ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pumarix suspension and emulsion for emulsion for injection
Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After mixing, 1 dose (0.5 ml) contains:

Split influenza virus, inactivated, containing antigen* equivalent to:

A/Indonesia/05/2005 (H5N1) like strain used (PR8-IBCDC-RG2) 3.75 micrograms**

* propagated in eggs
** haemagglutinin

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

AS03 adjuvant composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)

The suspension and emulsion, once mixed, form a multidose vaccine in a vial. See section 6.5 for the number of doses per vial.

Excipient with known effect: the vaccine contains 5 micrograms thiomersal

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Suspension and emulsion for emulsion for injection.
The suspension is a translucent to off white opalescent suspension, which may sediment slightly.
The emulsion is a whitish homogeneous liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation (see sections 4.2 and 5.1).

Pandemic influenza vaccine should be used in accordance with official guidance.

4.2 Posology and method of administration

Posology

Adults from the age of 18 years 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.

Persons previously vaccinated with one or two doses of AS03-containing vaccine containing HA derived from a different clade of the same subtype

Adults from the age of 18 years onwards: one dose of 0.5 ml at an elected date.

Paediatric population

There are very limited safety and immunogenicity data available on the administration of an AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) manufactured using a different process and on administration of half a dose of the same vaccine (i.e. 1.875 µg HA and half the amount of AS03 adjuvant) at 0 and 21 days in children aged 3 to 9 years. See sections 4.8 and 5.1.

The safety and efficacy of Pumarix in children aged less than 3 years and in children and adolescents aged 10 to 17 years have not been established. No data are available.

For further information, see section 5.1.

It is recommended that subjects who receive a first dose of Pumarix, complete the vaccination course with Pumarix.

Method of administration

Immunisation should be carried out by intramuscular injection preferably into the deltoid muscle or anterolateral thigh (depending on the muscle mass).

For instructions on mixing of the medicinal product before administration, see section 6.6.

4.3 Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (egg and chicken protein, ovalbumin, formaldehyde and sodium deoxycholate) of this vaccine. However, in a pandemic situation, it may be appropriate to give the vaccine provided that facilities for resuscitation should be immediately available in case of need.

4.4 Special warnings and precautions for use

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients listed in section 6.1, to thiomersal and to residues (egg and chicken protein, ovalbumin, formaldehyde and sodium deoxycholate).

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.

Pumarix should under no circumstances be administered intravascularly. There are no data with Pumarix 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.

There are no data on administration of AS03-adjuvanted vaccines before or following other types of influenza vaccines intended for pre-pandemic or pandemic use.

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

A protective immune response may not be elicited in all vaccinees (see section 5.1).

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

Paediatric population

Clinical data in children less than 6 years of age who received two doses of another Pandemic influenza vaccine (H5N1 manufactured in Dresden, Germany) indicate an increase in frequency of fever (axillary≥38°C) after the administration of the second dose. Therefore, monitoring of temperature and measures to lower the fever (such as antipyretic medication as seems clinically necessary) are recommended in young children (e.g. up to approximately 6 years of age) post-vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

There are no data on co-administration of Pumarix with other vaccines. If co-administration with another vaccine is considered, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

Following influenza vaccination, false-positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus and, especially, HTLV-1. In such cases, the Western blot method is negative. These transitory false-positive results may be due to IgM production in response to the vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are currently no data available on the use of Pumarix in pregnancy.

An AS03-containing vaccine containing HA from H1N1v has been administered to women in each trimester of pregnancy. Information on outcomes from estimated more than 200,000 women who have been vaccinated during pregnancy is currently limited. There was no evidence of an increased risk of adverse outcomes in over 100 pregnancies that were followed in a prospective clinical study.

Animal studies with Pumarix do not indicate reproductive toxicity (see section 5.3).

Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or fetal or neonatal toxicity.

The use of Pumarix may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations.

Breast-feeding

Pumarix may be used in lactating women.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

Some of the effects mentioned under section 4.8 “Undesirable Effects” may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Clinical studies have evaluated the incidence of adverse reactions in approximately 4,500 subjects 18 years old and above who received Pumarix or placebo.

