ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Celvapan suspension for injection
Influenza vaccine (H1N1)v (whole virion, Vero cell derived, inactivated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Whole virion influenza vaccine, inactivated containing antigen of 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 is 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 a clear to opalescent, translucent suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza caused by A(H1N1)v 2009 virus (See section 4.4).

Celvapan 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 clinical studies in healthy subjects who received two doses of Celvapan (H1N1)v.

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

Adults and older people
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
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 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.

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

4.4 Special warnings and precautions for use

The vaccine can only be expected to protect against influenza caused by A/California/07/2009 (H1N1)v-like strains.

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.

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)v vaccines.

4.5 Interaction 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 Fertility, pregnancy and lactation

The safety of Celvapan in pregnancy and lactation has been assessed in a limited number of pregnant women.

Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or fetal 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 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 Celvapan (H1N1)v

Adults and Older People

In a clinical study the 7.5 µg dose of Celvapan (H1N1)v was administered to adults aged 18 to 59 years (N = 101) and older people 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.

Adverse reactions from clinical trials with Celvapan (H1N1)v in a healthy adult and older people are listed in the table below.

Clinical Adverse Reactions (H1N1)v Studies		
System Organ Class (SOC)	Preferred MedDRA Term	Frequency[1]
INFECTIONS AND INFESTATIONS	Nasopharyngitis	Common
PSYCHIATRIC DISORDERS	Insomnia	Common
NERVOUS SYSTEM DISORDERS	Headache Dizziness	Very Common Common
EYE DISORDERS	Eye irritation	Common
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Pharyngolaryngeal pain	Common
GASTROINTESTINAL DISORDERS	Abdominal pain	Common
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis Rash Urticaria	Common Common Common
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia Myalgia	Common Common
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue Pyrexia Chills Malaise Injection site reactions • Injection site pain • Injection site induration • Injection site erythema • Injection site swelling • Injection site movement impairment	Very Common Common Common Common Common Common Common Common Common

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

Children and adolescents 3 to 17 years of age

In a 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 (H1N1)v. The incidence and nature of symptoms after the first and second vaccination were similar to that observed in the adult and older population using Celvapan.

Children aged 6 to 35 months

In a clinical trial the 7.5 µg dose of Celvapan (H1N1)v was administered to 69 infants and young children aged 6 to 35 months.

[1] represents the highest frequency observed either in the healthy adult or healthy older study population.

Adverse reactions from pediatric clinical trials with CELVAPAN (H1N1)v are listed in the table below.

Clinical Trial Adverse Reactions H1N1v studies				
System Organ Class (SOC)	Preferred MedDRA Term	Frequency		
		9 - 17 years	3 - 8 years	6 – 35 months
METABOLISM AND NUTRITION DISORDERS	Decreased appetite	-	-	Common
PSYCHIATRIC DISORDERS	Sleep disorder Restlessness	- -	-	Very common Common
NERVOUS SYSTEM DISORDERS	Headache Crying Somnolence	Common - -	Common - -	Common Common Common
EAR AND LABYRINTH DISORDERS	Vertigo	Common	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough	-	-	Common
GASTROINTESTINAL DISORDERS	Abdominal pain Nausea Vomiting Diarrhea	Common Common Common -	- Common Common Common	Common Common Common Common
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis Rash	- -	- -	Common Common
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Myalgia Pain in extremity	Common Common	- -	- -
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue Pyrexia Chills Irritability Malaise Injection site reactions • Injection site pain • Injection site induration • Injection site erythema • Injection site swelling	- - Common - - Very common Common Common Common	Common Common Common - - Common Common Common Common	- Very common Common Common Common Common Common Common Common

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

- <u>Clinical trials with a version of Celvapan containing a H5N1 vaccine strain</u>

Clinical trials were conducted with a version of Celvapan containing a H5N1 vaccine strain (see section 5.1) in approximately 3700 subjects (ranging in age from 18 to 60 years and above), and in special risk groups of approximately 300 subjects each, consisting of immune-compromised subjects and patients with chronic disease conditions.

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 safety profile in healthy subjects > 60 years of age, in immune-compromised subjects and patients with chronic disease conditions is similar to the safety profile in healthy subjects.

