ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER
Suspension for injection
Pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza vaccine (whole virion, inactivated) containing antigen * of:
A/Vietnam/1203/2004 (H5N1) 7.5 micrograms**per 0.5 ml dose

* produced in Vero cells
** haemagglutinin

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

The vaccine is available in a multidose container (see section 6.5 for the number of doses per vial).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Adults and children from 6 months onwards:
One dose of 0.5 ml at an elected date.

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

Method of administration
Immunization should be carried out by intramuscular injection into the deltoid muscle or anterolateral thigh, depending on the muscle mass.

For further information, see section 5.1.

4.3 Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to the active substance, to any of the excipients listed in section 6.1 or to 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 section 4.4.

4.4 Special warnings and precautions for use

- 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 occurred both in patients with a history of multiple allergies and in patients with no known allergy.

- 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 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 vaccinees (see section 5.1).

4.5 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. 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 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.

4.6 Fertility, pregnancy and lactation

The safety of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in pregnancy and lactation has not been assessed in clinical trials. Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or foetal or neonatal toxicity.

Animal reproductive and developmental toxicity 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 female fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).

The use of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations. PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may be used in lactating women.

Health care providers should carefully consider the potential risks and benefits for each specific patient before administering PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

4.7 Effects on ability to drive and use machines

Some undesirable effects mentioned under section 4.8 such as dizziness and vertigo may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

Adults, older people and special risk groups

Clinical trials were conducted with this H5N1 vaccine (see section 5.1 for more information on the H5N1 vaccines) in approximately 3500 subjects (ranging in age groups 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 older subjects.

Infants, children, and adolescents

Children and adolescents aged 3 to 17 years:
In a clinical trial 300 adolescents aged 9 to 17 years and 153 children aged 3 to 8 years were administered the H5N1 vaccine. The incidence and nature of symptoms after the first and second vaccination were similar to those observed in the healthy adults and older subjects.

Infants and children aged 6 to 35 months:
In a clinical trial the H5N1 vaccine was administered to 36 infants and children aged 6 to 35 months.

Adverse reactions are listed according to the following frequency below.

Summary of adverse reactions

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)

Adults and older people:

Adverse Reactions (Adults and Older People)		
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 Dizziness Somnolence Sensory disturbance (paresthesia, dysesthesia, oral dysesthesia, hypoesthesia, dysgeusia, and burning sensation) Syncope	Very common Uncommon Uncommon Common Uncommon
EYE DISORDERS	Conjunctivitis Eye irritation	Uncommon Uncommon
EAR AND LABYRINTH DISORDERS	Vertigo Ear pain Sudden hearing loss	Common Uncommon Uncommon
VASCULAR DISORDERS	Hypotension	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Oropharyngeal pain Cough Dyspnea Nasal congestion Rhinorrhea Dry throat	Common Common Uncommon Uncommon Uncommon Uncommon
GASTROINTESTINAL DISORDERS	Diarrhea Vomiting Nausea Abdominal pain Dyspepsia	Common Uncommon Uncommon Uncommon Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis Pruritis Rash Urticaria	Common Common Uncommon Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia Myalgia	Common Common
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue Pyrexia Chills Malaise Influenza-like illness Chest discomfort Injection Site Reactions • Injection site pain • Injection site induration • Injection site eyrthema • Injection site swelling • Injection site hemorrhage • Injection site irritation • Injection site pruritus • Injection site movement impairment	Very Common Common Common Common Uncommon Uncommon Very Common Common Common Common Common Uncommon Uncommon Uncommon

Infants, children and adolescents:

Adverse Reactions (Infants, Children and Adolescents)				
System Organ Class (SOC)	Preferred MedDRA Term	Frequency		
		6 – 35 months	3 – 8 years	9 – 17 years
INFECTIONS AND INFESTATIONS	Nasopharyngitis	Common	Common	Common
METABOLISM AND NUTRITION DISORDERS	Decreased appetite	Common	Uncommon	Uncommon
PSYCHIATRIC DISORDERS	Insomnia Sleep disorder	- Common	- -	Uncommon -
NERVOUS SYSTEM DISORDERS	Dizziness Headache Crying Somnolence Hypoaesthesia	- - Common Very Common -	- Common - - -	Uncommon Very Common - - Uncommon
EYE DISORDERS	Eye irritation	-	Uncommon	-
EAR AND LABYRINTH DISORDERS	Vertigo	-	-	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough Oropharyngeal pain Rhinorrhoea	- - -	Uncommon Common Uncommon	Uncommon Common Uncommon
GASTROINTESTINAL DISORDERS	Abdominal pain Nausea Vomiting Diarrhoea	- Common Common Common	- Common Common Uncommon	Common Common Common Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis Pruritus	Common -	Uncommon -	Common Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia Myalgia Pain in extremity	- - -	Common Common -	Common Common Uncommon
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Injection site pain Injection site induration Injection site erythema Injection site swelling Injection site hemorrhage Injection site pruritus Axillary pain Fatigue Pyrexia Chills Irritability Malaise Feeling Cold	Very common Common Common Common Common - - - Very Common - Very Common - -	Very common Common Common Common Common Uncommon Uncommon Common Common - - Common Uncommon	Very common Common Common Common Uncommon Uncommon Uncommon Common Uncommon Common - Common Uncommon

Post-marketing surveillance
For PANDEMIC INFLUENZA VACCINE H5N1 BAXTER post-marketing surveillance data are not yet available.

Class effects:
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: generalised skin reactions

Rare: neuralgia, transient thrombocytopenia

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been authorised under 'exceptional circumstances'. This means that for scientific reasons, it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMA) will review any new information which may become available every year and this SmPC will be updated as necessary.

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.

