ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Celvapan suspension for injection
Pandemic influenza vaccine (H1N1) (whole virion, Vero cell derived, inactivated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/California/07/2009 (H1N1)v 7.5 micrograms**
per 0.5 ml dose

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

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

This is a multidose container. See section 6.5 for the number of doses per vial.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

The vaccine is a clear to opalescent, translucent suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation (see sections 4.2 and 5.1).

Pandemic influenza vaccine should be used in accordance with Official Guidance.

4.2 Posology and method of administration

Posology

The dose recommendations take into account available data from on-going clinical studies in healthy subjects and from clinical studies in healthy subjects who received two doses of a version of Celvapan containing HA derived from A/Vietnam/1203/2004 (H5N1).

From clinical studies limited immunogenicity and safety data are available for Celvapan (H1N1) in healthy adult and elderly subjects and in children (see section 4.4, 4.8., and 5.1).

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

Children and adolescents aged 3 to 17 years
One dose of 0.5 ml at an elected date.
A second dose of vaccine should be given after an interval of at least three weeks.

Children aged 6 to 35 months
Limited data are available in infants and young children aged 6 to 35 months.- However, should vaccination be considered necessary, the experience with similarly constructed vaccines suggests that dosing in accordance with the adult dose may be appropriate.
The dosing used should take into account the extent of data and disease characteristics of the current influenza pandemic.

Children aged less than 6 months
Vaccination is not currently recommended in this age group.

For further information, see sections 4.8 and 5.1.

It is recommended that subjects who receive a first dose of Celvapan, complete the vaccination course with Celvapan (see section 4.4).

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

4.3 Contraindications

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

See section 4.4 for Special warnings and special precautions for use.

4.4 Special warnings and precautions for use

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

Hypersensitivity reactions, including anaphylaxis, have been reported following CELVAPAN vaccination (see section 4.8). Such reactions have occurred both in patients with a history of multiple allergies and in patients with no known allergy.

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

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

Celvapan should under no circumstances be administered intravascularly.

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

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

A protective response may not be elicited in all vaccinees (see section 5.1).

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

4.5 Interactions with other medicinal products and other forms of interaction

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

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

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

4.6 Pregnancy and lactation

There are currently no data available on the use of Celvapan in pregnancy. Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or fetal or neonatal toxicity.

Animal studies with Celvapan do not indicate reproductive toxicity (see section 5.3).

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

Celvapan may be used in lactating women.

4.7 Effects on ability to drive and use machines

Some undesirable effects mentioned under section 4.8 “Undesirable effects” may affect the ability to drive or use machines.

4.8 Undesirable effects

- Clinical trials with H5N1 mock-up vaccine

In clinical trials with the mock-up vaccine using an H5N1 vaccine strain (see section 5.1) in 3576 subjects (3116 between 18 and 59 years old, and 460 aged 60 and above), the following adverse reactions were assessed as at least possibly related by the investigator. Most of the reactions were mild in nature, of short duration and qualitatively similar to those induced by influenza vaccines. There were fewer reactions after the second dose of the vaccine compared with the first dose. The most frequently occurring adverse reaction was injection site pain, which was usually mild.

Adverse reactions from clinical trials with the mock-up vaccine are listed below (see section 5.1 for more information on mock-up vaccines).

Adverse reactions are listed according to the following frequency.
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)
Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Infections and infestations
Common: nasopharyngitis

Blood and the lymphatic system disorders
Uncommon: lymphadenopathy

Psychiatric disorders
Uncommon: insomnia, restlessness

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

Eye disorders
Uncommon: conjunctivitis

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

Vascular disorders
Uncommon: hypotension

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

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

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

Musculoskeletal and connective tissue disorders
Common: arthralgia, myalgia

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

- Clinical Trials with Celvapan (H1N1)

Adults and Elderly
In an ongoing clinical study the 7.5 µg dose of Celvapan H1N1 was administered to adults aged 18 to 59 years (N= 101) and elderly over 60 years of age (N=101). Safety data after the first and second vaccination suggest a similar safety profile to that reported for the influenza vaccines using a H5N1 strain, except for injection site pain, which was reported at a lower rate (common).

