**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

VEPACEL suspension for injection in multidose container
Prepandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Influenza virus (whole virion, inactivated), containing antigen* of strain:
A/Vietnam/1203/2004 (H5N1) 7.5 micrograms**

* produced in Vero cells
** 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.
Clear to opalescent suspension.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Active immunisation against H5N1 subtype of influenza A virus.

This indication is based on immunogenicity data from subjects from the age of 6 months onwards following administration of two doses of vaccine prepared with H5N1 subtype strains (see section 5.1).

The use of this vaccine should be in accordance with official recommendations.

### 4.2 Posology and method of administration

Posology
Adults and children from 6 months onwards:
One dose of 0.5 ml at an elected date.
A second dose of 0.5 ml should be given after an interval of at least three weeks.

*other paediatric Population*
No data is available on the safety and efficacy of VEPACEL in children younger than 6 months of age.

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

See section 6.6 for administration instructions.

## 4.3 Contraindications

History of anaphylactic reactions to the active substance, or to any of the excipients listed in section 6.1, or trace residues (formaldehyde, benzonase, sucrose, trypsin, Vero host cell protein). If vaccination is considered necessary, facilities for resuscitation should be immediately available in case of need (see section 4.4).

## 4.4 Special warnings and precautions for use

This vaccine may contain traces of formaldehyde, benzonase, sucrose, trypsin and Vero host cell protein, which are used during the manufacturing process. Therefore, hypersensitivity reactions may occur.

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.

Hypersensitivity reactions, including anaphylaxis, have been reported following use of a similar whole virion, Vero cell derived H1N1 influenza vaccine administered during a pandemic period. Such reactions have occurred both in patients with a history of multiple allergies and in patients with no known allergy.

Immunisation shall be postponed in patients with severe febrile illness or acute infection.

VEPACEL must not be administered intravascularly.

There are no data with VEPACEL 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 bleeding.

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

A protective immune response may not be induced in all individuals receiving the vaccine (see section 5.1).

## 4.5 Interaction with other medicinal products and other forms of interaction

There are no data on co-administration of VEPACEL with 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 VEPACEL unless it is necessary during a medical emergency to provide immediate protection. If necessary, VEPACEL may be given at the same time as normal or specific immunoglobulin into separate limbs.

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

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 VEPACEL in pregnancy and lactation has not been assessed in clinical trials.

Animal 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 fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).

Healthcare providers should carefully consider the potential risks and benefits for each specific patient before prescribing VEPACEL.

The use of VEPACEL during pregnancy and lactation may be considered in a pre-pandemic situation, taking into account official recommendations.

## 4.7 Effects on ability to drive and use machines

VEPACEL has minor influence on the ability to drive and use machines.

## 4.8 Undesirable effects

a) Summary of safety profile

- Adults, older people, and special risk groups

Clinical trials were conducted with the H5N1 vaccine (see section 5.1 for more information on the H5N1 vaccines) in approximately 3700 subjects (ranging in age groups from 18 to 59 years and 60 years and above) and special risk groups of approximately 300 subjects each, consisting of immunocompromised subjects and patients with chronic disease conditions. The adverse reactions observed are shown in the table below.

The safety profile in immunocompromised subjects and patients with chronic disease conditions is similar to the safety profile in healthy adults and older people.

- Infants, children, and adolescents

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

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

The observed adverse reactions from a paediatric clinical trial with the H5N1 vaccine are listed below.

b) Tabulated list of adverse reactions

Adverse reactions are listed according to the following frequency:
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)

| Adverse Reactions (adults and older people) | | |
|---|---|---|
| System Organ Class (SOC) | Preferred MedDRA Term | Frequency |
| INFECTIONS AND INFESTATIONS | Nasopharyngitis | Common |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | Lymphadenopathy | Uncommon |
| PSYCHIATRIC DISORDERS | Insomnia | Uncommon |
| NERVOUS SYSTEM DISORDERS | Headache | Very common |
| | Dizziness | Uncommon |
| | Somnolence | Uncommon |
| | Sensory disturbance (paresthesia, dysesthesia, oral dysesthesia, hypoesthesia, dysgeusia, and burning sensation) | Common |
| | Syncope | Uncommon |
| EYE DISORDERS | Conjunctivitis | Uncommon |
| | Eye irritation | Uncommon |
| EAR AND LABYRINTH DISORDERS | Vertigo | Common |
| | Ear pain | Uncommon |
| | Sudden hearing loss | Uncommon |
| VASCULAR DISORDERS | Hypotension | Uncommon |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | Oropharyngeal pain | Common |
| | Cough | Common |
| | Dyspnea | Uncommon |
| | Nasal congestion | Uncommon |
| | Rhinorrhea | Uncommon |
| | Dry throat | Uncommon |
| GASTROINTESTINAL DISORDERS | Diarrhea | Common |
| | Vomiting | Uncommon |
| | Nausea | Uncommon |
| | Abdominal pain | Uncommon |
| | Dyspepsia | Uncommon |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | Hyperhidrosis | Common |
| | Pruritis | Common |
| | Rash | Uncommon |
| | Urticaria | Uncommon |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | Arthralgia | Common |
| | Myalgia | Common |

| Adverse Reactions (adults and older people) | | |
|---|---|---|
| System Organ Class (SOC) | Preferred MedDRA Term | Frequency |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | Fatigue | Very Common |
| | Pyrexia | Common |
| | Chills | Common |
| | Malaise | Common |
| | Influenza-like illness | Uncommon |
| | Chest discomfort | Uncommon |
| | Injection Site Reactions | |
| | • Injection site pain | Very Common |
| | • Injection site induration | Common |
| | • Injection site eyrthema | Common |
| | • Injection site swelling | Common |
| | • Injection site hemorrhage | Common |
| | • Injection site irritation | Uncommon |
| | • Injection site pruritus | Uncommon |
| | • Injection site movement impairment | Uncommon |