Adults, older people and special risk groups

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

The immunogenicity of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (strain A/Vietnam/1203/2004) has been evaluated in three clinical studies in adults aged 18 – 59 years (N=961) and in older 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 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 older 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 ≥ 25 mm²

** either SRH area ≥ 25 mm² 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 neutralising antibody titres ≥ 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in older 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*	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 in patients with chronic disease conditions (N=123)

After vaccination the rate of subjects with neutralising 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:

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

Antibody persistence

Antibody persistence after vaccination with the 7.5 µg non-adjuvanted formulation of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (strain A/Vietnam/1203/2004) has been evaluated in a clinical study in adults aged 18 – 59 years and subjects aged 60 years and above at 6 months, 12 - 15 months and 24 months after the start of the primary vaccination series. The results indicate an overall decline in antibody levels over time.

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%
Month 12-15	20.7%	34.2%	18.9%	36.2%
Month 24	22.4%	18.4%	12.3%	22.8%

* SRH area ≥ 25 mm²

** MN titre ≥ 20

Cross-reactive immune response against related H5N1 strains

In a phase 3 study in adults (N=270) and older subjects (N=272) 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

Heterologous booster vaccinations

A booster vaccination with a 7.5 µg heterologous A/Indonesia/05/2005 vaccine strain has been administered in a time window 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 and in older people aged 60 years and above. A 12 to 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 to 24 months booster vaccination with the 7.5 µg 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

Infants, children, and adolescents

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

The immunogenicity of the A/Vietnam/1203/2004 strain vaccine has been evaluated in a clinical trial in children and adolescents aged 9 to 17 years (N=288), in children aged 3 to 8 years (N=146) and in infants and children aged 6 to 35 months (N=33) following a 0, 21 day schedule.

After vaccination, the seroprotection rate, seroconversion rate, and seroconversion factor for anti-HA antibody, as measured by SRH, in, infants, children, and adolescents aged 6 months to 17 years were as follows:

SRH assay	9 – 17 years 21 Days after		3 – 8 years 21 Days after		6 – 35 months 21 Days after	
	1st Dose	2nd Dose	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroprotection rate*	63.8%	75.1%	46.1%	75.4%	13.8%	63.0%
Seroconversion rate**	48.4%	63.5%	43.3%	78.3%	13.8%	77.8%
Seroconversion factor***	3.3	4.7	2.9	5.9	1.4	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 vaccination, the rate of subjects with neutralizing antibody titers ≥ 20, seroconversion rate and seroconversion factor, as measured by MN assay, in infants, children, and adolescents aged 6 months to 17 years were as follows:

MN assay	9 – 17 years 21 Days after		3 – 8 years 21 Days after		6 – 35 months 21 Days after	
	1st Dose	2nd Dose	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralization rate*	52.6%	85.4%	17.1%	72.9%	3.0%	68.8%
Seroconversion rate**	9.1%	31.8%	16.4%	72.2%	9.1%	65.6%
Seroconversion factor***	1.6	3.1	2.1	6.3	1.4	6.8

* MN titer ≥ 20

** ≥ 4-fold increase in MN titer

*** geometric mean increase

Heterologous Booster Vaccinations

A heterologous booster vaccination with a 7.5 µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered 12 months after a priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in children and adolescents aged 9 to 17 years (N=196), children aged 3 to 8 years (N=79) and infants and children aged 6 months to 35 months (N=25).

Seroprotection rates (SRH area ≥ 25 mm^2) at 21 days after a 12 months booster vaccination with the 7.5 mcg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains, were as follows:

Seroprotection rate*	9 – 17 years		3 – 8 years		6 – 35 months	
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
12 Month Booster	81.6%	86.2%	87.5%	86.1%	96.0%	96.0%

* SRH area ≥ 25 mm^2

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

Seroneutralization rate*	9 – 17 years		3 – 8 years		6 – 35 months	
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
12 Month Booster	94.1%	93.1%	94.7%	97.2%	100.0%	100.0%

* 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, 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 control 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/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 (leukopenia) changes associated with highly pathogenic avian influenza 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 toxicity studies do not indicate direct or indirect harmful effects with respect to female fertility, pregnancy, embryonal/ foetal development parturition or post natal development. Male fertility was not investigated in the reproductive and developmental toxicity studies, however there were no findings in the repeat-dose toxicity studies to indicate any vaccine-related changes to the tissues of the male reproductive tract.

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 mixed with other medicinal products.

6.3 Shelf life

1 year

After first opening, the medicinal 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

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

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use. Shake before use.
After shaking, the vaccine is an off-white, opalescent, translucent suspension.

Prior to administration, visually inspect the suspension for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

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.

7. MARKETING AUTHORISATION HOLDER

Resilience Biomanufacturing Ireland Limited
2 Shelbourne Buildings
Crampton Avenue
Dublin 4
D04 W3V6
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/09/571/001

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 October 2009
Date of latest renewal: 14 May 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA): http://www.ema.europa.eu/

DD/MM/YYYY

1. NAME OF THE MEDICINAL PRODUCT

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER
Suspension for injection
Pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza vaccine (whole virion, inactivated) containing antigen* of:
A/Vietnam/1203/2004 (H5N1) 7.5 micrograms**per 0.5 ml dose

* produced in Vero cells
** haemagglutinin

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

The vaccine is available in a single dose pre-filled syringe.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Adults and children from 6 months onwards:
One dose of 0.5 ml at an elected date.

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

Method of administration
Immunization should be carried out by intramuscular injection into the deltoid muscle or anterolateral thigh, depending on the muscle mass.

For further information, see section 5.1.

4.3 Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to the active substance, to any of the excipients listed in section 6.1 or to 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 section 4.4.

4.4 Special warnings and precautions for use

- 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 occurred both in patients with a history of multiple allergies and in patients with no known allergy.

- 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 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 vaccinees (see section 5.1).