In adults 18 to 64 years of age, the most frequently reported adverse reactions after vaccination were injection site pain (80.5%), muscle aches (37.2%), fatigue (25.2%), headache (25.1%), joint pain (17.7%) and shivering (11.1%).

In subjects > 64 years of age, the most frequently reported adverse reactions after vaccination were injection site pain (58.0%), muscle aches (19.7%), fatigue (13.5%), headache (12.4%) and joint pain (10.3%).

List of adverse reactions

Adverse reactions reported are listed according to the following frequency:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

Adverse reactions from clinical trials with the mock-up vaccine are listed here below (see section 5.1 for more information on mock-up vaccines).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
Uncommon: lymphadenopathy

Psychiatric disorders
Uncommon: insomnia

Nervous system disorders
Very common: headache
Uncommon: dizziness, paraesthesia

Ear and labyrinth disorders
Uncommon: vertigo

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea

Gastrointestinal disorders
Common: nausea, diarrhoea
Uncommon: abdominal pain, vomiting, dyspepsia, stomach discomfort

Skin and subcutaneous tissue disorders
Common: sweating
Uncommon: pruritus, rash

Musculoskeletal and connective tissue disorders
Very common: joint pain, muscle aches
Uncommon: back pain, musculoskeletal stiffness, neck pain, muscle spasms, pain in extremity

General disorders and administration site conditions
Very common: pain at the injection site, fatigue
Common: redness at the injection site, swelling at the injection site, fever, shivering
Uncommon: injection site reactions (such as bruising, induration, pruritus, warmth), asthenia, chest pain, malaise

No post-marketing surveillance data are available following Pumarix administration.

From post-marketing experience with AS03-containing vaccines containing 3.75 µg HA derived from A/California/7/2009 (H1N1), the following adverse reactions have been reported:

Immune system disorders
Anaphylaxis, allergic reactions

Nervous system disorders
Febrile convulsions

Skin and subcutaneous tissue disorders
Angioedema, generalised skin reactions, urticaria

In addition, from post-marketing surveillance with interpandemic trivalent vaccines, the following adverse reactions have been reported:

Rare:
Neuralgia, transient thrombocytopenia.

Very rare:
Vasculitis with transient renal involvement.
Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

Paediatric population

A clinical study (D-H5N1-009), evaluated the reactogenicity in children 3 to 5 and 6 to 9 years of age who received either two adult (i.e. 0.5 ml) doses or two half adult (i.e. 0.25 ml) doses (21 days apart) of another Pandemic influenza vaccine (H5N1 A/Vietnam/1194/2004 manufactured in Dresden, Germany).

The per-dose frequency of local and general solicited adverse reactions observed in the groups of children who received two adult (0.5 ml) doses was higher than that observed in the groups of children who received two half adult (i.e. 0.25 ml) doses, except for redness in the 6-9 years of age group. The

administration of a second half adult or an adult dose did not enhance the reactogenicity, except for rates of general symptoms which were higher after the second dose, particularly for rates of fever in <6 year olds. The per-dose frequency of adverse reactions was as follows:

Adverse reactions	3-5 years		6-9 years	
	Half dose	Full dose	Half dose	Full dose
Induration	9.9%	18.6%	12.0%	12.2%
Pain	48.5%	62.9%	68.0%	73.5%
Redness	10.9%	19.6%	13.0%	6.1%
Swelling	11.9%	24.7%	14.0%	20.4%
Fever (>38°C)	4.0%	11.3%	2.0%	17.3%
Fever (>39°C) - per-dose frequency	2.0%	5.2%	0%	7.1%
- per-subject frequency	3.9%	10.2%	0%	14.3%
Drowsiness	7.9%	13.4%	NA	NA
Irritability	7.9%	18.6%	NA	NA
Loss of appetite	6.9%	16.5%	NA	NA
Shivering	1.0%	12.4%	4.0%	14.3%

NA=not available

In other clinical studies where children 6 months to 17 years received another pandemic influenza vaccine (H5N1 A/Indonesia/05/2005 manufactured in Dresden, Germany), increases in the frequency of some side effects (including injection site pain, redness and fever) were seen after the second dose in children aged less than 6 years.