| Adverse Reactions (infants, children and adolescents) | | | | |
|---|---|---|---|---|
| System Organ Class (SOC) | Preferred MedDRA Term | Frequency | | |
| | | 6 – 35 months | 3 – 8 years | 9 – 17 years |
| INFECTIONS AND INFESTATIONS | Nasopharyngitis | Common | Common | Common |
| METABOLISM AND NUTRITION DISORDERS | Decreased appetite | Common | Uncommon | Uncommon |
| PSYCHIATRIC DISORDERS | Insomnia | - | - | Uncommon |
| | Sleep disorder | Common | - | - |
| NERVOUS SYSTEM DISORDERS | Dizziness | - | - | Uncommon |
| | Headache | - | Common | Very Common |
| | Crying | Common | - | - |
| | Somnolence | Very Common | - | - |
| | Hypoaesthesia | - | - | Uncommon |
| EYE DISORDERs | Eye irritation | - | Uncommon | - |
| EAR AND LABYRINTH DISORDERS | Vertigo | - | - | Uncommon |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | Cough | - | Uncommon | Uncommon |
| | Oropharyngeal pain | - | Common | Common |
| | Rhinorrhoea | - | Uncommon | Uncommon |
| GASTROINTESTINAL DISORDERS | Abdominal pain | - | - | Common |
| | Nausea | Common | Common | Common |
| | Vomiting | Common | Common | Common |
| | Diarrhoea | Common | Uncommon | Uncommon |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | Hyperhidrosis | Common | Uncommon | Common |
| | Pruritus | - | - | Uncommon |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | Arthralgia | - | Common | Common |
| | Myalgia | - | Common | Common |
| | Pain in extremity | - | - | Uncommon |

| Adverse Reactions (infants, children and adolescents) | | | | |
|---|---|---|---|---|
| System Organ Class (SOC) | Preferred MedDRA Term | Frequency | | |
| | | 6 – 35 months | 3 – 8 years | 9 – 17 years |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | Injection site pain | Very common | Very common | Very common |
| | Injection site induration | Common | Common | Common |
| | Injection site erythema | Common | Common | Common |
| | Injection site swelling | Common | Common | Common |
| | Injection site hemorrhage | Common | Common | Uncommon |
| | Injection site pruritus | - | Uncommon | Uncommon |
| | Axillary pain | - | Uncommon | Uncommon |
| | Fatigue | - | Common | Common |
| | Pyrexia | Very Common | Common | Uncommon |
| | Chills | - | - | Common |
| | Irritability | Very Common | - | |
| | Malaise | - | Common | Common |
| | Feeling Cold | - | Uncommon | Uncommon |

- Post-marketing surveillance

There are no post-marketing surveillance data available for VEPACEL.

Celvapan (H1N1)v
From post-marketing surveillance with a whole virion, Vero cell derived, H1N1 vaccine, the following adverse reactions have been reported (the frequency of these adverse reactions is not known as it cannot be estimated from the available data):

Immune system disorders: anaphylactic reaction, hypersensitivity
Nervous system disorders: febrile convulsion
Skin and subcutaneous tissue disorders: angioedema
Muscoluskeletal and connective tissue disorders: pain in extremity

Trivalent seasonal influenza vaccines
The following serious adverse reactions have been reported from post-marketing surveillance with egg-derived interpandemic trivalent vaccines:

Uncommon: generalised skin reactions
Rare: neuralgia, transient thrombocytopenia. 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.

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 for VEPACEL.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This section describes the clinical experience with the H5N1 vaccine.

Pandemic and Pre-pandemic 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 H5N1 vaccines will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with H5N1 vaccines are relevant for the pandemic and pre-pandemic vaccines.

Adults, older people, and special risk groups
*Immune response against A/Vietnam/1203/2004 (H5N1)*
The immunogenicity of the A/Vietnam/1203/2004 strain vaccine has been evaluated in three clinical studies in adults aged 18 – 59 years (N=961) and in two clinical studies in subjects aged 60 years and older (N=391) following a 0, 21 day schedule. In addition, the immunogenicity has also been evaluated in a Phase 3 study in specified risk groups of immunocompromised subjects (N=122) and patients with chronic disease conditions (N=123) following a 0, 21 day schedule.

*Immunogenicity in adults aged 18 to 59 years (N=961) and in subjects aged 60 years and older (N=391)*

After primary vaccination the rate of subjects with neutralising antibody titres > 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in older people aged 60 years and above were as follows:

| | 18 – 59 years 21 Days after | | 60 years and above 21 Days after | |
|---|---|---|---|---|
| | 1st Dose | 2nd Dose | 1st Dose | 2nd Dose |
| Seroneutralisation rate* | 44.4% | 69.7% | 51.9% | 69.2% |
| Seroconversion rate** | 32.7% | 56.0% | 13.3% | 23.9% |
| Seroconversion factor*** | 3.0 | 4.5 | 2.0 | 2.6 |

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

*Immunogenicity in immunocompromised subjects (N=122) and patients with chronic disease conditions (N=123)*

After vaccination the rate of subjects with neutralising antibody titres ≥ 20, seroconversion rate and seroconversion factor as measured by MN assay in immunocompromised subjects and patients with chronic disease conditions were as follows:

| | Immunocompromised subjects 21 Days after | | Patients with chronic disease conditions 21 Days after | |
|---|---|---|---|---|
| | 1st Dose | 2nd Dose | 1st Dose | 2nd Dose |
| Seroneutralisation rate* | 24.8% | 41.5% | 44.3% | 64.2% |
| Seroconversion rate** | 9.1% | 32.2% | 17.2% | 35.0% |
| Seroconversion factor*** | 1.6 | 2.5 | 2.3 | 3.0 |

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

*Cross-reactive immune response against related H5N1 strains*

In a clinical study in adults aged 18 to 59 years (N=265) and in older people aged 60 years and above (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 |
|---|---|---|
| | Strain A/Indonesia/05/2005 | |
| | 21 Days after 2nd Dose | 21 Days after 2nd Dose |
| Seroneutralisation rate* | 35.1% | 54.8% |

* MN titre ≥ 20

*Heterologous booster vaccinations*

A heterologous booster vaccination with a 7.5 µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered in a time frame of 12 to 24 months after priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in three clinical studies in adults aged 18 to 59 years and in older people aged 60 years and above. A 12 to 24 months heterologous booster has also been administered in a phase 3 study in immunocompromised subjects and patients with chronic disease conditions.

