Days after		60 years and above 21 Days after	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	44.4%	69.7%	51.9%	69.2%
Seroconversion rate**	32.7%	56.0%	13.3%	23.9%
Seroconversion factor***	3.0	4.5	2.0	2.6

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Immunogenicity in immunocompromised subjects (N = 122) and patients with chronic disease conditions (N = 123)

After vaccination the rate of subjects with neutralizing antibody titres ≥ 20, seroconversion rate and seroconversion factor as measured by MN assay in immunocompromised subjects and patients with chronic conditions were as follows:

	Immunocompromised subjects 21 Days After		Patients with chronic disease conditions 21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralisation rate*	24.8%	41.5%	44.3%	64.2%
Seroconversion rate**	9.1%	32.2%	17.2%	35.0%
Seroconversion factor***	1.6	2.5	2.3	3.0

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Cross-reactive immune response against related H5N1 strains

In a clinical study in adults aged 18 – 59 years (N = 265) and in elderly aged 60 years and above (N = 270) after vaccination with the A/Vietnam/1203/2004 strain vaccine, the rate of subjects with cross-neutralising antibodies as measured by MN (titre ≥ 20) was as follows:

	18 – 59 years	60 years and above
	Strain A/Indonesia/05/2005	
	21 Days after 2nd Dose	21 Days after 2nd Dose
Seroneutralisation rate*	35.1%	54.8%

* MN titre ≥ 20

Heterologous booster vaccinations

A heterologous booster vaccination with a 7.5µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered in a time frame of 12 – 24 months after priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in three clinical studies in adults aged 18 – 59 years and in elderly aged 60 years and above. A 12 – 24 months heterologous booster has also been administered in a Phase 3 study in immunocompromised subjects and patients with chronic disease conditions.

Seroneutralisation rates (MN titre ≥ 20) at 21 days after a 12 – 24 months booster vaccination with the 7.5mcg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

Seroneutralisation rate*	**18 – 59 years**		**60 years and above**	
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
12 – 24 months booster	89.8%	86.9%	82.9%	75.3%

* MN titre ≥ 20

Seroneutralisation rate*	**Immunocompromised subjects**		**Patients with chronic disease conditions**	
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
12 – 24 months booster	71.6%	65.7%	77.5%	70.8%

* MN titre ≥ 20

A booster with a 7.5µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine administered 12 months after a single dose priming vaccination with the A/Vietnam/ 1203/2004 strain vaccine was also evaluated in adults aged 18 – 59 years.

Seroneutralization rates (MN titer ≥ 20) at 21 days after a 12 months booster vaccination with the 7.5µg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

Seroneutralisation rate*	**18 – 59 years**	**60 years and above**
Tested against	A/Vietnam	A/Indonesia
12 months booster	85.9%	92.9%

* MN titre ≥ 20

Paediatric population

No data are available on VEPACEL for subjects under 18 years old.

The European Medicines Agency has deferred the obligation to submit the results of one study with *Vero Cell-Derived Whole Virus H5N1 Influenza Vaccine* in subjects of the paediatric population aged 6 months – 17 years in *"active immunization against H5N1 subtype of influenza A virus"*, see *Clinical Particulars/Posology and method of administration* for information on paediatric use.

Information from non-clinical studies

The protective efficacy of VEPACEL against morbidity and mortality induced by the infection with lethal doses of highly pathogenic avian influenza H5N1 virus was assessed non-clinically in a ferret challenge model.

Sixteen ferrets were divided into two cohorts and were vaccinated on days 0 and 21 with 7.5µg of the A/Vietnam/1203/2004 vaccine or were sham vaccinated. All ferrets were challenged intranasally on day 35 with a high dose of the highly virulent H5N1 virus strain A/Vietnam/1203/2004 and monitored for 14 days. Ferrets vaccinated with the 7.5µg dose of the A/Vietnam/1203/2004 vaccine demonstrated a high rate of seroconversion. The A/Vietnam/1203/2004 vaccine afforded protection against homologous challenge as evidenced by full survival, reduced weight loss, a less pronounced and shorter increase in temperature, a less marked reduction in lymphocyte counts and in reduction of inflammation and necrosis in brain and olfactory bulb in the vaccinated cohorts as compared to control animals. All control animals succumbed to the infection.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical studies demonstrated minor alterations in liver enzymes and calcium levels in a repeat dose toxicity study in rats. Clinically significant alterations in liver enzymes and calcium levels have not been seen to date in human clinical studies.

Animal reproductive and developmental toxicology studies do not indicate harmful effects in regard to female fertility, embryo-foetal and pre- and post-natal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Sodium chloride
Water for injections
Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be combined or mixed with other medicinal products.

6.3 Shelf-life

36 months.

After first opening, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Store in the original package in order to protect from light.

6.5 Nature and contents of the container

5mL suspension (10 x 0.5mL doses) in a vial (type I glass) with a stopper (bromobutyl rubber).

Pack sizes of 20 vials.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use. Shake before use. Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

The vaccine contains 10 doses of 0.5mL.

Each dose of 0.5mL is withdrawn into a syringe for injection.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE CLASSIFICATION

Prescription Only Medicine.

8. NAME AND ADDRESS

Manufacturer

Baxter AG
Industriestrasse 67 A-
1221 Vienna Austria

Distributor

Pharmacy Retailing (NZ) Limited
t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

9. DATE OF FIRST APPROVAL

Provisional Consent Granted 25 July 2013

10. DATE OF PREPARATION

01 May 2017

Summary of changes table

Section	Change
All	Format change to new data sheet format

This medicine has been granted provisional consent under section 23 of the Medicines Act 1981.

Based on Summary of Products Characteristics (EMA approved 17 February 2012)
Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.
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