4.5 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. 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 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.

4.6 Fertility, pregnancy and lactation

The safety of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER in pregnancy and lactation has not been assessed in clinical trials. Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or foetal or neonatal toxicity.

Animal reproductive and developmental toxicity 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 female fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).

The use of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations. PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may be used in lactating women.

Health care providers should carefully consider the potential risks and benefits for each specific patient before administering PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

4.7 Effects on ability to drive and use machines

Some undesirable effects mentioned under section 4.8 such as dizziness and vertigo may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

Adults, older people and special risk groups

Clinical trials were conducted with this H5N1 vaccine (see section 5.1 for more information on the H5N1 vaccines) in approximately 3500 subjects (ranging in age groups 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 older people subjects.

Infants, children, and adolescents

Children and adolescents aged 3 to 17 years:
In a clinical trial 300 adolescents aged 9 to 17 years and 153 children aged 3 to 8 years were administered the H5N1 vaccine. The incidence and nature of symptoms after the first and second vaccination were similar to those observed in the healthy adults and older subjects.

Infants and children aged 6 to 35 months:
In a clinical trial the H5N1 vaccine was administered to 36 infants and children aged 6 to 35 months.

Adverse reactions are listed according to the following frequency below.

Summary of adverse reactions

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)

Adults and older people:

Adverse Reactions (Adults and Older People)		
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 Dizziness Somnolence Sensory disturbance (paresthesia, dysesthesia, oral dysesthesia, hypoesthesia, dysgeusia, and burning sensation) Syncope	Very common Uncommon Uncommon Common Uncommon
EYE DISORDERS	Conjunctivitis Eye irritation	Uncommon Uncommon
EAR AND LABYRINTH DISORDERS	Vertigo Ear pain Sudden hearing loss	Common Uncommon Uncommon
VASCULAR DISORDERS	Hypotension	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Oropharyngeal pain Cough Dyspnea Nasal congestion Rhinorrhea Dry throat	Common Common Uncommon Uncommon Uncommon Uncommon
GASTROINTESTINAL DISORDERS	Diarrhea Vomiting Nausea Abdominal pain Dyspepsia	Common Uncommon Uncommon Uncommon Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis Pruritis Rash Urticaria	Common Common Uncommon Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia Myalgia	Common Common
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue Pyrexia Chills Malaise Influenza-like illness Chest discomfort Injection Site Reactions • Injection site pain • Injection site induration • Injection site eyrthema • Injection site swelling • Injection site hemorrhage • Injection site irritation • Injection site pruritus • Injection site movement impairment	Very Common Common Common Common Uncommon Uncommon Very Common Common Common Common Common Uncommon Uncommon Uncommon

Infants, children and adolescents:

Adverse Reactions (Infants, Children and Adolescents)				
System Organ Class (SOC)	Preferred MedDRA Term	Frequency		
		6 – 35 months	3 – 8 years	9 – 17 years
INFECTIONS AND INFESTATIONS	Nasopharyngitis	Common	Common	Common
METABOLISM AND NUTRITION DISORDERS	Decreased appetite	Common	Uncommon	Uncommon
PSYCHIATRIC DISORDERS	Insomnia Sleep disorder	- Common	- -	Uncommon -
NERVOUS SYSTEM DISORDERS	Dizziness Headache Crying Somnolence Hypoaesthesia	- - Common Very Common -	- Common - - -	Uncommon Very Common - - Uncommon
EYE DISORDERs	Eye irritation	-	Uncommon	-
EAR AND LABYRINTH DISORDERS	Vertigo	-	-	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough Oropharyngeal pain Rhinorrhoea	- - -	Uncommon Common Uncommon	Uncommon Common Uncommon
GASTROINTESTINAL DISORDERS	Abdominal pain Nausea Vomiting Diarrhoea	- Common Common Common	- Common Common Uncommon	Common Common Common Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis Pruritus	Common -	Uncommon -	Common Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia Myalgia Pain in extremity	- - -	Common Common -	Common Common Uncommon
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Injection site pain Injection site induration Injection site erythema Injection site swelling Injection site hemorrhage Injection site pruritus Axillary pain Fatigue Pyrexia Chills Irritability Malaise Feeling Cold	Very common Common Common Common Common - - - Very Common - Very Common - -	Very common Common Common Common Common Uncommon Uncommon Common Common - - Common Uncommon	Very common Common Common Common Uncommon Uncommon Uncommon Common Uncommon Common - Common Uncommon

Post-marketing surveillance

For PANDEMIC INFLUENZA VACCINE H5N1 BAXTER post-marketing surveillance data are not yet available.

Class effects:

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: generalised skin reactions

Rare: neuralgia, transient thrombocytopenia

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been authorised under 'exceptional circumstances'. This means that for scientific reasons, it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMA) will review any new information which may become available every year and this SmPC will be updated as necessary.

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.

Adults, older people and special risk groups

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

The immunogenicity of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (strain A/Vietnam/1203/2004) has been evaluated in three clinical studies in adults aged 18 – 59 years (N=961) and in older 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 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 older 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 ≥ 25 mm²
** either SRH area ≥ 25 mm² 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 neutralising antibody titres ≥ 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in older 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*	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 in patients with chronic disease conditions (N=123)

After vaccination the rate of subjects with neutralising 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:

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

Antibody persistence

Antibody persistence after vaccination with the 7.5 µg non-adjuvanted formulation of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (strain A/Vietnam/1203/2004) has been evaluated in a clinical study in adults aged 18 – 59 years and subjects aged 60 years and above at 6 months, 12 - 15 months and 24 months after the start of the primary vaccination series. The results indicate an overall decline in antibody levels over time.