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see section 4.4).

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB02.

Pharmacodynamic effects

This section describes the clinical experience with the mock-up vaccines following a two-dose administration.

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

Immune response against A/Indonesia/5/2005 (H5N1)

Adults

Clinical studies have evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/5/2005 in subjects from the age of 18 years onwards following a 0, 21 days schedule.

In a consistency study (Q-Pan-H5N1-002), the anti-haemagglutinin (anti-HA) antibody responses twenty-one days and six months after the second dose were as follows:

anti-HA antibody	Immune response to A/Indonesia/5/2005			
	18-60 years		>60 years	
	Day 42 N=1,488	Day 180 N=353	Day 42 N=479	Day 180 N=104
Seroprotection rate[1]	91%	62%	76.8%	63.5%
Seroconversion rate[2]	91%	62%	76.4%	62.5%
Seroconversion factor[3]	51.4	7.4	17.2	7.8

[1]seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40);
[2]seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre);
[3]seroconversion factor (i.e. ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty-one days after the second dose, a 4-fold increase in serum neutralising antibody against A/Indonesia/5/2005 was achieved in 94.4% of subjects aged 18-60 years and in 80.4% of subjects over 60 years of age. At day 42, 100% of subjects aged 18-60 years and 96.4% of subjects aged >60 years had a titre of at least 1:80.

In another clinical study (Q-Pan-H5N1-001), the anti-haemagglutinin (anti-HA) antibody responses in subjects aged 18-64 years were as follows:

anti-HA antibody	Immune response to A/Indonesia/5/2005		
	Day 21 N=145	Day 42 N=145	Day 180 N=141
Seroprotection rate[1]	42.1%	97.2%	54.6%
Seroconversion rate[2]	42.1%	97.2%	54.6%
Seroconversion factor[3]	4.5	92.9	5.6

[1]seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40);
[2]seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre);
[3]seroconversion factor (i.e. ratio of the post-vaccination GMT and the pre-vaccination GMT)

A 4-fold increase in serum neutralising antibody titres against A/Indonesia/5/2005 was achieved in 76.6% of subjects at day 21, 97.9% at day 42 and 91.5% at day 180 and 100% of subjects had a titre of at least 1:80 at day 42 and 180.

Administration of an AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) manufactured using a different process

Paediatric population

In a clinical study (D-Pan-H5N1-009, -023), children aged 3 to 5 and 6 to 9 years old received two doses of either a full (0.5 ml) or a half dose (0.25 ml) of an AS03-adjuvanted vaccine containing 3.75

µg HA derived from A/Vietnam/1194/2004 (H5N1) at 0 and 21 days. At day 42 and six months after the second dose, the anti-HA antibody responses were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004							
	3 to 5 years				6 to 9 years			
	Day 42		Day 180		Day 42		Day 180	
	Half dose N=49	Full dose N=44	Half dose N=50	Full dose N=29	Half dose N=43	Full dose N=43	Half dose N=44	Full dose N=41
Seroprotection rate[1]	95.9%	100%	56.0%	82.8%	100%	100%	63.6%	78%
Seroconversion rate[2]	95.9%	100%	56.0%	82.8%	100%	100%	61.0%	78%
Seroconversion factor[3]	78.5	191.3	5.9	16	108.1	176.7	6.1	12.3

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

The clinical relevance of the haemagglutination inhibition (HI) titre ≥1:40 in children is unknown.

At day 42, the neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Vietnam/1194/2004			
	21 days after 2nd dose			
	3 to 5 years		6 to 9 years	
	Half dose N=47	Full dose N=42	Half dose N=42	Full dose N=42
GMT[1]	1044.4	4578.3	1155.1	3032.5
Seroconversion rate[2]	95.6%	97.4%	100%	100%
≥1:80[3]	100%	100%	100%	100%

[1] Geometric Mean Titre
[2] 4-fold increase in serum neutralising antibody titre
[3] % of subjects reaching a serum neutralising antibody titre of at least 1:80

The European Medicines Agency has deferred the obligation to submit the results of studies with Pumarix in one or more subsets of the paediatric population in influenza infection caused by an influenza strain contained in the vaccine or related to a strain contained in the vaccine. (see section 4.2 for information on paediatric use).

