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 an off-white, 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

This pandemic influenza vaccine H1N1 has been authorised based on data obtained with a version containing H5N1 antigen supplemented with data obtained with the vaccine containing H1N1 antigen. The Clinical Particulars section will be updated in accordance with emerging additional data.

There is currently no clinical experience with Celvapan (H1N1) in adults, elderly, children or adolescents.
The decision to use Celvapan (H1N1) in each age group defined below should take into account the extent of the clinical data available with a version of the vaccine containing H5N1 antigen and the disease characteristics of the current influenza pandemic.

The dose recommendations are based on the safety and immunogenicity data available on the administration of vaccine containing 7.5µg HA derived from A/Vietnam/1203/2004 (H5N1) at day 0 and 21 to adults, including the elderly.

See sections 4.4, 4.8 and 5.1.

Posology
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 6 months to 17 years of age
No data are available in children or adolescents. 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.

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 606 subjects (326 between 18 and 59 years old, and 280 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
Common: headache, dizziness
Uncommon: somnolence, dysaesthesia

Eye disorders
Uncommon: conjunctivitis

Ear and labyrinth disorders
Common: vertigo
Uncommon: sudden hearing loss

Vascular disorders
Uncommon: hypotension

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

Gastrointestinal disorders
Uncommon: 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
Common: pyrexia, chills, fatigue, malaise, induration, erythema, swelling and haemorrhage at the injection site
Uncommon: injection site irritation

- Clinical Trials with Celvapan (H1N1)

Limited preliminary safety data after the first dose from clinical trials in adults aged over 18 years (N=387) and children aged from 9 to 17 years (N=101), 3 to 8 years (N=24) and 6 to 35 months (N=21) investigating two different dose levels (3.75µg or 7.5µg) of Celvapan H1N1v suggest a comparable safety profile with that reported for the H5N1 mock-up vaccine formulation.

- Post-marketing surveillance

For cell-based influenza vaccines, post-marketing surveillance data are not yet available. From post-marketing surveillance with egg-derived interpandemic trivalent vaccines, the following serious adverse reactions have been reported:

Uncommon:
Generalised skin reactions including pruritus, urticaria, and non-specific rash.

Rare:
Neuralgia, paraesthesia, convulsions, 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 (EMEA) will regularly review any new information which may become available and this SPC will be updated as necessary.

This section describes the clinical experience with the mock-up vaccine using an H5N1 strain 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.

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 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 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 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 neutralizing antibody titres ≥ 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 ≥ 20
** ≥ 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 ≥ 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

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 $\geq$ 25 mm²
** MN titre $\geq$ 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 $\geq$ 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 $\geq$ 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 $\geq$ 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 (EMEA): http://www.emea.europa.eu/

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER 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 OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

Celvapan 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 Celvapan takes due account of the officially declared pandemic strain.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

  - The MAH shall agree with Member States to measures facilitating the identification and traceability of the A/H1N1 pandemic 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 Sates 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.

- **OTHER CONDITIONS**

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.

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 1.16 (dated 12 August 2009) presented in Module 1.8.1. of the marketing authorisation application, is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

PSUR submission during the influenza pandemic:

During a pandemic situation, the frequency of submission of periodic safety update reports specified in Article 24 of Regulation (EC) No 726/2004 will not be adequate for the safety monitoring of a pandemic vaccine for which high levels of exposure are expected within a short period of time. Such situation requires rapid notification of safety information that may have the greatest implications for benefit-risk balance in a pandemic. Prompt analysis of cumulative safety information, in light of the extent of exposure, will be crucial for regulatory decisions and protection of the population to be vaccinated.
The MAH shall submit on a monthly basis a simplified periodic safety update report with the timelines, format and content as defined in the CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009) and any subsequent update.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 002 (dated 2 September 2009) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the continous reassessment of the benefit/risk profile.