Seroneutralisation rates (MN titre ≥ 20) at 21 days after a 12 to 24 months booster vaccination with the 7.5 µg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

| Seroneutralisation rate* | 18 – 59 years | | 60 years and above | |
|---|---|---|---|---|
| Tested against | A/Vietnam | A/Indonesia | A/Vietnam | A/Indonesia |
| 12 – 24 months booster | 89.8% | 86.9% | 82.9% | 75.3% |

* MN titre ≥ 20

| Seroneutralisation rate* | Immunocompromised subjects | | Patients with chronic disease conditions | |
|---|---|---|---|---|
| Tested against | A/Vietnam | A/Indonesia | A/Vietnam | A/Indonesia |
| 12 – 24 months booster | 71.6% | 65.7% | 77.5% | 70.8% |

* MN titre ≥ 20

A booster with a 7.5 µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine administered 12 months after a single dose priming vaccination with the A/Vietnam/1203/2004 strain vaccine was also evaluated in adults aged 18 to 59 years.

Seroneutralisation rates (MN titre ≥ 20) at 21 days after a 12 months booster vaccination with the 7.5 µg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

| Seroneutralisation rate* | | |
|---|---|---|
| Tested against | A/Vietnam | A/Indonesia |
| 12 Month Booster | 85.9% | 92.9% |

* MN titre ≥ 20

Infants, children, and adolescents

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

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

After vaccination, the rate of subjects with neutralizing antibody titers ≥ 20, seroconversion rate and seroconversion factor, as measured by MN assay, in infants, children, and adolescents aged 6 months to 17 years were as follows:

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

* MN titer ≥ 20
** ≥ 4-fold increase in MN titer
*** geometric mean increase

*Heterologous Booster Vaccinations*

A heterologous booster vaccination with a 7.5 µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered 12 months after a priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in children and adolescents aged 9 to 17 years (N=196), children aged 3 to 8 years (N=79) and infants and children aged 6 months to 35 months (N=26).

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

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

* MN titer ≥ 20

Information from non-clinical studies
The protective efficacy of VEPACEL 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.

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 survival, reduced weight loss, a less pronounced and shorter increase in temperature, a less marked reduction in lymphocyte counts and in reduction of inflammation and necrosis in brain and olfactory bulb in the vaccinated cohorts as compared to control animals. All control animals succumbed to the infection.



## 5.2 Pharmacokinetic properties

Not applicable.

## 5.3 Preclinical safety data

Non-clinical studies demonstrated minor alterations in liver enzymes and calcium levels in a repeat dose toxicity study in rats. Clinically significant alterations in liver enzymes and calcium levels have not been seen to date in human clinical studies.

Animal reproductive and developmental 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

2 years

After first opening, the vaccine 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 to 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.
Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

The vaccine contains 10 doses of 0.5 ml.
Each dose of 0.5 ml is withdrawn into a syringe for injection.

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

## 7. MARKETING AUTHORISATION HOLDER

Ology Bioservices Ireland LTD
Wilton Park House
Wilton Place
Dublin 2
D02P447
Ireland

## 8. MARKETING AUTHORISATION NUMBER

EU/1/12/752/001

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

Date of first authorisation: 17/02/2012
Date of latest renewal: 04/01/2017

## 10. DATE OF REVISION OF THE TEXT

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

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

VEPACEL suspension for injection in pre-filled syringe
Prepandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Influenza virus (whole virion, inactivated), containing antigen* of strain:
A/Vietnam/1203/2004 (H5N1) 7.5 micrograms**

* produced in Vero cells
** haemagglutinin

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

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Suspension for injection.
Clear to opalescent suspension.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Active immunisation against H5N1 subtype of influenza A virus.

This indication is based on immunogenicity data from subjects from the age of 6 months onwards following administration of two doses of vaccine prepared with H5N1 subtype strains (see section 5.1).

The use of this vaccine should be in accordance with official recommendations.

### 4.2 Posology and method of administration

Posology
Adults and children from 6 months onwards:
One dose of 0.5 ml at an elected date.
A second dose of 0.5 ml should be given after an interval of at least three weeks.

*other paediatric Population*
No data is available on the safety and efficacy of VEPACEL in children younger than 6 months of age.

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

See section 6.6. for administration instructions.

## 4.3 Contraindications

History of anaphylactic reactions to the active substance, or to any of the excipients listed in section 6.1, or trace residues (formaldehyde, benzonase, sucrose, trypsin, Vero host cell protein).
If vaccination is considered necessary, facilities for resuscitation should be immediately available in case of need (see section 4.4).

## 4.4 Special warnings and precautions for use

This vaccine may contain traces of formaldehyde, benzonase, sucrose, trypsin and Vero host cell protein, which are used during the manufacturing process. Therefore, hypersensitivity reactions may occur.

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.

Hypersensitivity reactions, including anaphylaxis, have been reported following use of a similar whole virion, Vero cell derived H1N1 influenza vaccine administered during a pandemic period. Such reactions have occurred both in patients with a history of multiple allergies and in patients with no known allergy.

Immunisation shall be postponed in patients with severe febrile illness or acute infection.

VEPACEL must not be administered intravascularly.

There are no data with VEPACEL 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 bleeding.

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

A protective immune response may not be induced in all individuals receiving the vaccine (see section 5.1).

## 4.5 Interaction with other medicinal products and other forms of interaction

There are no data on co-administration of VEPACEL with 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 VEPACEL unless it is necessary during a medical emergency to provide immediate protection. If necessary, VEPACEL may be given at the same time as normal or specific immunoglobulin into separate limbs.

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

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 VEPACEL in pregnancy and lactation has not been assessed in clinical trials.

