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 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.

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
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58 Richard Pearse Drive
Airport Oaks
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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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