Children and adolescents 3 to 17 years of age
In an ongoing clinical trial 51 children and adolescents aged 9 to 17 years and 51 children aged 3 to 8 years were administered the 7.5 µg dose of Celvapan H1N1v. The incidence and nature of symptoms

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

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

- Post-marketing surveillance

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

The frequency of these adverse reactions is not known.

Immune system disorder:
Anaphylactic reaction*, Hypersensitivity*

Nervous system disorders:
Febrile convulsion

Skin and subcutaneous tissue disorders:
Angioedema

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

Musculoskeletal and connective tissue disorders:
Pain in extremity (in the majority of cases reported as pain in the injection site arm)

General disorders and administration site conditions
Influenza-like illness

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

Very common reactions reported in children above 5 years of age, adolescents and adults:
Injection site reactions, fatigue, headache, muscle pain, gastrointestinal symptoms

Very common reactions reported in children aged 6 months to 5 years:
Injection site reactions, drowsiness, irritability, loss of appetite.

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

Uncommon:
Generalised skin reactions

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

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

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This medicinal product has been authorised under "Exceptional Circumstances". The European Medicines Agency (EMA) will regularly review any new information which may become available and this SPC will be updated as necessary.
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.

Clinical studies with Celvapan (H1N1)v currently provide:
- Limited safety and immunogenicity data obtained three weeks after administration of two doses of Celvapan (H1N1) to healthy adults aged 18 years and older.
- Limited safety and immunogenicity data obtained three weeks after administration of two doses of Celvapan (H1N1) to healthy children aged 6 months to 17 years.

Clinical studies in which a version of Celvapan containing HA derived from A/Vietnam/1203/2004 (H5N1) was administered at day 0 and at day 21 provide:
- Safety and immunogenicity data in healthy adults, including the elderly

Immune response against A/California/07/2009(H1N1v)

The immunogenicity of the vaccine containing 7.5 µg non-adjuvanted HA derived from strain A/California/07/2009 (H1N1)v has been evaluated in two clinical studies in adults aged 18 years and older (N=200), and in children and adolescents aged 3 to 17 years (N=101), following a 0, 21 day schedule. Preliminary data are available for infants and young children aged 6 to 35 months (N=65).

Adults aged 18 years and older

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

SRH Assay	All subjects		Seronegative subjects at baseline ($\leq 4mm^2$)	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
18 to 59 years	N=99		N=33	
Seroprotection rate*	75.8% (66.1; 83.8)	80.8% (71.7; 88.0)	69.7% (51.3; 84.4)	78.8% (61.1; 91.0)
Seroconversion rate**	64.6% (54.4; 74.0)	70.7% (60.7; 79.4)	69.7% (51.3; 84.4)	78.8% (61.1; 91.0)
Seroconversion factor***	3.4 (2.8 ; 4.3)	4.1 (3.3 ; 5.1)	7.1 (4.5 ; 11.0)	9.5 (6.5 ; 13.8)
≥60 years	N=101		N=22	
Seroprotection rate*	76.2% (66.7; 84.1)	82.2% (73.3; 89.1)	50.0% (28.2; 71.8)	63.6% (40.7; 82.8)
Seroconversion rate**	28.7% (20.1; 38.6)	35.6% (26.4; 45.8)	50.0% (28.2; 71.8)	63.6% (40.7; 82.8)
Seroconversion factor***	1.8 (1.5 ; 2.1)	2.0 (1.7 ; 2.4)	3.9 (2.3 ; 6.7)	5.6 (3.4 ; 9.2)

* SRH area > 25 mm²

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

*** geometric mean increase

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

MN Assay	All subjects		Seronegative subjects at baseline (<1:10)	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
18 to 59 years	N=100	N=99	N=39	N=38
Seroneutralization rate*	87.0% (78.8; 92.9)	98.0% (92.9; 99.8)	74.4% (57.9; 87.0)	97.4% (86.2; 99.9)
Seroconversion rate**	80.0% (70.8; 87.3)	86.9% (78.6; 92.8)	84.6% (69.5; 94.1)	97.4% (86.2; 99.9)
Seroconversion factor***	21.3 (14.6 ; 31.2)	29.0 (20.5 ; 41.0)	28.8 (15.2 ; 54.5)	55.3 (32.0 ; 95.6)
≥60 years	N=101		N= 34	N=38
Seroneutralization rate*	70.3% (60.4; 79.0)	82.2% (73.3; 89.1)	55.9% (37.9; 72.8)	76.3% (59.8; 88.6)
Seroconversion rate**	55.4% (45.2; 65.3)	71.3% (61.4%; 79.9)	73.5% (55.6; 87.1)	94.7% (82.3; 99.4)
Seroconversion factor***	5.0 (3.8 ; 6.6)	7.6 (5.9 ; 9.9)	7.1 (4.4 ; 11.3)	15.0 (10.1 ; 22.2)