- Post-marketing surveillance

Pandemic Observational Study with Celvapan (H1N1)v

In an observational safety study including 3216 subjects aged 6 months to 60 years and older, the nature of adverse events was consistent with those observed in other clinical studies in adults and children. The following adverse reactions were reported at a higher frequency category than in the other clinical studies:

Adults aged 18 years and older:

Very common: Injection site pain, injection site redness, muscle pain
Uncommon: influenza like illness

Children and adolescents aged 5 to 17 years:

Very common: fatigue, headache
Uncommon: cough

Children aged 6 months to 5 years:

Very common: Injection site redness, drowsiness, irritability, loss of appetite, crying

Celvapan (H1N1)v

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

The frequency of these adverse reactions is not known.

Immune system disorder:

Anaphylactic reaction*, Hypersensitivity*

Nervous system disorders:

Febrile convulsion
Hypoaesthesia

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

Trivalent seasonal influenza vaccines

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

Uncommon:

Generalised skin reactions

Rare:

Neuralgia, paraesthesia, 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

Clinical studies with Celvapan (H1N1)v currently provide:

- Safety and immunogenicity data obtained three weeks after administration of two doses of Celvapan (H1N1)v in healthy adults aged 18 years and older.
- Safety and immunogenicity data obtained three weeks after administration of two doses of Celvapan (H1N1)v 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 older people.
- Safety and immunogenicity data in special risk groups (immunocompromised and chronically ill)

Immune response against A/California/07/2009(H1N1)v

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 clinical studies in adults aged 18 years and older (N = 200), in children and adolescents aged 3 to 17 years (N = 102), and in infants and young children aged 6 to 35 months (N = 68) following a 0, 21 day schedule.

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 older 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 mm² 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 older 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

Persistence of anti-HA antibodies 180 days after the first vaccination as measured by single radial haemolysis (SRH) and microneutralisation assay (MN) in adults aged 18 to 59 years and in older subjects aged 60 years and above was as follows:

Antibody persistence	All subjects		Seronegative subjects at baseline (< 1:10)	
	Day 181		Day 181	
	SRH	MN	SRH	MN
18 to 59 years	N = 98	N = 98	N = 33	N = 32
Seroprotection / Seroneutralization rate*	80.6% (71.4;87.9)	94.9% (88.5;98.3)	78.8% (61.1;91,0)	90.6% (75.0;98.0)
Seroconversion rate**	68.4% (58.2;77.4)	83.7% (74.8;90.4)	78.8% (61.1;91.0)	96.9% (83.8;99.9)
Seroconversion factor***	3.6 (2.9;4.4)	15.0 (11.0;20.4)	8.0 (5.7;11.4)	30.0 (17.7;50.8)
≥ 60 years	N = 101	N = 101	N = 22	N = 24
Seroprotection / Seroneutralization rate*	80.2% (71.1;87.5)	79.2% (68.9;85.8)	59.1% (36.4;79.3)	66.7% (44.7;84.4)
Seroconversion rate**	30.7% (21.9;40,7)	54.5% (44.2;64.4)	59.1% (36.4;79.3)	83.3% (62.6;95.3)
Seroconversion factor***	1.8 (1.5;2,1)	4.6 (3.7;5.7)	4.6 (2.9;7.3)	8.9 (5.6;14.0)

* SRH area > 25 mm²; MN titre ≥ 1:40;

** either SRH area > 25 mm² if baseline sample negative or 50% increase in SRH area if baseline sample > 4 mm²; > 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 ($\leq 4mm^2$)	
	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 mm² 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 = 3[illegible]	
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)	29.3 (17.9; 47.7)	137.5 (99.5; 189.9)

* MN titre ≥ 1:40
** ≥ 4-fold increase in MN titre
*** geometric mean increase

Persistence of anti-HA antibodies 180 days and 360 days after the first vaccination as measured by single radial hemolysis (SRH) and microneutralization (MN) assay in children and adolescents aged 3 to 17 years was as follows:

Antibody persistence	Day 181		Day 361	
	SRH	MN	SRH	MN
9 to 17 years	N=50	N=47	N=29	N=27
Seroprotection / Seroneutralization rate*	98.0% (89.4; 99.9)	100% (92.5; 100.0)	96.6% (82.2; 99.9)	88.9% (70.8; 97.6)
Seroconversion rate**	92.0% (80.8; 97.8)	100% (92.5; 100.0)	93.1% (77.2; 99.2)	96.3% (81.0; 99.9)
Seroconversion factor***	7.8 (6.2; 9.9)	66.4 (47.4; 93.1)	6.5 (4.7; 9.0)	26.7 (16.6; 43.1)
3 to 8 years	N=51	N=47	N=33	N=31
Seroprotection / Seroneutralization rate*	79.6% (65.7; 89.8)	100% (92.5; 100.0)	54.5% (36.4; 71.9)	100% (88.8; 100.0)
Seroconversion rate**	77.6% (63.4; 88.2)	100% (92.5; 100.0)	57.6% (39.2; 74.5)	96.8% (83.3; 99.9)
Seroconversion factor***	5.6 (4.5; 7.1)	59.5 (45.1; 78.3)	4.5 (3.4; 6.1)	26.5 (18.5; 37.9)

* SRH area > 25 mm²; MN titer ≥1:40;
** either SRH area > 25 mm² if baseline sample negative or 50% increase in SRH area if baseline sample > 4 mm²; > 4-fold increase in MN titer;
*** 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 ($\leq 4mm^2$)	
	21 Days After		21 Days After	
	1st Dose	2nd Dose	1st Dose	2nd Dose
6 to 11 months	N = 19		N = 15	
Seroprotection rate*	31.6% (12.6; 56.6)	78.9% (54.4; 93.9)	33.3% (11.8; 61.6)	80.0% (51.9; 95.7)
Seroconversion rate**	31.6% (12.6; 56.6)	84.2% (60.4; 96.6)	33.3% (11.8; 61.6)	80.0% (51.9; 95.7)
Seroconversion factor***	1.9 (1.2; 3.0)	7.6 (4.9; 11.7)	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 mm² 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 neutralising 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 = 17	N = 19	N = 17	N = 19
Seroneutralization rate*	35.3% (14.2; 61.7)	100% (82.4; 100.0)	35.3% (14.2; 61.7)	100% (82.4; 100.0)
Seroconversion rate**	76.5% (50.1; 93.2)	100% (82.4;100.0)	76.5% (50.1; 93.2)	100% (82.4;100.0)
Seroconversion factor***	4.5 (2.7; 7.5)	60.6 (27.9; 131.7)	4.5 (2.7; 7.5)	60.6 (27.9; 131.7)
12 to 35 months	N = 49		N = 48	
Seroneutralization rate*	55.1% (40.2; 69.3)	100% (92.7; 100.0)	54.2% (39.2; 68.6)	100.0% (92.6; 100.0)
Seroconversion rate**	75.5% (61.1; 86.7)	100% (92.7;100.0)	75.0% (60.4; 86.4)	100.0% (92.6; 100.0)
Seroconversion factor***	6.6 (4.6; 9.4)	108.0 (75.5; 154.5)	6.7 (4.7; 9.6)	112.4 (78.7; 160.5)

* MN titre ≥ 1:40

** ≥ 4-fold increase in MN titre

*** geometric mean increase

Persistence of anti-HA antibodies 180 days and 360 days after the first vaccination as measured by single radial hemolysis (SRH) and microneutralization assay (MN) in infants and young children aged 6 to 35 months was as follows:

Antibody persistence	Day 181		Day 361	
	SRH	MN	SRH	MN
12 to 35 months	N=47	N=47	N=31	N=31
Seroprotection / Seroneutralization rate*	68.1% (52.9; 80.9)	100% (92.5; 100.0)	48.8% (30.2; 66.9)	90.3% (74.2; 98.0)
Seroconversion rate**	63.8% (48.5; 77.3)	100% (92.5; 100.0)	45.2% (27.3; 64.0)	93.5% (78.6; 99.2)
Seroconversion factor***	5.7 (4.7; 7.0)	40.2 (29.2; 55.4)	4.1 (3.0; 5.5)	18.3 (11.2; 29.8)
6 to 11 months	N=16	N=13	N=13	N=11
Seroprotection / Seroneutralization rate*	37.5% (15.2; 64.6)	100% (75.3; 100.0)	30.8% (9.1; 61.4)	81.8% (48.2; 97.7)
Seroconversion rate**	37.5% (15.2; 64.6)	100% (75.3; 100.0)	30.8% (9.1; 61.4)	100% (71.5; 100.0)
Seroconversion factor***	2.9 (2.0; 4.4)	19.3 (13.8; 27.0)	2.6 (1.5; 4.5)	17.6 (7.1; 43.4)