Animal 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 fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).

Healthcare providers should carefully consider the potential risks and benefits for each specific patient before prescribing VEPACEL.

The use of VEPACEL during pregnancy and lactation may be considered in a pre-pandemic situation, taking into account official recommendations.

## 4.7 Effects on ability to drive and use machines

VEPACEL has minor influence on the ability to drive and use machines.

## 4.8 Undesirable effects

a) Summary of safety profile

- Adults, older people, and special risk groups

Clinical trials were conducted with the H5N1 vaccine (see section 5.1 for more information on the H5N1 vaccines) in approximately 3700 subjects (ranging in age groups from 18 to 59 years and 60 years and above) and special risk groups of approximately 300 subjects each, consisting of immunocompromised subjects and patients with chronic disease conditions. The adverse reactions observed are shown in the table below.

The safety profile in immunocompromised subjects and patients with chronic disease conditions is similar to the safety profile in healthy adults and older people.

- Infants, children, and adolescents

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

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

The observed adverse reactions from a paediatric clinical trial with the H5N1 vaccine are listed below.

b) Tabulated list of adverse reactions

Adverse reactions are listed according to the following frequency:
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)

| Adverse Reactions (adults and older people) | | |
|---|---|---|
| System Organ Class (SOC) | Preferred MedDRA Term | Frequency |
| INFECTIONS AND INFESTATIONS | Nasopharyngitis | Common |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | Lymphadenopathy | Uncommon |
| PSYCHIATRIC DISORDERS | Insomnia | Uncommon |
| NERVOUS SYSTEM DISORDERS | Headache | Very common |
| | Dizziness | Uncommon |
| | Somnolence | Uncommon |
| | Sensory disturbance (paresthesia, dysesthesia, oral dysesthesia, hypoesthesia, dysgeusia, and burning sensation) | Common |
| | Syncope | Uncommon |
| EYE DISORDERS | Conjunctivitis | Uncommon |
| | Eye irritation | Uncommon |
| EAR AND LABYRINTH DISORDERS | Vertigo | Common |
| | Ear pain | Uncommon |
| | Sudden hearing loss | Uncommon |
| VASCULAR DISORDERS | Hypotension | Uncommon |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | Oropharyngeal pain | Common |
| | Cough | Common |
| | Dyspnea | Uncommon |
| | Nasal congestion | Uncommon |
| | Rhinorrhea | Uncommon |
| | Dry throat | Uncommon |
| GASTROINTESTINAL DISORDERS | Diarrhea | Common |
| | Vomiting | Uncommon |
| | Nausea | Uncommon |
| | Abdominal pain | Uncommon |
| | Dyspepsia | Uncommon |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | Hyperhidrosis | Common |
| | Pruritis | Common |
| | Rash | Uncommon |
| | Urticaria | Uncommon |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | Arthralgia | Common |
| | Myalgia | Common |

| Adverse Reactions (adults and older people) | | |
|---|---|---|
| System Organ Class (SOC) | Preferred MedDRA Term | Frequency |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | Fatigue | Very Common |
| | Pyrexia | Common |
| | Chills | Common |
| | Malaise | Common |
| | Influenza-like illness | Uncommon |
| | Chest discomfort | Uncommon |
| | Injection Site Reactions | |
| | • Injection site pain | Very Common |
| | • Injection site induration | Common |
| | • Injection site eyrthema | Common |
| | • Injection site swelling | Common |
| | • Injection site hemorrhage | Common |
| | • Injection site irritation | Uncommon |
| | • Injection site pruritus | Uncommon |
| | • Injection site movement impairment | Uncommon |

| Adverse Reactions (Infants, children and adolescents) | | | | |
|---|---|---|---|---|
| System Organ Class (SOC) | Preferred MedDRA Term | Frequency | | |
| | | 6 – 35 months | 3 – 8 years | 9 – 17 years |
| INFECTIONS AND INFESTATIONS | Nasopharyngitis | Common | Common | Common |
| METABOLISM AND NUTRITION DISORDERS | Decreased appetite | Common | Uncommon | Uncommon |
| PSYCHIATRIC DISORDERS | Insomnia | - | - | Uncommon |
| | Sleep disorder | Common | - | - |
| NERVOUS SYSTEM DISORDERS | Dizziness | - | - | Uncommon |
| | Headache | - | Common | Very Common |
| | Crying | Common | - | - |
| | Somnolence | Very Common | - | - |
| | Hypoaesthesia | - | - | Uncommon |
| EYE DISORDERs | Eye irritation | - | Uncommon | - |
| EAR AND LABYRINTH DISORDERS | Vertigo | - | - | Uncommon |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | Cough | - | Uncommon | Uncommon |
| | Oropharyngeal pain | - | Common | Common |
| | Rhinorrhoea | - | Uncommon | Uncommon |
| GASTROINTESTINAL DISORDERS | Abdominal pain | - | - | Common |
| | Nausea | Common | Common | Common |
| | Vomiting | Common | Common | Common |
| | Diarrhoea | Common | Uncommon | Uncommon |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | Hyperhidrosis | Common | Uncommon | Common |
| | Pruritus | - | - | Uncommon |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | Arthralgia | - | Common | Common |
| | Myalgia | - | Common | Common |
| | Pain in extremity | - | - | Uncommon |

| Adverse Reactions (Infants, children and adolescents) | | | | |
|---|---|---|---|---|
| System Organ Class (SOC) | Preferred MedDRA Term | Frequency | | |
| | | 6 – 35 months | 3 – 8 years | 9 – 17 years |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | Injection site pain | Very common | Very common | Very common |
| | Injection site induration | Common | Common | Common |
| | Injection site erythema | Common | Common | Common |
| | Injection site swelling | Common | Common | Common |
| | Injection site hemorrhage | Common | Common | Uncommon |
| | Injection site pruritus | - | Uncommon | Uncommon |
| | Axillary pain | - | Uncommon | Uncommon |
| | Fatigue | - | Common | Common |
| | Pyrexia | Very Common | Common | Uncommon |
| | Chills | - | - | Common |
| | Irritability | Very Common | - | |
| | Malaise | - | Common | Common |
| | Feeling Cold | - | Uncommon | Uncommon |

- Post-marketing surveillance

There are no post-marketing surveillance data available for VEPACEL.