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%
Month 12-15	20.7%	34.2%	18.9%	36.2%
Month 24	22.4%	18.4%	12.3%	22.8%

* SRH area ≥ 25 mm²

** MN titre ≥ 20

Cross-reactive immune response against related H5N1 strains

In a phase 3 study in adults (N=270) and older subjects (N=272) 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

Heterologous booster vaccinations

A booster vaccination with a 7.5 µg heterologous A/Indonesia/05/2005 vaccine strain has been administered in a time window 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 and in older aged 60 years and above. A 12 to 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 to 24 months booster vaccination with the 7.5 µg 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

Infants, children, and adolescents

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

The immunogenicity of the A/Vietnam/1203/2004 strain vaccine has been evaluated in a clinical trial in children and adolescents aged 9 to 17 years (N=288), in children aged 3 to 8 years (N=146) and in infants and children aged 6 to 35 months (N=33) following a 0, 21 day schedule.

After vaccination, the seroprotection rate, seroconversion rate, and seroconversion factor for anti-HA antibody, as measured by SRH, in, infants, children, and adolescents aged 6 months to 17 years were as follows:

SRH assay	9 – 17 years 21 Days after		3 – 8 years 21 Days after		6 – 35 months 21 Days after	
	1st Dose	2nd Dose	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroprotection rate*	63.8%	75.1%	46.1%	75.4%	13.8%	63.0%
Seroconversion rate**	48.4%	63.5%	43.3%	78.3%	13.8%	77.8%
Seroconversion factor***	3.3	4.7	2.9	5.9	1.4	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 vaccination, the rate of subjects with neutralizing antibody titers ≥ 20, seroconversion rate and seroconversion factor, as measured by MN assay, in infants, children, and adolescents aged 6 months to 17 years were as follows:

MN assay	9 – 17 years 21 Days after		3 – 8 years 21 Days after		6 – 35 months 21 Days after	
	1st Dose	2nd Dose	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralization rate*	52.6%	85.4%	17.1%	72.9%	3.0%	68.8%
Seroconversion rate**	9.1%	31.8%	16.4%	72.2%	9.1%	65.6%
Seroconversion factor***	1.6	3.1	2.1	6.3	1.4	6.8

* MN titer ≥ 20

** ≥ 4-fold increase in MN titer

*** geometric mean increase

Heterologous Booster Vaccinations

A heterologous booster vaccination with a 7.5 µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered 12 months after a priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in children and adolescents aged 9 to 17 years (N=196), children aged 3 to 8 years (N=79) and infants and children aged 6 months to 35 months (N=25).

Seroprotection rates (SRH area ≥ 25 mm^2) at 21 days after a 12 months booster vaccination with the 7.5 µg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains, were as follows:

Seroprotection rate*	9 – 17 years		3 – 8 years		6 – 35 months	
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
12 Month Booster	81.6%	86.2%	87.5%	86.1%	96.0%	96.0%

* SRH area ≥ 25 mm^2

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

Seroneutralization rate*	9 – 17 years		3 – 8 years		6 – 35 months	
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
12 Month Booster	94.1%	93.1%	94.7%	97.2%	100.0%	100.0%

* 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, 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 control 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/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 (leukopenia) changes associated with highly pathogenic avian influenza 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 toxicity studies do not indicate direct or indirect harmful effects with respect to female fertility, pregnancy, embryonal/ foetal development parturition or post natal development. Male fertility was not investigated in the reproductive and developmental toxicity studies, however there were no findings in the repeat-dose toxicity studies to indicate any vaccine-related changes to the tissues of the male reproductive tract.

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 mixed with other medicinal products.

6.3 Shelf life

1 year

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

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.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use. Shake before use.
After shaking, the vaccine is an off-white, opalescent, translucent suspension.

Prior to administration, visually inspect the suspension for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

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.

7. MARKETING AUTHORISATION HOLDER

Resilience Biomanufacturing Ireland Limited
2 Shelbourne Buildings
Crampton Avenue
Dublin 4
D04 W3V6
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/09/571/002

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 October 2009
Date of latest renewal: 14 May 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA): http://www.ema.europa.eu/

DD/MM/YYYY

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Baxter BioScience s.r.o.
Jevany Bohumil 138
CZ-281 63 Kostelec nad Cernymi lesy
Czech Republic

Baxter AG
Uferstrasse 15
A-2304 Orth/Donau
Austria

Name and address of the manufacturer responsible for batch release

Baxter AG
Uferstrasse 15
A-2304 Orth/Donau
Austria

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER can only be marketed when there is an official WHO/EU declaration of an influenza pandemic, on the condition that the Marketing Authorisation Holder for PANDEMIC INFLUENZA VACCINE H5N1 BAXTER takes due account of the officially declared pandemic strain.

- **Official batch release**

In accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Outside of the pandemic period, the normal PSUR periodicity and format will be maintained, with a specific review of AESI. This should include data from ongoing studies, or actual use if applicable, of the ‘mock-up’ strains.

During a pandemic situation, the resources must be concentrated on a timely and effective monitoring of the safety profile of the influenza vaccines used during the pandemic. Moreover, a 6-monthly cycle may be too long to allow assessment of the safety of a vaccine for which high levels of exposure are expected within a short period of time. Therefore, 6-monthly or annual PSURs falling within the pandemic period will be replaced by monthly “simplified PSURs” (S-PSUR) accompanied by a summary of vaccine distribution.

Frequency of submission

- The clock should start from the first Monday after shipment of the first batch of vaccine.
- First data-lock point is 30 days later.
- S-PSUR submission to the Rapporteur and CHMP members on Day 45.
- Rapporteur's assessment report is circulated to CHMP members on Day 50.
- CHMP report is circulated to the vaccine manufacturer on Day 55.
- Reporting to be monthly for the first 6 months.
- Periodicity should be reviewed by the MAH and the (Co-)Rapporteur at 6 monthly intervals.