* SRH area > 25 mm²; MN titer ≥ 1:40;

** either SRH area > 25 mm² if baseline sample negative or 50% increase in SRH area if baseline sample >4 mm²; > 4-fold increase in MN titer;

*** geometric mean increase

Following a 12-month booster vaccination with a licensed trivalent virosomal influenza vaccine for the 2010/2011 Northern hemisphere influenza season, seroprotection rates, seroconversion rates and serconversion factors (compared to pre-booster antibody levels) for the H1N1 component as measured by SRH and MN assays were as follows:

21-28 Days Post Booster	SRH	MN	SRH	MN
	9 to 17 years		3 to 8 years	
	N=29	N=27	N=33	N=31
Seroprotection / Seroneutralization rate*	100% (88.1; 100.0)	100% (87.2; 100.0)	100% (89.4; 100.0)	100% (88.8; 100.0)
Seroconversion rate**	40.0% (22.7; 59.4)	93.1% (77.2; 99.2)	85.3% (68.9; 95.0)	100% (89.7; 100.0)
Seroconversion factor***	1.5 (1.3; 1.7)	13.7 (9.4; 20.0)	2.7 (2.2; 3.4)	29.8 (20.1; 44.1)
	12 to 35 months		6 to 11 months	
	N=31	N=29	N=11	N=9
Seroprotection / Seroneutralization rate*	100% (88.8; 100.0)	100% (88.1; 100.0)	100% (71.5; 100.0)	100% (66.4; 100.0)
Seroconversion rate**	87.1% (70.2; 96.4)	96.6% (82.2; 99.9)	90.9% (58.7; 99.8)	100% (71.5; 100.0)
Seroconversion factor***	3.6 (2.8; 4.6)	38.7 (23.9; 62.7)	4.9 (2.7; 8.9)	29.1 (11.6; 73.1)

* SRH area > 25 mm²; MN titer ≥1:40;

** either SRH area > 25 mm² if baseline sample negative or 50% increase in SRH area if baseline sample >4 mm²; > 4-fold increase in MN titer;

*** geometric mean increase

<u>Immune response against a version of Celvapan containing A/H5N1 vaccine strains</u>

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 older subjects aged 60 years and older (N = 272) following a 0, 21 day schedule.

The seroprotection rates, seroconversion rates and seroconversion factors reported in adults and older subjects were comparable with Celvapan (H1N1)v.

Results from Vaccine Effectiveness Study in Jersey

Pandemic vaccine effectiveness against the medically-attended influenza like illness (ILI) with laboratory-confirmation as A(H1N1)v, was assessed for the vaccination campaign in Jersey 2009/2010 in a case control study (test-negative design). Younger children 6 months to 9 years received Celvapan, while older children from 9 to 18 years of age received an adjuvanted split pandemic vaccine. There were no reported vaccine failures in either of these paediatric age groups. Crude vaccine effectiveness of one dose of pandemic vaccine among children was 100% (95% CI: 70-100%).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-Clinical data obtained with Celvapan containing a 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

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after first opening of the medicinal product, see section 6.3.

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

Nanotherapeutics Bohumil, s.r.o.
Bohumil 138
28163 Jevany
Czech Republic

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/506/001

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

04/03/2009

10. DATE OF REVISION OF THE TEXT

MM/YYYY

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

ANNEX II

A. MANUFACTURER(S) 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

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

Name and address of the manufacturers of the biological active substance(s)

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(s) responsible for batch release

Baxter AG
Uferstrasse 15
A-2304 Orth/Donau
Austria

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 Directive 2001/83/EC, 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 AUTHORIZATION

- 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.

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

- **Risk Management Plan (RMP)**

The MAH shall perform 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.

- **Additional risk minimisation measures**

  - The MAH shall agree with Member States to measures facilitating the identification and traceability of the A/(H1N1)v vaccine administered to each patient, in order to minimise medication errors and aid patients and health care professionals to report adverse reactions. This may include the provision by the MAH of stickers with invented name and batch number with each pack of the vaccine.