Cross-reactive immune responses elicited by AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/5/2005 (H5N1):

In the consistency study (Q-Pan-H5N1-002), a 4-fold increase in serum neutralising antibody against A/Vietnam/1194/2004 was at day 42 achieved in 65.5% of subjects aged 18-60 years and in 24.1% of subjects over 60 years of age. A titre of 1:80 was achieved in 84.2% of subjects aged 18-60 years and in 92.6% of subjects aged >60 years.

In another clinical study (Q-Pan-H5N1-001), anti-HA responses against A/Vietnam/1194/2004 following administration of AS03-adjuvanted vaccine containing 3.75 µg derived from A/Indonesia/5/2005 were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004		
	Day 21 N=145	Day 42 N=145	Day 180 N=141
Seroprotection rate[1]	15.2%	64.1%	10.6%
Seroconversion rate[2]	13.1%	62.1%	9.2%
Seroconversion factor[3]	1.9	7.6	1.7

[1]seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40);
[2]seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre);
[3]seroconversion factor (i.e. ratio of the post-vaccination GMT and the pre-vaccination GMT)

A 4-fold increase in serum neutralising antibody against A/Vietnam/1194/2004 was achieved in 44.7% of subjects at day 21, 53.2% at day 42 and 38.3% at day 180. A titre of 1:80 was achieved in 95.7% of subjects at days 21 and 42 and in 85.1% at day 180.

One dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 manufactured using a different process administered after one or two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 manufactured using a different process

In a clinical study (D-Pan-H5N1-012), subjects aged 18-60 years received a dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from either A/Vietnam/1194/2004 or Indonesia/5/2005 six months after they had received one or two priming doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 on day 0 or on days 0 and 21 respectively. The anti-HA responses were as follows:

anti-HA antibody	Against A/Vietnam 21 days after boosting with A/Vietnam N=46		Against A/Indonesia 21 days after boosting with A/Indonesia N=49	
	After one priming dose	After two priming doses	After one priming dose	After two priming doses
Seroprotection rate[1]	89.6%	91.3%	98.1%	93.9%
Booster seroconversion rate[2]	87.5%	82.6%	98.1%	91.8%
Booster factor[3]	29.2	11.5	55.3	45.6

[1] seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]booster seroconversion rate: proportion of subjects who were either seronegative at pre-booster and have a protective post-vaccination titre of ≥1:40, or who were seropositive at pre-booster and have a 4-fold increase in titre;
[3]booster factor: ratio of the post-booster geometric mean titre (GMT) and the pre-booster GMT.

Regardless of whether one or two doses of priming vaccine had been given 6 months earlier, the seroprotection rates against A/Indonesia were >80% after a dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 and the seroprotection rates against A/Vietnam were >90% after a dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005. All subjects achieved a neutralising antibody titre of at least 1:80 against each of the two strains regardless of the HA type in the vaccine and the previous number of doses.

In another clinical study, 39 subjects aged 18-60 years received a dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/5/2005 fourteen months after they had received two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 administered on day 0 and day 21. The seroprotection rate against A/Indonesia 21 days after booster vaccination was 92% and 69.2% at day 180.

One dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Turkey/Turkey/1/2005 administered after two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from Indonesia/5/2005

In a clinical study (Q-Pan-H5N1-010), a booster dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Turkey/Turkey/1/2005 was given 15 months after primary vaccination. Ten days after the booster dose, the seroprotection rate against A/Turkey/Turkey/1/2005 and A/Indonesia/5/2005 was 99.2%. Forty-two days after the booster dose, the seroprotection rate against both strains was 98.4%.

Information from non-clinical studies

The ability to induce protection against homologous and heterologous vaccine strains was assessed non-clinically with A/Indonesia/05/05 (H5N1) using ferret challenge models.