* MN titre ≥1:40

** > 4-fold increase in MN titre

*** geometric mean increase

Children and adolescents (3 – 17 years of age)

The seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody as measured by single radial haemolysis (SRH) in children and adolescents aged 3 to 17 years were as follows:

SRH Assay	All subjects		Seronegative subjects at baseline (≤4mm^2)	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
3 to 8 years	N=51		N=31	
Seroprotection rate*	51.0% (36.6; 65.2)	88.2% (76.1; 95.6)	58.1% (39.1; 75.5)	93.5% (78.6; 99.2)
Seroconversion rate**	47.1% (32.9; 61.5)	88.2% (76.1; 95.6)	58.1% (39.1; 75.5)	93.5% (78.6; 99.2)
Seroconversion factor***	3.5 (2.5 ; 4.9)	8.6 (6.6 ; 11.3)	5.8 (3.9 ; 8.8)	15.0 (12.4 ; 18.1)
9 to 17 years	N=50		N=29	
Seroprotection rate*	80.0% (66.3; 90.0)	88.0% (75.7; 95.5)	82.8% (64.2; 94.2)	93.1% (77.2; 99.2)
Seroconversion rate**	74.0% (59.7; 85.4)	84.0% (70.9; 92.8)	82.8% (64.2; 94.2)	93.1% (77.2; 99.2)
Seroconversion factor***	6.8 (5.0 ; 9.2)	8.9 (6.6 ; 11.9)	9.8 (6.9 ; 14.0)	13.8 (10.3 ; 18.4)

* SRH area > 25 mm²

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

*** geometric mean increase

After vaccination the rate of subjects with neutralizing antibody titres ≥ 40, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in children and adolescents aged 3 to 17 years were as follows:

MN Assay	All subjects		Seronegative subjects at baseline (<1:10)	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
3 to 8 years	N=51		N=47	
Seroneutralization rate*	84.3% (71.4; 93.0)	100.0% (93.0; 100.0)	83.0% (69.2; 92.4)	100.0% (92.5; 100.0)
Seroconversion rate**	94.1% (83.8; 98.8)	100.0% (93.0; 100.0)	93.6% (82.5; 98.7)	100.0% (92.5; 100.0)
Seroconversion factor***	12.9 (9.5; 17.5)	156.9 (119.4; 206.2)	13.5 (9.7; 18.8)	168.2 (131.1; 215.7)
9 to 17 years	N=51		N=34	
Seroneutralization rate*	94.1 % (83.8; 98.8)	100.0% (93.0; 100.0)	91.2% (76.3; 98.1)	100.0% (89.7; 100.0)
Seroconversion rate**	100.0% (93.0; 100.0)	100.0% (93.0; 100.0)	100.0% (89.7; 100.0)	100.0% (89.7; 100.0)
Seroconversion factor***	33.3 (22.2; 50.0)	115.6 (87.4; 152.8)	29.2 (17.9; 47.7)	137.5 (99.5; 189.9)

* MN titre ≥1:40

** ≥ 4-fold increase in MN titre

*** geometric mean increase

Infants and children aged 6–35 months

The seroprotection rate, seroconversion rate and seroconversion factor for anti-HA antibody as measured by single radial haemolysis (SRH) in children aged 6 to 35 months were as follows:

SRH Assay	All subjects		Seronegative subjects at baseline (≤4mm^2)	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
6 to 11 months	N=16		N=15	
Seroprotection rate*	31.3% (11.0; 58.7)	81.3% (54.4; 96.0)	33.3% (11.8; 61.6)	80.0% (51.9; 95.7)
Seroconversion rate**	31.3% (11.0; 58.7)	81.3% (54.4; 96.0)	33.3% (11.8; 61.6)	80.0% (51.9; 95.7)
Seroconversion factor***	2.0 (1.1 ; 3.4)	9.2 (5.9 ; 14.5)	2.1 (1.1 ; 3.7)	9.0 (5.6 ; 14.5)
12 to 35 months	N=49		N=40	
Seroprotection rate*	24.5% (13.3; 38.9)	95.9% (86.0; 99.5)	20.0% (9.1;35.6)	95.0% (83.1;99.4)
Seroconversion rate**	22.4% (11.8; 36.6)	91.8% (80.4; 97.7)	20.0% (9.1; 35.6)	95.0% (83.1; 99.4)
Seroconversion factor***	1.8 (1.4 ; 2.5)	11.2 (9.3 ; 13.4)	1.8 (1.3 ; 2.5)	12.5 (10.7 ; 14.5)

* SRH area > 25 mm²

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

*** geometric mean increase

After vaccination the rate of subjects with neutralizing antibody titres ≥ 40, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in children aged 6 to 35 months were as follows:

MN Assay	All subjects		Seronegative subjects at baseline (<1:10)	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
6 to 11 months	N=8		N=8	
Seroneutralization rate*	25.0% (3.2; 65.1)	100% (63.1; 100.0)	25.0% (3.2; 65.1)	100% (63.1; 100.0)
Seroconversion rate**	50.0% (15.7; 84.3)	100% (63.1;100.0)	50.0% (15.7; 84.3)	100% (63.1;100.0)
Seroconversion factor***	3.0 (1.1; 7.9)	33.4 (11.4; 98.2)	3.0 (1.1; 7.9)	33.4 (11.4; 98.2)
12 to 35 months	N=37		N=36	
Seroneutralization rate*	51.4% (34.4; 68.1)	100% (90.5; 100.0)	50.0% (32.9; 67.1)	100.0% (90.3; 100.0)
Seroconversion rate**	70.3% (53.0; 84.1)	100% (90.5;100.0)	69.4% (51.9; 83.7)	100.0% (90.3; 100.0)
Seroconversion factor***	5.3 (3.7; 7.8)	94.8 (60.6; 148.5)	5.4 (3.6 ; 8.0)	99.7 (63.5 ; 156.3)

* MN titre ≥1:40

** ≥ 4-fold increase in MN titre

*** geometric mean increase

Immune response against A/Vietnam/1203/2004

The immunogenicity of the vaccine containing 7.5 µg non-adjuvanted HA derived from strain A/Vietnam/1203/2004 has been evaluated in two clinical studies in adults aged 18 – 59 years (N=312) and in elderly subjects aged 60 years and older (N=272) following a 0, 21 day schedule.

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

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

* SRH area $\geq$ 25 mm²

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

*** geometric mean increase

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

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

* MN titre $\geq$ 20

** $\geq$ 4-fold increase in MN titre

*** geometric mean increase

Cross-reactive Immune Response Against Related H5N1 Strains

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

[a] 21 days after 2nd dose

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

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

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

Antibody Persistence and Booster Vaccination with Homologous and Heterologous Vaccine Strains

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

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

* SRH area ≥ 25 mm²
** MN titre ≥ 20

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

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

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

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

* MN titer ≥ 1:20

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

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

Information from non-clinical studies

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

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

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

In a second study, sixty-six ferrets were divided into 6 cohorts of 11 ferrets and were immunized on days 0 and 21 with 3.75 µg or 7.5 µg of the Indonesia vaccine or were sham vaccinated. The ferrets were challenged intranasally on day 35 with a high dose of either the clade 2 H5N1 virus A/Indonesia/05/2005 or the clade 1 H5N1 virus A/Vietnam/1203/2004 and monitored for 14 days. The A/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 data obtained with the pandemic vaccine using an H5N1 vaccine strain demonstrated alterations in liver enzymes and calcium levels in repeat dose toxicity studies in rats. Such alterations in liver function have not been seen to date in human clinical studies. Alterations in calcium metabolism have not been examined in human clinical studies.

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

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 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.
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 AUTHORIZATION HOLDER

Baxter AG
Industriestrasse 67
A-1221 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER

EU/1/08/506/001

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

04/03/2009

10. DATE OF REVISION OF THE TEXT

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