Celvapan (H1N1)v
From post-marketing surveillance with a whole virion, Vero cell derived, H1N1 vaccine, the following adverse reactions have been reported (the frequency of these adverse reactions is not known as it cannot be estimated from the available data):

Immune system disorders: anaphylactic reaction, hypersensitivity
Nervous system disorders: febrile convulsion
Skin and subcutaneous tissue disorders: angioedema
Muscoluskeletal and connective tissue disorders: pain in extremity

Trivalent seasonal influenza vaccines
The following serious adverse reactions have been reported from post-marketing surveillance with egg-derived interpandemic trivalent vaccines:

Uncommon: generalised skin reactions
Rare: neuralgia, transient thrombocytopenia. 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.

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 for VEPACEL.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

This section describes the clinical experience with the H5N1 vaccine.

Pandemic and Pre-pandemic 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 H5N1 vaccines will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with H5N1 vaccines are relevant for the pandemic and pre-pandemic vaccines.

Adults, older people, and special risk groups

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

The immunogenicity of the A/Vietnam/1203/2004 strain vaccine has been evaluated in three clinical studies in adults aged 18 – 59 years (N=961) and in two clinical studies in subjects aged 60 years and older (N=391) following a 0, 21 day schedule. In addition, the immunogenicity has also been evaluated in a Phase 3 study in specified risk groups of immunocompromised subjects (N=122) and patients with chronic disease conditions (N=123) following a 0, 21 day schedule.

*Immunogenicity in adults aged 18 to 59 years (N=961) and in subjects aged 60 years and older (N=391)*

After primary vaccination the rate of subjects with neutralising antibody titres > 20, seroconversion rate and seroconversion factor as measured by microneutralisation assay (MN) in adults aged 18 to 59 years and in older people aged 60 years and above were as follows:

| | 18 – 59 years 21 Days after | | 60 years and above 21 Days after | |
|---|---|---|---|---|
| | 1st Dose | 2nd Dose | 1st Dose | 2nd Dose |
| Seroneutralisation rate* | 44.4% | 69.7% | 51.9% | 69.2% |
| Seroconversion rate** | 32.7% | 56.0% | 13.3% | 23.9% |
| Seroconversion factor*** | 3.0 | 4.5 | 2.0 | 2.6 |

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

*Immunogenicity in immunocompromised subjects (N=122) and patients with chronic disease conditions (N=123)*

After vaccination the rate of subjects with neutralising antibody titres ≥ 20, seroconversion rate and seroconversion factor as measured by MN assay in immunocompromised subjects and patients with chronic disease conditions were as follows:

| | Immunocompromised subjects 21 Days after | | Patients with chronic disease conditions 21 Days after | |
|---|---|---|---|---|
| | 1st Dose | 2nd Dose | 1st Dose | 2nd Dose |
| Seroneutralisation rate* | 24.8% | 41.5% | 44.3% | 64.2% |
| Seroconversion rate** | 9.1% | 32.2% | 17.2% | 35.0% |
| Seroconversion factor*** | 1.6 | 2.5 | 2.3 | 3.0 |

* MN titre ≥ 20
** ≥ 4-fold increase in MN titre
*** geometric mean increase

*Cross-reactive immune response against related H5N1 strains*

In a clinical study in adults aged 18 to 59 years (N=265) and in older people aged 60 years and above (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 |
|---|---|---|
| | Strain A/Indonesia/05/2005 | |
| | 21 Days after 2nd Dose | 21 Days after 2nd Dose |
| Seroneutralisation rate* | 35.1% | 54.8% |

* MN titre ≥ 20

*Heterologous booster vaccinations*

A heterologous booster vaccination with a 7.5 µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered in a time frame of 12 to 24 months after priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in three clinical studies in adults aged 18 to 59 years and in older people aged 60 years and above. A 12 to 24 months heterologous booster has also been administered in a phase 3 study in immunocompromised subjects and patients with chronic disease conditions.

Seroneutralisation rates (MN titre ≥ 20) at 21 days after a 12 to 24 months booster vaccination with the 7.5 µg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

| Seroneutralisation rate* | 18 – 59 years | | 60 years and above | |
|---|---|---|---|---|
| Tested against | A/Vietnam | A/Indonesia | A/Vietnam | A/Indonesia |
| 12 – 24 months booster | 89.8% | 86.0% | 82.9% | 75.3% |

* MN titre ≥ 20

| Seroneutralisation rate* | Immunocompromised subjects | | Patients with chronic disease conditions | |
|---|---|---|---|---|
| Tested against | A/Vietnam | A/Indonesia | A/Vietnam | A/Indonesia |
| 12 – 24 months booster | 71.6% | 65.7% | 77.5% | 70.8% |

* MN titre ≥ 20

A booster with a 7.5 µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine administered 12 months after a single dose priming vaccination with the A/Vietnam/1203/2004 strain vaccine was also evaluated in adults aged 18 to 59 years.

Seroneutralisation rates (MN titre ≥ 20) at 21 days after a 12 months booster vaccination with the 7.5 µg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains were as follows:

| Seroneutralisation rate* | | |
|---|---|---|
| Tested against | A/Vietnam | A/Indonesia |
| 12 Month Booster | 85.9% | 92.9% |

* MN titre ≥ 20

Infants, children, and adolescents

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

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

After vaccination, the rate of subjects with neutralizing antibody titers ≥ 20, seroconversion rate and seroconversion factor, as measured by MN assay, in infants, children, and adolescents aged 6 months to 17 years were as follows:

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

* MN titer ≥ 20
** ≥ 4-fold increase in MN titer
*** geometric mean increase

*Heterologous Booster Vaccinations*

A heterologous booster vaccination with a 7.5 µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered 12 months after a priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in children and adolescents aged 9 to 17 years (N=196), children aged 3 to 8 years (N=79) and infants and children aged 6 months to 35 months (N=26).