When it has been agreed by the CHMP that the S-PSUR is no longer necessary, a full PSUR covering the period since the data lock point of the last routine PSUR will be submitted within a time frame to be agreed with the Rapporteur.

Format of the simplified PSUR

Only spontaneously reported data should be included in the S-PSUR. The report should include the following Tables of aggregate data (using the pre-defined templates attached in Annex 2).

1. An overview for all spontaneous cases per country, stratified according to type of report (medically confirmed or non-medically confirmed) and seriousness, for the period covered by the report and cumulatively.

2. An overview for all spontaneous adverse reactions by SOC, High Level Term (HLT) and Preferred Term (PT), stratified according to type of report (medically confirmed or non-medically confirmed) and including the number of fatal reports, for the period covered by the report and cumulatively.

3. Adverse Events of Special Interest stratified according to type of report (medically confirmed or non-medically confirmed). AESIs will be defined as follows:

- Neuritis:	PT "Neuritis"
- Convulsion:	narrow SMQ "Convulsions"
- Anaphylaxis:	narrow SMQ "Anaphylactic reaction" and narrow SMQ "Angioedema"
- Encephalitis:	narrow SMQ "Non-infectious encephalitis"
- Vasculitis:	narrow SMQ "Vasculitis"
- Guillain-Barré syndrome:	narrow SMQ "Guillain-Barré syndrome"
- Demyelination:	narrow SMQ "Demyelination" (as GBS is also included in this SMQ, there will be an overlap in the number of cases for these two categories).
- Bell's palsy:	PT "Bell's palsy"
- Vaccination failure:	PT "Vaccination failure".

4. Serious unlisted adverse reactions (SOC, HLT, PTs) stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

5. All spontaneous adverse reactions by age group, per SOC, HLT and PT, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively. The following age groups will be used: < 2 years, 2-8 years, ≥ 9 years.

6. All spontaneous adverse reactions (SOC, HLT, PT) occurring in pregnant women, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

The following principles should be followed when compiling the data:

- Except for Table 1, all tables will be based on number of reactions (presented on PT level, sorted by System Organ Class [SOC] and High Level Term [HLT]) and not number of cases.
- All tables will be based on generic and not product-specific data[1]. Product-specific data can be evaluated during signal work-up.
- "Cumulatively" means since the use of the vaccine; events not reported during the period of interest should not be presented in the tables.
- All non-medically confirmed events are those that have been entered into the database by the data-lock point. Those which have not yet been entered should be reported in the following S-PSUR.
- A line listing of fatal cases will be provided in an Annex.

A short summary should be provided in which validated signals and areas of concern are highlighted, taking into account information arising from the prospective cohort study described in 4.5. In the event of multiple signals, signal work-up may be prioritised and appropriate timelines for submission of a full signal evaluation report should be provided.

Vaccine distribution report

To put the safety report into context, a summary of vaccine distribution should be included and should provide details of the number of doses of vaccine distributed in

i) EU member states for the reporting period by batch number,
ii) EU member states cumulatively and
iii) the rest of the world.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perfom the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

[1] Based on the assumption that product name will not be provided in a significant proportion of cases.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
During the pandemic, the applicant will collect clinical safety and effectiveness data of the pandemic vaccine and submit this information to the CHMP for evaluation.	Depending on and after implementation of vaccine when first pandemic will take place.
During the pandemic, the applicant will conduct a prospective cohort study as identified in the Pharmacovigilance plan.	Depending on and after implementation of vaccine when first pandemic will take place.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 10-DOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER, suspension for injection
Pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Influenza vaccine (whole virion, inactivated) containing antigen of*:

A/Vietnam/1203/2004 (H5N1) 7.5 microgram**
per 0.5 ml dose

* produced in Vero cells
** haemagglutinin

3. LIST OF EXCIPIENTS

Trometamol,
sodium chloride,
water for injections,
polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
20 multidose vials (10 doses per vial – 0.5 ml per dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use.
The vaccine should be allowed to reach room temperature before use.
Shake before use.
After first opening, the vial is to be used within a maximum of 3 hours.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not inject intravascularly.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Resilience Biomanufacturing Ireland Limited
2 Shelbourne Buildings
Crampton Avenue
Dublin 4
D04 W3V6
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/571/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER, suspension for injection
Pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Influenza vaccine (whole virion, inactivated) containing antigen*

A/Vietnam/1203/2004 (H5N1) 7.5 microgram**
per 0.5 ml dose

* produced in Vero cells
** haemagglutinin

3. LIST OF EXCIPIENTS

Trometamol,
sodium chloride,
water for injections,
polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
One single dose pre-filled syringe (containing 0.5ml suspension)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use.
The vaccine should be allowed to reach room temperature before use.
Shake before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not inject intravascularly.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Resilience Biomanufacturing Ireland Limited
2 Shelbourne Buildings
Crampton Avenue
Dublin 4
D04 W3V6
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/571/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL FOR 10-DOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER suspension for injection
Pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)
I.M.

2. METHOD OF ADMINISTRATION

Shake before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Multidose vial (10 doses of 0.5 ml per vial)

6. OTHER

After first opening, the vial is to be used within a maximum of 3 hours.

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Ireland

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL- SINGLE DOSE PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER suspension for injection
Pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)
I.M.

2. METHOD OF ADMINISTRATION

Shake before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose syringe (0.5ml)

6. OTHER

Resilience Biomanufacturing Ireland Limited
2 Shelbourne Buildings
Crampton Avenue
Dublin 4
D04 W3V6
Ireland

B. PACKAGE LEAFLET

Package leaflet: Information for the user

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER
suspension for injection
Pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

Read all of this leaflet carefully, before you are vaccinated because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PANDEMIC INFLUENZA VACCINE H5N1 BAXTER is and what it is used for

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER is a vaccine used in individuals aged 6 months adults and older. It is used to prevent influenza (flu) in an officially declared pandemic.

