

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

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

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

A/Vietnam/1203/2004 (H5N1) per 0.5 ml dose	7.5 micrograms**
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\* 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. Pandemic influenza vaccine should be used in accordance with official guidance.

CELVAPAN has been evaluated in adults 18-59 years of age and in elderly 60 years of age and above.

### **4.2 Posology and method of administration**

Adults: first dose of 0.5 ml at an elected date.

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

There is no data on CELVAPAN vaccination dose and schedule for subjects under 18 years old and for subjects with co-morbidities (e.g. immunosuppressed subjects). In a pandemic situation administration of the vaccine in those populations shall follow national recommendations.

For further information, see section 5.1.

Immunization should be carried out by intramuscular injection into the deltoid muscle.

### **4.3 Contraindications**

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (e.g. formaldehyde, benzoin, sucrose) of this vaccine. However, in a pandemic situation, it may be appropriate to give the vaccine, provided that facilities for resuscitation are immediately available in case of need.

See section 4.4.

### **4.4 Special warnings and precautions for use**

Caution is needed when administering 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, benzoin, 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 induced in all vaccinees (see section 5.1).

### **4.5 Interactions with other medicinal products and other forms of interaction**

CELVAPAN should not be given at the same time as other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

Immunoglobulin is not to be given with CELVAPAN. If it is necessary to provide immediate protection, CELVAPAN may be given at the same time as normal or specific immunoglobulin. Injections of CELVAPAN and immunoglobulin should be made into separate limbs.

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

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the results. The transient false positive reactions could be due to the IgM response by the vaccine.

#### **4.6 Pregnancy and lactation**

Data from vaccinations with interpandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. Therefore, for pregnant women, administration of the pandemic influenza vaccine is recommended, irrespective of their stage of pregnancy.

The vaccine CELVAPAN may be used during lactation.

#### **4.7 Effects on ability to drive and use machines**

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

#### **4.8 Undesirable effects**

In clinical trials with the mock-up vaccine (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 are listed according to the following frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ ).

Not known (cannot be estimated from the available data)

##### 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

#### 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

#### Post-marketing surveillance

For cell-based influenza vaccines, post-marketing surveillance data are not yet available. From post-marketing surveillance with egg-derived inter-pandemic 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 section describes the clinical experience with the mock-up vaccine following a two-dose administration.

Mock-up vaccines contain influenza antigens that are different from those in the currently circulating influenza viruses. These antigens can be considered as 'novel' antigens and simulate a situation where the target population for vaccination is immunologically naïve. Data obtained with the mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with mock-up vaccines are relevant for the pandemic vaccines.

### Immune response against the vaccine strain contained in CELVAPAN (A/Vietnam/1203/2004)

The immunogenicity of the 7.5 µg non-adjuvanted formulation of CELVAPAN (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		60 years and above	
	21 Days After		21 Days After	
	1 <sup>st</sup> Dose	2 <sup>nd</sup> Dose	1 <sup>st</sup> Dose	2 <sup>nd</sup> 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 mm<sup>2</sup>

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

\*\*\* geometric mean increase

After primary 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		60 years and above	
	21 Days After		21 Days After	
	1 <sup>st</sup> Dose	2 <sup>nd</sup> Dose	1 <sup>st</sup> Dose	2 <sup>nd</sup> 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:

Tested against	18 – 59 years		60 years and above	
	Day 42 <sup>a</sup>	Day 180	Day 42 <sup>a</sup>	Day 180
Seroneutralisation rate*	35.1%	14.4%	54.8%	28.0%

\* MN titre  $\geq$  20

<sup>a</sup> 21 days after 2<sup>nd</sup> 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  $\geq 20$ , seroconversion rates and seroconversion factor for cross-neutralising antibodies as measured by MN in subjects who received the 7.5  $\mu\text{g}$  non-adjuvanted formulation (N=42) were as follows:

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

\* MN titre  $\geq 20$   
\*\*  $\geq 4$ -fold increase in MN titre  
\*\*\* geometric mean increase  
<sup>a</sup> 21 days after 2<sup>nd</sup> dose

### Antibody Persistence and Booster Vaccination with Homologous and Heterologous Vaccine Strains

Antibody persistence after vaccination with the 7.5  $\mu\text{g}$  non-adjuvanted formulation of CELVAPAN (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*/ Seroneutralisation rate**	18 – 59 years		60 years and above	
	SRH Assay	MN Assay	SRH Assay	MN Assay
Month 6	28.1%	37.9%	26.7%	40.5%