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

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

* MN titer ≥ 20

Information from non-clinical studies
The protective efficacy of VEPACEL 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.

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 survival, reduced weight loss, a less pronounced and shorter increase in temperature, a less marked reduction in lymphocyte counts and in reduction of inflammation and necrosis in brain and olfactory bulb in the vaccinated cohorts as compared to control animals. All control animals succumbed to the infection.



## 5.2 Pharmacokinetic properties

Not applicable.

## 5.3 Preclinical safety data

Non-clinical studies demonstrated minor alterations in liver enzymes and calcium levels in a repeat dose toxicity study in rats. Clinically significant alterations in liver enzymes and calcium levels have not been seen to date in human clinical studies.

Animal reproductive and developmental 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

2 years

### 6.4 Special precautions for storage

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

### 6.5 Nature and contents of the container

One pack of 1 single dose pre-filled syringe (type I glass) containing 0.5 ml suspension for injection, with a latex-free plunger stopper (halogenated-butyl rubber) without needles.

### 6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use. Shake before use.
Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

After removing the syringe cap, attach the needle immediately and remove the needle shield prior to administration.

Once the needle is attached, the vaccine must be administered immediately.

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



## 7. MARKETING AUTHORISATION HOLDER

Ology Bioservices Ireland LTD
Wilton Park House
Wilton Place
Dublin 2
D02P447
Ireland

## 8. MARKETING AUTHORISATION NUMBER

EU/1/12/752/002

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

Date of first authorisation: 17/02/2012
Date of latest renewal: 04/01/2017

## 10. DATE OF REVISION OF THE TEXT

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

**ANNEX II**

**A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) 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 manufacturer(s) 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

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

- **Official batch release**

In accordance with Article 114 of 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 AUTHORISATION

- **Periodic Safety Update Reports**

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

PSUR submission when VEPACEL is used during an 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 and the prepandemic vaccine is used, the MAH shall submit more frequent simplified periodic safety update reports with a format and a periodicity defined in the "CHMP Recommendations for the Core Risk Management Plan for Influenza Vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context" (EMEA/49993/2008), and any subsequent update.

## 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.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON – 10 DOSE VIAL**

## 1. NAME OF THE MEDICINAL PRODUCT

VEPACEL suspension for injection in multidose container
Prepandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:

Influenza virus (whole virion, inactivated) containing antigen of strain :
A/Vietnam/1203/2004 (H5N1) 7.5 micrograms

## 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 of 0.5 ml per vial)

## 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 vaccine should be used immediately (within 3 hours maximum).

## 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

## 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

Ology Bioservices Ireland LTD
Wilton Park House
Wilton Place
Dublin 2
D02P447
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/752/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON – PRE-FILLED SYRINGE**

## 1. NAME OF THE MEDICINAL PRODUCT

VEPACEL suspension for injection in a pre-filled syringe
Prepandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:

Influenza virus (whole virion, inactivated) containing antigen of strain:
A/Vietnam/1203/2004 (H5N1) 7.5 micrograms

## 3. LIST OF EXCIPIENTS

Trometamol
Sodium Chloride
Water for injections
Polysorbate 80

## 4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 pre-filled syringe (0.5 ml)

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 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

Ology Bioservices Ireland LTD
Wilton Park House
Wilton Place
Dublin 2
D02P447
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/752/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 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

VEPACEL suspension for injection
Prepandemic influenza vaccine (H5N1)
I.M.

## 2. METHOD OF ADMINISTRATION

Shake before use

## 3. EXPIRY DATE

EXP
After first opening, use immediately (within 3 hours max)

## 4. BATCH NUMBER

Lot

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

Multidose vial (10 doses of 0.5 ml)

## 6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL - SINGLE DOSE PRE-FILLED SYRINGE**

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

VEPACEL suspension for injection
Prepandemic influenza vaccine (H5N1)
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

Pre-filled syringe (0.5ml)

## 6. OTHER

**MINIMUM PARTICULARS ATTACHED TO THE OUTER CARTON OF MULTIDOSE CONTAINER AND PRE-FILLED SYRINGE**

**PEEL OFF´S (1 PEEL OFF PER DOSIS)**

**1. NAME OF THE MEDICINAL PRODUCT**

VEPACEL

**2. ACTIVE SUBSTANCE**

A/Vietnam/1203/2004 (H5N1)

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Ology Bioservices Ireland Ltd Logo

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the user**
**VEPACEL suspension for injection**
Prepandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**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 of the 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 VEPACEL is and what it is used for
2. What you need to know before you receive VEPACEL
3. How VEPACEL is given
4. Possible side effects
5. How to store VEPACEL
6. Contents of the pack and other information




## 1. What VEPACEL is and what it is used for

VEPACEL is a vaccine for use in individuals aged 6 months and older. It is intended to be given before the next influenza (flu) pandemic to prevent flu caused by the H5N1 type of the virus.

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 are usually more severe.

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

As with all vaccines, VEPACEL may not fully protect all persons who are vaccinated.

## 2. What you need to know before you receive VEPACEL

**You should not receive VEPACEL**

- if you have previously had a severe allergic reaction to any ingredient of VEPACEL (these are listed at the end of the leaflet – section 6) or to any substances that may be present in trace (very low) amounts: formaldehyde, benzonase, sucrose, trypsin, Vero host cell protein.
  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.

**Warnings and precautions**

You should tell your doctor before vaccination:
- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be problem, but your doctor should advise whether you could still be vaccinated with VEPACEL.
- if you have had any allergic reaction to any ingredient of the vaccine (see section 6 at the end of the leaflet) or trace residues (formaldehyde, benzonase, sucrose, trypsin, Vero host cell protein). Allergic reactions, including sudden life-threatening allergic reactions (anaphylaxis) have been reported following use of a similar vaccine for H1N1 influenza during a pandemic period. Such reactions have occurred both in patients with a history of multiple allergies and in patients with no known allergy.
- if you have a weakened immune system as for example because of immunosuppressive therapy, e.g. taking of corticosteroids or treatment for cancer.
- if you have a bleeding problem or bruise easily.