Pandemic flu is a type of influenza that occurs every few decades and which spreads rapidly to affect most countries and regions around the world. The symptoms (signs) of pandemic flu are similar to those of an 'ordinary' flu but are usually more severe.

The vaccine works by helping the body to produce its own protection (antibodies) against the disease.

2. What you need to know before your are vaccinated with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Do not use PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

- if you previously had a serious allergic reaction (i.e. life-threatening) to PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.
- if you are allergic to any of the ingredients or trace residues (formaldehyde, benzonase, sucrose) contained in the vaccine. The active substance and other ingredients in PANDEMIC INFLUENZA VACCINE H5N1 BAXTER are listed in section 6 at the end of the leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. However, in a pandemic situation, your doctor may recommend to give the vaccine.

Warnings and precautions:

You should tell your doctor before vaccination

- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be a problem, but your doctor should advise whether you could still be vaccinated with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER;

- if you have had any allergic reaction, to any ingredient contained in the vaccine (see section 6 at the end of the leaflet) or to formaldehyde, benzonase or sucrose. Allergic reactions, including sudden and life-threatening allergic reactions (anaphylaxis), have been reported with a similar H1N1 influenza vaccine (swine flu vaccine) given during a pandemic period. Such reactions have happened both in people who have allergies and in those who do not;
- if you have a poor immune response (for example because of immunosuppressive therapy, e.g. corticosteroid treatments or chemotherapy for cancer);
- if you are having a blood test to look for evidence of infection with certain viruses. In the first few weeks after vaccination with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently received PANDEMIC INFLUENZA VACCINE H5N1 BAXTER;
- if you have a bleeding problem or bruise easily.

The vaccine should never be given into a blood vessel.
There is no information on the use of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER under the skin.

Other medicines and PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or have recently received any other vaccine.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER should not be given at the same time as other vaccines. However, if this cannot be avoided, the other vaccine should be injected into the other limb. You should be aware that the side effects may be intensified.

If you take any medicines that reduce immunity to infections or have any other type of treatment (such as radiotherapy) that affects the immune system, PANDEMIC INFLUENZA VACCINE H5N1 BAXTER can still be given but your response to the vaccine may be poor.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER should not be given at the same time as immunoglobulins. However, if this cannot be avoided, the immunoglobulins should be injected into the other limb.

Pregnancy, breast-feeding and fertility

If your are pregnant or breast-feeding, think you may be pregnant or planning to have a baby, ask your doctor for advice if you should receive PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

Driving and using machines

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may make you feel dizzy or sick which may affect your ability to drive or use machines.

3. How to use PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Infants, children and adolescents from the age of 6 months to 17 years and adults from the age of 18 years and older:
One dose of 0.5 ml will be given. A second dose of 0.5 ml should be given after an interval of at least three weeks.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER is given as an injection into the muscle (usually in the upper arm or upper thigh, depending on the muscle mass).

The vaccine should never be given into a vein.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, PANDEMIC INFLUENZA VACCINE H5N1 BAXTER can cause side effects, although not everybody gets them.

In the clinical studies conducted in adults and older people with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER, most side effects were mild in nature and short term. The side-effects are generally similar to those related to the influenza vaccine. There were fewer side effects after the second vaccination compared with the first. The most frequently occurring side effect was injection site pain, which was usually mild.

The following side effects have been reported in clinical studies in adults and older people.

Very common (may affect more than 1 in 10 vaccinees):
- pain at the injection site
- fatigue (feeling tired)
- headache

Common (may affect up to 1 in 10 vaccinees):
- runny nose and sore throat
- vertigo (motion sickness)
- pain in mouth and throat
- cough
- diarrhoea
- increased sweating
- itching
- joint or muscle pain
- fever
- chills
- malaise (generally feeling unwell),
- hardness, redness, swelling or minor bleeding at the injection site
- abnormal, reduced sensation

Uncommon (may affect more than 1 in 100 vaccinees):
- swollen glands
- insomnia (difficulty sleeping)
- dizziness
- sleepiness
- conjunctivitis (an inflammation of the eye), eye irritation
- sudden hearing loss, ear pain
- reduced blood pressure, feeling faint (syncope)
- shortness of breath
- dry throat
- stuffy or runny nose
- feeling sick
- vomiting
- stomach pain, indigestion
- rash, hives
- irritation or itching at the injection site, bruising or stiff arm
- chest discomfort
- flu-like illness

In the clinical studies conducted in infants, children and adolescents, the incidence and nature of symptoms after the first and second vaccination were similar to those occurred in adults and older people.

The following side effects have been reported in a clinical study in infants aged 6 to 35 months.

Very common (affects more than 1 in 10 vaccinees):
- sleepiness
- fever
- irritability
- pain at the injection site

Common (affects 1 to 10 in 100 vaccinees):
- runny nose and sore throat
- decreased appetite
- sleep disorder
- crying
- vomiting
- feeling sick
- diarrhoea
- increased sweating
- hardness, redness, swelling or bruising at the injection site

The following side effects have been reported in clinical studies in children aged 3 to 8 years.

Very common (affects more than 1 user in 10):
- pain at the injection site

Common (affects 1 to 10 in 100 vaccinees):
- runny nose and sore throat
- headache
- pain in mouth and throat
- vomiting
- feeling sick
- pain in joint or muscle
- hardness, redness, swelling or bruising at the injection site
- fatigue (feeling tired)
- fever
- malaise

Uncommon (affects 1 to 10 in 1,000 vaccinees):
- decreased appetite
- eye irritation
- cough
- runny nose
- diarrhoea
- increased sweating
- pain in the armpit
- itching where the injection was given
- feeling cold

The following side effects have been reported in clinical studies in adolescents aged 9 to 17 years.