\* SRH area  $\geq 25 \text{ mm}^2$   
\*\* 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  $\mu\text{g}$  and 7.5  $\mu\text{g}$ ) 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  $\mu\text{g}$  dose of the A/Vietnam strain vaccine. Twenty-one days after a booster vaccination with the 7.5  $\mu\text{g}$  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  $\mu\text{g}$  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 $\mu\text{g}$ 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 $\mu\text{g}$ 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  $\mu$ g 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  $\mu$ g 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:

The protective efficacy of CELVAPAN 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  $\mu$ g 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  $\mu$ g 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  $\mu$ g or 7.5  $\mu$ g of the Indonesia vaccine or were sham vaccinated. The ferrets were challenged intranasally on day 35 with a high dose of either the clade 2 H5N1 virus A/Indonesia/05/2005 or the clade 1 H5N1 virus A/Vietnam/1203/2004 and monitored for 14 days. The A/Indonesia/05/2005 vaccine was shown to be efficacious with 100% survival, reduced incidence of fever, reduced weight loss, reduced virus burden, and reduced haematological (leukopenia and lymphopenia) changes in the vaccinated cohorts following homologous challenge. Similarly, the A/Indonesia/05/2005 vaccine was efficacious against a heterologous challenge, showing a vaccine dose dependent survivorship in the vaccinated cohorts as compared to the control cohort. Similar to the homologous challenge, vaccination against a heterologous challenge reduced virus burden, and reduced haematological (leukopenia) changes associated with highly pathogenic avian influenza infection.

## **5.2 Pharmacokinetic properties**

Not applicable.

## **5.3 Preclinical safety data**

Non-Clinical studies demonstrated 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.

As of yet data from non-clinical studies concerning reproduction and development are not available.

## **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**

## **9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

## **10. DATE OF REVISION OF THE TEXT**

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

## **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  
2304 Orth/Donau  
Austria

Name and address of the manufacturer responsible for batch release

Baxter AG  
Industriestrasse 67  
A-1221 Vienna  
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**

Not applicable

**• OTHER CONDITIONS**

*Pharmacovigilance system*

The MAH must ensure that the system of pharmacovigilance, as described in version V01 (dated June 2006) presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

*Risk Management Plan*

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version RMP V 2.0 (dated 14 Aug 2008) 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.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

#### *PSURs*

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 risk-benefit balance in a pandemic. Prompt analysis of cumulative safety information, in light of extent of exposure, will be crucial for regulatory decisions and protection of the population to be vaccinated. In addition, during a pandemic, resources needed for an in-depth evaluation of Periodic Safety Update Reports in the format as defined in Volume 9a of the Rules Governing Medicinal Product in the European Union may not be adequate for a rapid identification of a new safety issue.

In consequence, as soon as the pandemic is declared (Phase 6 of the WHO global Influenza preparedness plan) and the pandemic vaccine is used, the MAH shall submit periodic safety update reports with periodicity and format defined as follows:

#### *Frequency of submission*

- The clock will start from the first Monday after shipment of the first batch of vaccine.
- First data-lock point is 14 days later.
- Report submission is no later than day 22 (i.e. the following Monday).
- Reporting to be fortnightly for the first 3 months of the pandemic.
- Periodicity will be reviewed by the MAH and the (Co-) Rapporteur at 3 monthly intervals.

#### *Format*

The report shall include the following Tables of aggregate data using the agreed templates:

1. Fatal and/or life-threatening reactions – for each Preferred Term (PT), including the proportion of fatal reports
2. Adverse Events of Special Interest (PTs)
3. Serious unexpected reactions (PTs)
4. All events occurring in the following age groups: 6-23 months, 2-8 years, 8-17 years, 18-60 years, >60 years  
All events occurring in pregnant women
5. All events reported by patients that have been entered into the database by data-lock point
6. A cumulative overview of all events reported during the period, stratified according to type of reporter (patient or health care professional), seriousness, expectedness, and whether spontaneous or solicited.

Presentation of data will take into consideration the following recommendations:

- Serious expected reactions will be reviewed by the MAH as part of their signal detection procedures and will only form part of the report if an issue of concern arises.
- All tables will be based on number of events (presented on PT level, sorted by System Organ Class [SOC]) and not number of cases.
- Tables 1 to 4 will be based on events reported from healthcare professionals only.
- In Tables 1 to 5, numbers will be provided for events received during the reporting period and cumulatively.

- All tables will be based on generic and not product-specific data. Product-specific data can be evaluated during signal work-up.
- No line listings are required – these can be provided in signal evaluation reports as necessary.