If you need a blood test to look for evidence of infection with certain viruses in the first few weeks after vaccination with VEPACEL, the result of the test may not be correct. Tell the doctor requesting the test that you have recently received VEPACEL.

The vaccine should never be given into a blood vessel.

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

**Other medicines and VEPACEL**

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

There is no information on administration of VEPACEL with other vaccines. However, if this cannot be avoided, the other vaccine should not be injected into the same arm used for VEPACEL.
You should be aware that side effects may be intensified.

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

VEPACEL should not be given at the same time as immunoglobulins. However, if this cannot be avoided, the immunoglobulins should not be injected into the same arm used for VEPACEL.

**Pregnancy, breast-feeding**

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

**Driving and using machines**

VEPACEL may affect your ability to drive and use machines.

## 3. How VEPACEL is given

Your doctor or nurse will administer the vaccine in accordance with official recommendations. The vaccine will be injected into the muscle of the upper arm (deltoid muscle) or upper thigh, depending on the muscle mass. The vaccine should never be given into a vein.

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

## 4. Possible side effects

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

In the clinical studies conducted in adults and older people most side effects were mild in nature and short term. The side effects are generally similar to those related to the 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 following side effects have been reported in clinical studies in adults and older people.

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

Common (affects 1 to 10 users in 100):
- runny nose and sore throat
- vertigo (a spinning sensation)
- pain in mouth and throat
- cough
- diarrhoea
- increased sweating
- itching
- pain in joint or muscle
- fever
- chills
- malaise (generally feeling unwell)
- hardness, redness, swelling or bruising at the injection site
- abnormal, reduced sensation

Uncommon (affects 1 to 10 users in 1,000):
- swollen glands
- insomnia (difficulty sleeping)
- dizziness
- sleepiness
- conjunctivitis (an inflammation of the eye), eye irritation
- ear pain
- reduced blood pressure, feeling faint (syncope)
- shortness of breath
- stuffy or runny nose
- dry throat
- vomiting

- feeling sick
- stomach pain, upset stomach
- rash, hives
- chest discomfort
- flu-like illness
- injection-site reaction such as irritation, itching, bruising or stiff arm
- sudden hearing loss

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

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

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

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

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

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

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

Uncommon (affects 1 to 10 users in 1,000):
- decreased appetite
- eye irritation
- cough
- runny nose
- diarrhoea
- increased sweating

- itching where the injection was given
- pain in the armpit
- feeling cold

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

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

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

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

There are no post-marketing data available for VEPACEL.

Side effects observed with a similar influenza vaccine (Celvapan)
The side effects listed below have occurred with a similar influenza vaccine (Celvapan) in adults and children during the H1N1 pandemic flu vaccination programme:
- allergic reactions, including anaphylactic reactions leading to a dangerous decrease in blood pressure which, if untreated, may lead to shock
- fits due to fever
- pain in arms and/or legs (in the majority of cases reported as pain in the vaccination arm)
- swelling of tissue just below the skin

Side effects observed with flu vaccines given routinely every year
In the days or weeks after vaccination with vaccines given routinely every year to prevent flu, the side effects listed below have occurred. These side effects may occur with VEPACEL.

Uncommon (affects 1 to 10 users in 1,000):
- generalised skin reactions including urticaria (hives)

Rare (affects 1 to 10 users in 10,000):
- 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.
- severe stabbing or throbbing pain along one or more nerves
- low blood platelet count which can result in bleeding or bruising

Very rare (affects less than 1 user in 10,000):
- 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

**Reporting of side effects**
If you get any side effects talk to your doctor or nurse. 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 VEPACEL

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

Do not use this medicine after the expiry date which is stated on the carton and the label. 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 vaccine should be used immediately (within a maximum period of 3 hours).

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

## 6. Contents of the pack and other information

**What VEPACEL contains**

- The active substance is:
  1 dose (0.5 ml) contains:
  Influenza virus (whole virion, inactivated), containing antigen of*strain:
  A/Vietnam/1203/2004 (H5N1) 7.5 micrograms**
  * produced in Vero cells
  ** haemagglutinin

- The other ingredients are
  Trometamol
  Sodium chloride
  Water for injections
  Polysorbate 80.

**What VEPACEL looks like and contents of the pack**

VEPACEL is presented as a suspension for injection in multidose vial (10 doses of 0.5 ml per vial) in pack size of 20 vials.

The suspension is clear to opalescent.

**Marketing Authorisation Holder**

Ology Bioservices Ireland LTD
Wilton Park House
Wilton Place
Dublin 2
D02P447
Ireland

**Manufacturer**

Baxter AG
Uferstrasse 15
A-2304 Orth/Donau
Austria

**This leaflet was last revised in**

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

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The following information is intended for healthcare professionals only:

Multidose vial (10 doses of 0.5 ml per vial)

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

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

The vaccine should not be administered intravascularly.

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

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

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

**Package leaflet: Information for the user**
**VEPACEL suspension for injection**
Prepandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**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 of the 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 VEPACEL is and what it is used for
2. What you need to know before you receive VEPACEL
3. How VEPACEL is given
4. Possible side effects
5. How to store VEPACEL
6. Contents of the pack and other information




## 1. What VEPACEL is and what it is used for

VEPACEL is a vaccine for use in individuals aged 6 months and older. It is intended to be given before the next influenza (flu) pandemic to prevent flu caused by the H5N1 type of the virus.

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 are usually more severe.

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

As with all vaccines, VEPACEL may not fully protect all persons who are vaccinated.

## 2. What you need to know before you receive VEPACEL

**You should not receive VEPACEL**

- if you have previously had a severe allergic reaction to any ingredient of VEPACEL (these are listed at the end of the leaflet – section 6) or to any substances that may be present in trace (very low) amounts: formaldehyde, benzonase, sucrose, trypsin, Vero host cell protein.
  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.