Very common (affects more than 1 in 10 vaccinees):
- headache
- pain at the injection site

Common (affects 1 to 10 in 100 vaccinees):
- runny nose and sore throat
- pain in mouth and throat
- stomach pain
- feeling sick
- vomiting
- increased sweating
- pain in joint or muscle
- hardness, redness or swelling at the injection site
- fatigue (feeling tired)
- chills
- malaise

Uncommon (affects 1 to 10 in 1,000 vaccinees):
- decreased appetite
- insomnia (difficulty sleeping)
- dizziness
- abnormal, reduced sensation
- vertigo (a spinning sensation)
- cough
- runny nose
- diarrhoea
- itching
- pain in extremity
- pain in the armpit
- bruising at the injection site
- itching where the injection was given
- fever
- feeling cold

The side effects listed below have occurred with a similar influenza vaccine (Celvapan) in adults and children during the H1N1 pandemic flu vaccination programme. The frequency cannot be estimated from the available data.

- allergic reactions, including severe reactions leading to a dangerous decrease in blood pressure which, if untreated, may lead to shock.
- fits
- pain in arms and or legs (in the majority of cases reported as pain in the vaccination arm)
- swelling of tissue just below the skin

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Keep this medicine out of the sight and reach of children.

Do not use PANDEMIC INFLUENZA VACCINE H5N1 BAXTER after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What PANDEMIC INFLUENZA VACCINE H5N1 BAXTER contains

Active substance:
Whole virion H5N1 influenza vaccine, inactivated, containing antigen of*:

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

* produced in Vero cells
** haemagglutinin

The other ingredients are: trometamol, sodium chloride, water for injections, polysorbate 80.

What PANDEMIC INFLUENZA VACCINE H5N1 BAXTER looks like and contents of the pack

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER is an off-white, opalescent, translucent liquid.
The vaccine is available as 1 pack containing 20 multidose vials (type I glass) of 5 ml suspension (10 doses).

Marketing Authorisation Holder:
Resilience Biomanufacturing Ireland Limited
2 Shelbourne Buildings
Crampton Avenue
Dublin 4
D04 W3V6
Ireland

Manufacturer:
Baxter AG
Uferstrasse 15
A-2304 Orth/Donau
Austria

This leaflet was last revised in {MM/YYYY}.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been authorised under “exceptional circumstances”. This means that for scientific reasons, it has been impossible to get complete information on this medicine. The European Agency (EMA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu/

The following information is intended for health care professionals only:

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

After shaking, the vaccine is an off-white, opalescent, translucent suspension.

Prior to administration, visually inspect the suspension for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

The vaccine should not be administered intravascularly.

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

After first opening, the vial is to be used within a maximum of 3 hours.

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

Package leaflet: Information for the user

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER
suspension for injection
Pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

Read all of this leaflet carefully, before you are vaccinated because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PANDEMIC INFLUENZA VACCINE H5N1 BAXTER is and what it is used for

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER is a vaccine used in individuals aged 6 months and older. It is used to prevent influenza (flu) in an officially declared pandemic.

Pandemic flu is a type of influenza that occurs every few decades and which spreads rapidly to affect most countries and regions around the world. The symptoms (signs) of pandemic flu are similar to those of an 'ordinary' flu but are usually more severe.

The vaccine works by helping the body to produce its own protection (antibodies) against the disease.

2. What you need to know before you are vaccinated with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Do not use PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

- if you previously had a serious allergic reaction (i.e. life-threatening) to PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.
- if you are allergic to any of the ingredients or trace residues (formaldehyde, benzonase, sucrose) contained in the vaccine. The active substance and other ingredients in PANDEMIC INFLUENZA VACCINE H5N1 BAXTER are listed in section 6 at the end of the leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. However, in a pandemic situation, your doctor may recommend to give the vaccine.

Warnings and precautions:

You should tell your doctor before vaccination

- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be a problem, but your doctor should advise whether you could still be vaccinated with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER;

- if you have had any allergic reaction, to any ingredient contained in the vaccine (see section 6 at the end of the leaflet) or to formaldehyde, benzonase or sucrose. Allergic reactions, including sudden and life-threatening allergic reactions (anaphylaxis), have been reported with a similar H1N1 influenza vaccine (swine flu vaccine) given during a pandemic period. Such reactions have happened both in people who have allergies and in those who do not;
- if you have a poor immune response (for example because of immunosuppressive therapy, e.g. corticosteroid treatments or chemotherapy for cancer);
- if you are having a blood test to look for evidence of infection with certain viruses. In the first few weeks after vaccination with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently received PANDEMIC INFLUENZA VACCINE H5N1 BAXTER;
- if you have a bleeding problem or bruise easily.

The vaccine should never be given into a blood vessel.
There is no information on the use of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER under the skin.

Other medicines and PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or have recently received any other vaccine.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER should not be given at the same time as other vaccines. However, if this cannot be avoided, the other vaccine should be injected into the other limb. You should be aware that the side effects may be intensified.

If you take any medicines that reduce immunity to infections or have any other type of treatment (such as radiotherapy) that affects the immune system, PANDEMIC INFLUENZA VACCINE H5N1 BAXTER can still be given but your response to the vaccine may be poor.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER should not be given at the same time as immunoglobulins. However, if this cannot be avoided, the immunoglobulins should be injected into the other limb.

Pregnancy, breast-feeding and fertility

If your are pregnant or breast-feeding, think you may be pregnant or planning to have a baby, ask your doctor for advice if you should receive PANDEMIC INFLUENZA VACCINE H5N1 BAXTER.

Driving and using machines

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may make you feel dizzy or sick which may affect your ability to drive or use machines.