  - The MAH shall agree with Member States on mechanisms allowing patients and health care professionals to have continuous access to updated information regarding Celvapan.

  - The MAH shall agree with Member States on the provision of a targeted communication to health care professionals which should address the following:

    - The correct way to prepare the vaccine prior to administration.

    - Adverse events to be prioritised for reporting, i.e. fatal and life-threatening adverse reactions, unexpected severe adverse reactions, adverse events of special interest (AESI).

    - The minimal data elements to be transmitted in individual case safety reports in order to facilitate the evaluation and the identification of the vaccine administered to each subject, including the invented name, the vaccine manufacturer and the batch number.

    - If a specific notification system has been put in place, how to report adverse reactions.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Celvapan suspension for injection
Influenza vaccine (H1N1)v (whole virion, Vero cell derived, inactivated)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Whole virus influenza vaccine, inactivated containing antigen of strain*:

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

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

Nanotherapeutics Bohumil, s.r.o.
Bohumil 138
28163 Jevany
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/506/001

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.

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

Celvapan suspension for injection
Influenza vaccine (H1N1)v (whole virion, Vero cell derived, inactivated)

Intramuscular use

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.

Nanotherapeutics Bohumil, s.r.o.
Bohumil 138
28163 Jevany
Czech Republic

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

CELVAPAN suspension for injection
Influenza vaccine (H1N1)v (whole virion, Vero cell derived, inactivated)

Read all of this leaflet carefully before you receive this vaccine 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 nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Celvapan is and what it is used for

Celvapan is a vaccine to prevent influenza (flu) caused by A(H1N1)v 2009 virus

When a person is given the vaccine, the immune system (the body's natural defense system) will produce its own protection (antibodies) against the disease. None of the ingredients in the vaccine can cause flu.

2. What you need to know before you receive Celvapan

You should not receive Celvapan:

- if you previously had a sudden life-threatening allergic reaction to any ingredient of Celvapan or to any of the substances that may be present in trace amounts as follows: formaldehyde, benzonase, sucrose.
  - Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

  If you are not sure, talk to your doctor or nurse before having this vaccine.

Take special care with Celvapan:

Check with your doctor or nurse before you are given Celvapan if

- you have had any allergic reaction other than a sudden life-threatening allergic reaction to any ingredient contained in the vaccine, to formaldehyde, benzonase, or to sucrose. (see section 6. Further information).
- 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 problem, but your doctor or nurse should advise whether you could still be vaccinated with Celvapan.
- you have problems with your immune system, since your response to the vaccine may then be poor.

- you are having a blood test to look for evidence of infection with certain viruses. In the first few weeks after vaccination with Celvapan the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently been given Celvapan.
- you have a bleeding condition or a bleeding problem or you bruise easily.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before having Celvapan. This is because the vaccination may not be recommended, or may need to be delayed.

Other medicines and Celvapan

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

There is no information on administration of the vaccine Celvapan with other vaccines. However, if this cannot be avoided, the vaccines should be injected into separate limbs. In such cases, you should be aware that the side effects may be more intense.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, think you may be pregnant, or are planning to have a baby. Your doctor will discuss with you whether you should be given Celvapan.

The vaccine may be used during breast-feeding.

Driving and using machines

Some effects mentioned under section 4. "Possible side effects" may affect your ability to drive or use machines.

3. How Celvapan is given

Your doctor or nurse will administer the vaccine in accordance with official recommendations.
The vaccine will be injected into a muscle (usually in the upper arm). The vaccine should never be given into a vein.

<u>Adults and older people:</u>

A dose (0.5 ml) of the vaccine will be given.
A second dose of the vaccine should be given after an interval of at least three weeks.

<u>Children and adolescents aged 6 months to 17 years of age:</u>

A dose (0.5 ml) of the vaccine will be given.
A second dose of the vaccine should be given after an interval of at least three weeks.

<u>Children aged less than 6 months:</u>

Vaccination is not currently recommended in this age group.

When Celvapan is given for the first dose, it is recommended that Celvapan (and not another vaccine against (H1N1)v) be given for the complete vaccination course.

4. Possible side effects

Like all medicines, Celvapan can cause side effects, although not everybody gets them.

Allergic reactions may occur following vaccination, in rare cases leading to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.

