

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 ($\geq 38^{\circ}\text{C}$) 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 ($\geq 38^{\circ}\text{C}$) 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 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 Percentage¹
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: <ul style="list-style-type: none"> • 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 Percentage¹
	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 ($\geq 1/10$); Common ($\geq 1/100 - < 1/10$), Uncommon ($\geq 1/1,000 - < 1/100$), Rare ($\geq 1/10,000 - < 1/1,000$), 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	
	1 st Dose	2 nd Dose	1 st Dose	2 nd 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 \geq 25mm²

** either SRH area \geq 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 \geq 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	
	1 st Dose	2 nd Dose	1 st Dose	2 nd 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 \geq 20

** \geq 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		60 years and above	
	21 Days After		21 Days After	
	1 st Dose	2 nd Dose	1 st Dose	2 nd 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 $\geq 25\text{mm}^2$

** either SRH area $\geq 25\text{mm}^2$ if baseline sample negative or 50% increase in SRH area if baseline sample $> 4\text{mm}^2$

*** 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		Patients with chronic disease conditions	
	21 Days After		21 Days After	
	1 st Dose	2 nd Dose	1 st Dose	2 nd 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 $\geq 25\text{mm}^2$

** either SRH area $\geq 25\text{mm}^2$ if baseline sample negative or 50% increase in SRH area if baseline sample $> 4\text{mm}^2$

*** 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		60 years and above	
	21 Days After			
	1 st Dose	2 nd Dose	1 st Dose	2 nd 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		Patients with chronic disease conditions	
	21 Days After			
	1 st Dose	2 nd Dose	1 st Dose	2 nd 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		60 years and above	
	Day 42 ^a	Day 180	Day 42 ^a	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 $\geq 25\text{mm}^2$) 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 7.5 μg 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 7.5 μg 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 $\geq 25\text{mm}^2$

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 7.5 μg 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 7.5 μg 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***

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MEDICINE CLASSIFICATION

Prescription Only Medicine.

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

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