A short summary shall also be provided with the periodic safety update reports, in which any area of concern should be highlighted, signal work-up prioritised (if the event of multiple signals) and appropriate timelines for submission of a full signal evaluation report provided. All signal evaluation reports should be provided, including those that were subsequently not identified as being signals.

A summary of vaccine distribution shall be included and provide details of the number of doses of vaccine distributed in:

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

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

#### **C. 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 annual reassessment of the benefit/risk profile in case the Pandemic will be declared.

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

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

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

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Whole virus influenza vaccine, inactivated containing antigen of pandemic strain\*:  
A/Vietnam/1203/2004 (H5N1) 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/0/00/000/000

**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 (whole virion, Vero cell derived, inactivated)  
Pandemic influenza vaccine  
I.M.

**2. METHOD OF ADMINISTRATION**

Shake before use

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

Multidose vial (10 doses of 0.5 ml per vial)

**6. OTHER**

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

BAXTER AG  
A-1221 Vienna  
Austria

**B. PACKAGE LEAFLET**

## PACKAGE LEAFLET: INFORMATION FOR THE USER

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

**Read all of this leaflet carefully before you start receiving this vaccine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for you. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet**

1. What CELVAPAN is and what it is used for
2. Before you receive CELVAPAN
3. How CELVAPAN is given
4. Possible side effects
5. How to store CELVAPAN
6. Further information

#### **1. WHAT CELVAPAN IS AND WHAT IT IS USED FOR**

CELVAPAN is a vaccine used in adults of 18 years of age and older. It is used to prevent influenza (flu) in an officially declared pandemic.

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

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

#### **2. BEFORE YOU RECEIVE CELVAPAN**

##### **Do not use CELVAPAN:**

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

##### **Take special care with CELVAPAN:**

You should tell your doctor before vaccination

- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be problem, but your doctor should advise whether you could still be vaccinated with CELVAPAN.
- if you have a poor immune response (as for example because of immunosuppressive therapy, e.g. corticosteroid treatments or chemotherapy for cancer);

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

There is no information on the use of CELVAPAN below 18 years of age. In case of pandemic national recommendations will be followed.

#### **Taking other medicines:**

- Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or have recently received any other vaccine.
- CELVAPAN should not be given at the same time as other vaccines. However, if this cannot be avoided, the other vaccine should be injected into the other limb. You should be aware that the side effects may be intensified.
- If you take any medicines that reduce immunity to infections or have any other type of treatment (such as radiotherapy) that affects the immune system, CELVAPAN can still be given but your response to the vaccine may be poor.
- CELVAPAN should not be given at the same time as immunoglobulins. However, if this cannot be avoided, the immunoglobulins should be injected into the other limb.

#### **Pregnancy and breast-feeding**

Tell your doctor if you are pregnant, think you may be pregnant, plan to become pregnant, or are breast-feeding. Your doctor will decide if you should receive CELVAPAN.

#### **Driving and using machines**

CELVAPAN may make you feel dizzy or sick which may affect your ability to drive or use machines.

### **3. HOW CELVAPAN IS GIVEN**

Adults from the age of 18 years and older will receive two injections of CELVAPAN. The time period between the first and the second injection must be at least three weeks.

CELVAPAN is given as an injection into the muscle (usually in the upper arm).

The vaccine should never be given into a vein.

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

### **4. POSSIBLE SIDE EFFECTS**

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

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

The following side effects have been reported in clinical studies.

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)  
not known (frequency cannot be estimated from the available data).

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

Other side effects which have occurred in the days or weeks after vaccination with flu vaccines include:

Uncommon:

- Generalized skin reactions such as itching, hives or rash

Rare:

- Nerve pain (neuralgia)
- Tingling and numbness
- Fits
- Transient low blood platelet count
- Allergic reactions, in rare cases leading to shock (a dangerous decrease of blood pressure, which, if untreated, may lead to collapse, coma and death)

Very rare:

- Inflammation of blood vessels (vasculitis) with s transient kidney problems
- Inflammation of the brain and spinal chord (encephalomyelitis)
- Temporary inflammation of the nerves, causing pain, weakness and paralysis in the extremities and often progressing to the chest and face

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

## 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/Vietnam/1203/2004 (H5N1) 7.5 micrograms\*\*

per 0.5 ml dose

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

\*\* haemagglutinin

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. 1 pack of CELVAPAN contains 20 multidose vials of 5 ml suspension for injection for 10 doses.

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A-1221 Vienna,  
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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 last approved in {MM/YYYY}.**

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

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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.”