Clinical	The MAH commits to provide abridged reports for the following studies performed in adults: Study 820902 (H1N1 clinical trial) -post dose 2 safety & immunogenicity	 30 November 2009
Clinical	The MAH commits to provide abridged reports for the following studies performed in children: Study 820903 (H1N1 clinical trial) - post dose 1 safety - post dose 1 immunogenicity -post dose 2 safety & immunogenicity	 Cohort 2: 5 November 2009 Children 9-17 years of age: 2 November 2009 Children 3-8 years of age: 11 December 2009 12 February 2010
Clinical	The MAH commits to provide the results of the effectiveness studies carried out in accordance with the study protocols published by ECDC.	Results of studies to be provided within two weeks of availability.
Pharmacovigilance	The MAH will conduct a prospective cohort safety study in at least 9,000 patients in different age groups, including immunocompromised subjects, in accordance with the protocol submitted with the Risk Management Plan. Observed-to-Expected analyses will be performed.	Interim and final results will be submitted in accordance with the protocol.
Pharmacovigilance	The MAH commits to provide the results of a study in a pregnancy registry.	Results to be provided in the simplified PSUR.
Pharmacovigilance	The MAH commits to establish the mechanism to promptly investigate issues affecting the benefit-risk balance of the vaccine.	Agree with EMEA on design of additional studies for emerging benefit-risk evaluation within 1 month of the Commission Decision granting the Variation.

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
Pandemic influenza vaccine (H1N1) (whole virion, Vero cell derived, inactivated)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

A/California/07/2009 (H1N1) 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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

Baxter AG
Industriestrasse 67
A-1221 Vienna
Austria

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
Pandemic influenza vaccine (H1N1) (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.

BAXTER AG
A-1221 Vienna
Austria

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

For the most up-to-date information please consult the website of the European Medicines Agency (EMEA): http://www.emea.europa.eu/.

Read all of this leaflet carefully before you receive this vaccine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet

1. WHAT CELVAPAN IS AND WHAT IT IS USED FOR

Celvapan is a vaccine to prevent pandemic influenza (flu).

Pandemic flu is a type of influenza that occurs every few decades and which spreads rapidly around the world. The symptoms of pandemic flu are similar to those of an ordinary flu but may be more severe.

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. 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. However, in a pandemic situation, it may be appropriate for you to have the vaccine provided that appropriate medical treatment is immediately available in case of an allergic reaction.

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

Take special care with 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).

- 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 problem, but your doctor or nurse should advise whether you could still be vaccinated with Celvapan,

- if 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,

In any of these cases, TELL YOUR DOCTOR OR NURSE, as vaccination may not be recommended, or may need to be delayed.

Please inform your doctor or nurse if you have a bleeding problem or bruise easily.

Taking other medicines

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 plan to become pregnant. You should discuss with your doctor whether you should receive 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 recommendation.
The vaccine will be injected into a muscle (usually in the upper arm).

Adults and elderly
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.

Children and adolescents aged 6 months to 17 years of age
If it is considered that you or your child needs to be vaccinated, you/he/she may receive one dose of 0.5 ml vaccine and a second dose of 0.5 ml at least three weeks later.

Children aged less than 6 months
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) 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.

In the clinical studies with a similar vaccine, most side effects were mild in nature and short term. The side-effects are generally similar to those related to the seasonal flu 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 frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)

The side effects listed below have occurred with Celvapan (H5N1) in clinical studies in adults, including the elderly:

Very common:
- pain at the injection site

Common:
- runny nose and sore throat,
- headache, dizziness, vertigo (motion sickness)
- sweating more than usual,
- joint or muscle pain,
- chills, fatigue (feeling tired), malaise (generally feeling unwell), fever,
- tissue hardening, redness, swelling or bruising at the injection site

Uncommon:
- swollen glands,
- insomnia (difficulty sleeping), restlessness,
- impaired perception of touch, pain, heat and cold, sleepiness,
- conjunctivitis (an inflammation of the eye),
- sudden hearing loss,
- reduced blood pressure,
- shortness of breath, cough, congestion of the nose,
- nausea, vomiting, diarrhoea, stomach pain,
- rash, itching,
- irritation at the injection site

These side effects usually disappear within 1-2 days without treatment. If they persist, CONSULT YOUR DOCTOR.

From ongoing clinical trials, where a first dose of Celvapan (H1N1) was given to a limited number of adults, elderly and children similar adverse events were observed in the first days after vaccination to those previously seen with Celvapan (H5N1) vaccine.

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

Uncommon:
- generalised skin reactions including urticaria (hives)

Rare:
- Allergic reactions leading to a dangerous decrease of blood pressure, which, if untreated, may lead to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.
- Fits
- 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.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE CELVAPAN

Keep out of the reach and sight 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Celvapan contains

Active substance:

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

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

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

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

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 an off-white, opalescent, translucent liquid.
One pack of Celvapan contains 20 multidose vials of 5 ml suspension for injection for 10 doses.

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Manufacturer:
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder given below:

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This leaflet was approved in

This medicine has been authorised under "Exceptional Circumstances". The European Agency (EMEA) will regularly review any new information on the medicine and this package leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.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.