**Warnings and precautions**

You should tell your doctor before vaccination:
- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be problem, but your doctor should advise whether you could still be vaccinated with VEPACEL.
- if you have had any allergic reaction to any ingredient of the vaccine (see section 6 at the end of the leaflet) or trace residues (formaldehyde, benzonase, sucrose, trypsin, Vero host cell protein). Allergic reactions, including sudden life-threatening allergic reactions (anaphylaxis) have been reported following use of a similar vaccine for H1N1 influenza during a pandemic period. Such reactions have occurred both in patients with a history of multiple allergies and in patients with no known allergy.
- if you have a weakened immune system as for example because of immunosuppressive therapy, e.g. taking of corticosteroids or treatment for cancer.
- if you have a bleeding problem or bruise easily.

If you need a blood test to look for evidence of infection with certain viruses in the first few weeks after vaccination with VEPACEL, the result of the test may not be correct. Tell the doctor requesting the test that you have recently received VEPACEL.

The vaccine should never be given into a blood vessel.
There is no information on the use of VEPACEL under the skin.

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

**Other medicines and VEPACEL**

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

There is no information on administration of VEPACEL with other vaccines. However, if this cannot be avoided, the other vaccine should not be injected into the same arm used for VEPACEL.
You should be aware that side effects may be intensified.

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

VEPACEL should not be given at the same time as immunoglobulins. However, if this cannot be avoided, the immunoglobulins should not be injected into the same arm used for VEPACEL.

**Pregnancy, breast-feeding and fertility**

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

**Driving and using machines**

VEPACEL may affect your ability to drive and use machines.

## 3. How VEPACEL is given

Your doctor or nurse will administer the vaccine in accordance with official recommendations. The vaccine will be injected into the muscle of the upper arm (deltoid muscle) or upper thigh, depending on the muscle mass. The vaccine should never be given into a vein.

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

## 4. Possible side effects

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

In the clinical studies conducted in adults and older people most side effects were mild in nature and short term. The side effects are generally similar to those related to the 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 following side effects have been reported in clinical studies in adults and older people

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

Common (affects 1 to 10 users in 100):
- runny nose and sore throat
- vertigo (a spinning sensation)
- pain in mouth and throat
- cough
- diarrhoea
- increased sweating
- itching
- pain in joint or muscle
- fever
- chills
- malaise (generally feeling unwell)
- hardness, redness, swelling or bruising at the injection site
- abnormal, reduced sensation

Uncommon (affects 1 to 10 users in 1,000):
- swollen glands
- insomnia (difficulty sleeping)
- dizziness
- sleepiness
- conjunctivitis (an inflammation of the eye), eye irritation
- ear pain
- reduced blood pressure, feeling faint (syncope)
- shortness of breath
- stuffy nose
- dry throat
- vomiting

- feeling sick
- stomach pain, upset stomach
- rash, hives
- chest discomfort
- flu-like illness
- injection-site reaction such as irritation, itching, bruising or stiff arm
- sudden hearing loss

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

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

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

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

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

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

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

Uncommon (affects 1 to 10 users in 1,000):
- decreased appetite
- eye irritation
- cough
- runny nose
- diarrhoea
- increased sweating

- itching where the injection was given
- pain in the armpit
- feeling cold

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

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

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

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

There are no post-marketing data available for VEPACEL.

Side effects observed with a similar influenza vaccine (Celvapan)
The side effects listed below have occurred with a similar influenza vaccine (Celvapan) in adults and children during the H1N1 pandemic flu vaccination programme:
- allergic reactions, including anaphylactic reactions leading to a dangerous decrease in blood pressure which, if untreated, may lead to shock
- fits due to fever
- pain in arms and/or legs (in the majority of cases reported as pain in the vaccination arm)
- swelling of tissue just below the skin

Side effects observed with flu vaccines given routinely every year
In the days or weeks after vaccination with vaccines given routinely every year to prevent flu, the side effects listed below have occurred. These side effects may occur with VEPACEL.

Uncommon (affects 1 to 10 users in 1,000):
- generalised skin reactions including urticaria (hives)

Rare (affects 1 to 10 users in 10,000):
- 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.
- severe stabbing or throbbing pain along one or more nerves
- low blood platelet count which can result in bleeding or bruising

Very rare (affects less than 1 user in 10,000):
- 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

**Reporting of side effects**
If you get any side effects talk to your doctor or nurse. 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 VEPACEL

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

Do not use this medicine after the expiry date which is stated on the carton and the label. The expiry date refers to the last day of that month.

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

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

## 6. Contents of the pack and other information

**What VEPACEL contains**

- The active substance is:
  One dose (0.5 ml) contains:
  Influenza virus (whole virion, inactivated), containing antigen of*strain :
  A/Vietnam/1203/2004 (H5N1) 7.5 micrograms**
  * produced in Vero cells
  ** haemagglutinin

- The other ingredients are
  Trometamol
  Sodium chloride
  Water for injections
  Polysorbate 80.

**What VEPACEL looks like and contents of the pack**

VEPACEL is presented as a suspension for injection in a pre-filled syringe.

1 pack of a pre-filled syringe containing a single dose of 0.5 ml suspension for injection with a latex-free plunger (halogeno-butyl-rubber) without needles.

The suspension is clear to opalescent.

**Marketing Authorisation Holder**

Ology Bioservices Ireland LTD
Wilton Park House
Wilton Place
Dublin 2
D02P447
Ireland

**Manufacturer**

Baxter AG
Uferstrasse 15
A-2304 Orth/Donau
Austria

**This leaflet was last revised in May 2015**

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

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The following information is intended for healthcare professionals only:

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

After shaking, the vaccine is a clear to opalescent suspension.

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

The vaccine should not be administered intravascularly.

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

After removing the syringe cap, attach the needle immediately and remove the needle shield prior to administration.

Once the needle is attached, the vaccine must be administered immediately.