3. How to use PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Infants, children and adolescents from the age of 6 months to 17 years and adults from the age of 18 years and older:
One dose of 0.5 ml will be given. A second dose of 0.5 ml should be given after an interval of at least three weeks.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER is given as an injection into the muscle (usually in the upper arm or upper thigh, depending on the muscle mass).

The vaccine should never be given into a vein.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, PANDEMIC INFLUENZA VACCINE H5N1 BAXTER can cause side effects, although not everybody gets them.

In the clinical studies conducted in adults and older people with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER, most side effects were mild in nature and short term. The side-effects are generally similar to those related to the influenza vaccine. There were fewer side effects after the second vaccination compared with the first. The most frequently occurring side effect was injection site pain, which was usually mild.

The following side effects have been reported in clinical studies in adults and older people.

Very common (may affect more than 1 in 10 vaccinees):
- pain at the injection site
- fatigue (feeling tired)
- headache

Common (may affect up to 1 in 10 vaccinees):
- runny nose and sore throat
- vertigo (motion sickness)
- pain in mouth and throat
- cough
- diarrhoea
- increased sweating
- itching
- joint or muscle pain
- fever
- chills
- malaise (generally feeling unwell)
- hardness, redness, swelling or minor bleeding at the injection site
- abnormal, reduced sensation

Uncommon (may affect more than 1 in 100 vaccinees):
- swollen glands
- insomnia (difficulty sleeping)
- dizziness
- sleepiness
- conjunctivitis (an inflammation of the eye), eye irritation
- sudden hearing loss, ear pain
- reduced blood pressure, feeling faint (syncope)
- shortness of breath
- dry throat
- stuffy or runny nose
- feeling sick
- vomiting
- stomach pain, indigestion
- rash, hives
- irritation or itching at the injection site, bruising or stiff arm
- chest discomfort
- flu-like illness

In the clinical studies conducted in infants, children and adolescents, the incidence and nature of symptoms after the first and second vaccination were similar to those occurred in adults and older people.

The following side effects have been reported in a clinical study in infants aged 6 to 35 months.

Very common (affects more than 1 in 10 vaccinees):
- sleepiness
- fever
- irritability
- pain at the injection site

Common (affects 1 to 10 in 100 vaccinees):
- runny nose and sore throat
- decreased appetite
- sleep disorder
- crying
- vomiting, feeling sick, diarrhoea
- increased sweating
- hardness, redness, swelling or bruising at the injection site

The following side effects have been reported in clinical studies in children aged 3 to 8 years.

Very common (affects more than 1 user in 10):
- pain at the injection site

Common (affects 1 to 10 in 100 vaccinees):
- runny nose and sore throat
- headache
- pain in mouth and throat
- vomiting
- feeling sick
- pain in joint or muscle
- hardness redness, swelling or bruising at the injection site
- fatigue (feeling tired)
- fever
- malaise,

Uncommon (affects 1 to 10 in 1,000 vaccinees):
- decreased appetite
- eye irritation
- cough
- runny nose
- diarrhoea
- increased sweating
- pain in the armpit
- itching where the injection was given
- feeling cold

The following side effects have been reported in clinical studies in adolescents aged 9 to 17 years.

Very common (affects more than 1 in 10 vaccinees):
- headache
- pain at the injection site

Common (affects 1 to 10 in 100 vaccinees):
- runny nose and sore throat
- pain in mouth and throat
- stomach pain
- feeling sick
- vomiting
- increased sweating
- pain in joint or muscle
- hardness, redness or swelling at the injection site
- fatigue (feeling tired)
- chills
- malaise

Uncommon (affects 1 to 10 in 1,000 vaccinees):
- decreased appetite
- insomnia (difficulty sleeping)
- dizziness
- abnormal, reduced sensation
- vertigo (a spinning sensation)
- cough
- runny nose
- diarrhoea
- itching
- pain in extremity
- pain in the armpit
- bruising at the injection site
- itching where the injection was given
- fever
- feeling cold

The side effects listed below have occurred with a similar influenza vaccine (Celvapan) in adults and children during the H1N1 pandemic flu vaccination programme. The frequency cannot be estimated from the available data.

- allergic reactions, including severe reactions leading to a dangerous decrease in blood pressure which, if untreated, may lead to shock.
- fits
- pain in arms and or legs (in the majority of cases reported as pain in the vaccination arm)
- swelling of tissue just below the skin

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

Keep this medicine out of the sight and reach of children.

Do not use PANDEMIC INFLUENZA VACCINE H5N1 BAXTER after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What PANDEMIC INFLUENZA VACCINE H5N1 BAXTER contains

Active substance:
Whole virion H5N1 influenza vaccine, inactivated, containing antigen of*:

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

* produced in Vero cells
** haemagglutinin

The other ingredients are: trometamol, sodium chloride, water for injections, polysorbate 80.

What PANDEMIC INFLUENZA VACCINE H5N1 BAXTER looks like and contents of the pack

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER is an off-white, opalescent, translucent liquid.
The vaccine is available or as 1 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.

Marketing Authorisation Holder:
Resilience Biomanufacturing Ireland Limited
2 Shelbourne Buildings
Crampton Avenue
Dublin 4
D04 W3V6
Ireland

Manufacturer:
Baxter AG
Uferstrasse 15
A-2304 Orth/Donau
Austria

This leaflet was last revised in {MM/YYYY}.

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been authorised under “exceptional circumstances”. This means that for scientific reasons, it has been impossible to get complete information on this medicine. The European Agency (EMA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu/

The following information is intended for health care professionals only:

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

After shaking, the vaccine is an off-white, opalescent, translucent suspension.

Prior to administration, visually inspect the suspension for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

The vaccine should not be administered intravascularly.

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

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.