Baxter

0000272

1. NAME OF THE MEDICINAL PRODUCT

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER

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)	7.5 micrograms**

per 0.5 ml dose

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

This vaccine complies with the WHO recommendation and EU decision for the pandemic.
This is a multidose container. See section 6.5 for the number of doses per vial.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
The vaccine is an off-white, opalescent, translucent suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance.
PANDEMIC INFLUENZA VACCINE H5N1 BAXTER 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 PANDEMIC INFLUENZA VACCINE H5N1 BAXTER 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, benzonase, 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 administrating this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance(s), to any of the excipients and to trace residues e.g. formaldehyde, benzonase, or sucrose.
As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.
If the pandemic situation allows, immunisation shall be postponed in patients with severe febrile illness or acute infection.
PANDEMIC INFLUENZA VACCINE H5N1 BAXTER should under no circumstances be administered intravascularly.
There are no data with PANDEMIC INFLUENZA VACCINE H5N1 BAXTER 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

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER 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 PANDEMIC INFLUENZA VACCINE H5N1 BAXTER. If it is necessary to provide immediate protection, PANDEMIC INFLUENZA VACCINE H5N1 BAXTER may be given at the same time as normal or specific immunoglobulin. Injections of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER 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 PANDEMIC INFLUENZA VACCINE H5N1 BAXTER 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 (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000).

Not known (cannot be estimated from the available data)

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 interpandemic trivalent vaccines, the following serious adverse reactions have been reported:

Uncommon:

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

Rare:

Neuralgia, paraesthesia, convulsions, transient thrombocytopenia.

Allergic reactions, in rare cases leading to shock, have been reported.

Very rare:

Vasculitis with transient renal involvement.

Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB01

PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been authorised under “exceptional circumstances”. This means that for scientific reasons, it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary.

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 PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (A/Vietnam/1203/2004)

The immunogenicity of the 7.5 µg non-adjuvanted formulation of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (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	
	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroprotection rate*	55.5%	65.4%	57.9%	67.7%
Seroconversion rate**	51.3%	62.1%	52.4%	62.4%
Seroconversion factor***	3.7	4.8	3.6	4.6

* SRH area > 25 mm²
** either SRH area ≥ 25 mm² if baseline sample negative or 50% increase in SRH area if baseline sample > 4 mm²
*** geometric mean increase

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

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

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

Cross-reactive Immune Response Against Related H5N1 Strains

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

	18 – 59 years		60 years and above	
	Day 42 [a]	Day 180	Day 42 [a]	Day 180
Tested against	Strain A/Indonesia/05/2005			
Seroneutralisation rate*	35.1%	14.4%	54.8%	28.0%

* MN titre > 20
[a] 21 days after 2nd dose

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

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

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

Antibody Persistence and Booster Vaccination with Homologous and Heterologous Vaccine Strains

Antibody persistence after vaccination with the 7.5 µg non-adjuvanted formulation of PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (strain A/Vietnam/1203/2004) has been evaluated in two clinical studies in adults aged 18 – 59 years (N=285) and in one clinical study in elderly subjects aged 60 years and above (N=258) up to 6 months after the start of the primary vaccination series. The results indicate an overall decline in antibody levels over time. Data on later time points (months 12 and 24) are not yet available.

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

* SRH area ≥ 25 mm²
** MN titre ≥ 20

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

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

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

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

* MN titer ≥ 1:20

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

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

Information from non-clinical studies

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

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

In a second study, sixty-six ferrets were divided into 6 cohorts of 11 ferrets and were immunized on days 0 and 21 with 3.75 µg or 7.5 µg of the Indonesia vaccine or were sham vaccinated. The ferrets were challenged intranasally on day 35 with a high dose of either the clade 2 H5N1 virus A/Indonesia/05/2005 or the clade 1 H5N1 virus A/Vietnam/1203/2004 and monitored for 14 days. The A/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

12 months

After first opening, the product should be used immediately, or within 3 hours at controlled room temperature (up to 25°C), or whichever is less.

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. The rubber stopper should not be removed from the vial for withdrawal of the individual doses by sterile syringes.

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

7. PRODUCT OWNER

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8. DATE OF REVISION OF THE TEXT

March 2012