Side effects from clinical studies in adults and older people

The side effects listed below have occurred with Celvapan (H1N1)v in clinical studies in adults, including older people. In the clinical studies, most side effects were mild in nature and short term.

Very common:

- Headache
- Feeling tired

Common:

- Runny nose and sore throat
- Insomnia (difficulty sleeping)
- Dizziness
- Eye irritation
- Stomach pain
- Increased sweating
- Rash, hives
- Joint and muscle pain
- Fever, shivering, generally feeling unwell
- Pain, redness, swelling or a hard lump where the injection was given, reduced movement in the arm injected

Side effects from clinical studies in children

Children and adolescents 6 months to 17 years of age

In a clinical study the frequency and type of side effects after the first and second injection were basically similar to that seen in the adult and older population using Celvapan. However, some differences in frequency and type of side effects were observed. Specifically, headache, vertigo (spinning feeling), cough, feeling sick, vomiting, diarrhoea, pain in the arms or legs and tiredness were observed commonly in children and adolescents.

Additionally, in the case of the 9 to 17 year olds pain at the injection site was very common.

In children aged 6 to 35 months disturbed sleep and fever were very common, and decreased appetite, restlessness, irritability, crying and drowsiness were common.

Side effects from the Pandemic Observational Study with CELVAPAN (H1N1)v

Results from a clinical study done on marketed vaccine confirmed the safety profile as observed in the clinical studies. The following adverse reactions were reported at a higher frequency category than in the other clinical studies:

Adults aged 18 years and older:

Very common: Pain and redness where the injection was given, aching muscles
Uncommon: Influenza like illness

Children and adolescents aged 5 to 17 years:

Very common: Feeling tired, headache
Uncommon: Cough

Children aged 6 months to 5 years:

Very common: Redness where the injection was given, drowsiness, irritability, loss of appetite, crying

- **Clinical trials with a similar vaccine**

In a study with a similar influenza vaccine (containing a H5N1 vaccine strain) that included healthy adults and older people, subjects with a weakened immune system and patients with long-term conditions, the safety profile was similar to that in healthy adults.

- **Side effects observed during post-marketing surveillance**

The side effects listed below have occurred with Celvapan (H1N1)v in adults and children during the pandemic flu vaccination program.

- Allergic reactions, including anaphylactic reactions leading to a dangerous decrease in blood pressure which, if untreated, may lead to shock. Your doctors know that this might happen and will have emergency treatment ready to use.
- Fits due to fever
- Reduced skin sensitivity
- Pain in arms and or legs (in the majority of cases reported as pain in the vaccination arm)
- Flu-like illness
- Swelling of tissue just below the skin.

- **Side effects observed with flu vaccines given routinely every year**

The side effects listed below have occurred in the days or weeks after vaccination with vaccines given routinely every year to prevent flu. They may also happen with Celvapan.

Uncommon:

- generalized skin reactions including urticaria (hives)

Rare:

- severe stabbing or throbbing pain along one or more nerves
- low blood platelet count which can result in bleeding or bruising

Very rare:

- vasculitis (inflammation of blood vessels which can cause skin rashes, joint pain and kidney problems)
- neurological disorders such as encephalomyelitis (inflammation of the central nervous system), neuritis (inflammation of nerves) and a type of paralysis known as Guillain-Barré Syndrome

If any of these side effects occur, please tell your doctor or nurse immediately.

Reporting of side effects
If you get any of the side effects talk to your doctor. 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 Celvapan

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

Do not use Celvapan 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.

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

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

6. Contents of the pack and other information

What Celvapan contains

Active substance:

Whole virion influenza vaccine, inactivated, containing antigen of 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)
** haemagglutinin

Other ingredients:

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

What Celvapan looks like and contents of the pack

Celvapan is a clear to opalescent, translucent liquid.
One pack of Celvapan contains 20 multidose vials of 5 ml suspension for injection for 10 doses.

Marketing Authorization Holder:

Nanotherapeutics Bohumil, s.r.o.
Bohumil 138
28163 Jevany
Czech Republic
Manufacturer:

Baxter AG
Uferstrasse 15
A-2304 Orth/Donau
Austria

This leaflet was last revised in {month/YYYY}

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 medical or health care professionals only:

Prior to administration, the vaccine should be allowed to reach room temperature and the vial should be shaken well.

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.

The vaccine should not be administered intravascularly.

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