- Challenge with a homologous pandemic H5N1 strain (A/Indonesia/5/05)

In this protection experiment, the ferrets (six ferrets/group) were immunized intramuscularly with vaccine candidate containing three different doses of H5N1 antigen (7.5, 3.8 and 1.9 µg of HA antigen) adjuvanted with the standard dose or half dose of AS03. Control groups included ferrets immunized with adjuvant alone and non-adjuvanted vaccine (7.5 micrograms HA). Ferrets immunized with the non adjuvanted H5N1 influenza vaccine were not protected from death and showed similar lung viral loads and degree of viral shedding in the upper respiratory tract as those exhibited by ferrets immunized with the adjuvant alone. Conversely the combination of a range of doses of H5N1 antigen with AS03 adjuvant was able to protect against mortality and to reduce lung virus loads and viral shedding after intra-tracheal challenge with a homologous wild type H5N1 virus. Serological testing indicated a direct correlation between vaccines induced HI and neutralising antibody titres in protected animals compared to antigen and adjuvant controls.

- Challenge with a heterologous pandemic H5N1 strain (A/Hong Kong/156/97)

In this protection experiment, the ferrets (six ferrets/group) were immunized intramuscularly with vaccine candidate containing four different doses of H5N1 antigen (3.75, 1.5, 0.6 and 0.24 µg of HA antigen) adjuvanted with half dose of AS03. In addition, one group of six ferrets were immunized with vaccine candidate containing 3.75 µg H5N1 + full dose of AS03 and one control group included ferrets immunized with non-adjuvanted vaccine (3.75 micrograms HA). The results of this heterologous challenge study indicate 80.7%-100% protection in all adjuvanted candidate vaccines compared to 43% protection with the non adjuvanted vaccine, showing the benefit of AS03 adjuvantation.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with Pumarix reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, female fertility, embryo-fetal and postnatal toxicity (up to the end of the lactation period).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Suspension vial:
Thiomersal
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Water for injections

Emulsion vial:
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

18 months.
After mixing, the vaccine should be used within 24 hours. Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C.

6.4 Special precautions for storage

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

For storage conditions after mixing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

One pack containing:
- one pack of 50 vials (type I glass) of 2.5 ml suspension with a stopper (butyl rubber).
- two packs of 25 vials (type I glass) of 2.5 ml emulsion with a stopper (butyl rubber).

The volume after mixing 1 vial of suspension (2.5 ml) with 1 vial of emulsion (2.5 ml) corresponds to 10 doses of vaccine (5 ml).

6.6 Special precautions for disposal and other handling

Pumarix consists of two containers:
Suspension: multidose vial containing the antigen,
Emulsion: multidose vial containing the adjuvant.

Prior to administration, the two components should be mixed.

Instructions for mixing and administration of the vaccine:

1. Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should be brought to room temperature (allow a minimum of 15 minutes). Whitish sediments may be observed in the suspension vial; these sediments are part of the normal physical appearance of the suspension. The emulsion presents as a whitish appearance.
2. Each vial should be shaken and inspected visually for any foreign particulate matter (other than the white sediments described above) and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
3. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a 5 ml syringe and by adding it to the vial containing the antigen. It is recommended to equip the syringe with a 23-G needle. However, in the case this needle size would not be available, a 21-G needle might be used. The vial containing the adjuvant should be maintained in upside down position to facilitate the withdrawal of the full content.
4. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish emulsion. In the event of other variation being observed, discard the vaccine.
5. The volume of the Pumarix vial after mixing is at least 5 ml. The vaccine should be administered in accordance with the recommended posology (see section 4.2).
6. The vial should be shaken prior to each administration and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
7. Each vaccine dose of 0.5 ml is withdrawn into a 1 ml syringe for injection and administered intramuscularly. It is recommended to equip the syringe with a needle gauge not larger than 23-G.
8. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2°C – 8°C) or at room temperature (25°C – 30°C). If the mixed vaccine is stored in a refrigerator, it should be brought to room temperature (allow a minimum of 15 minutes) before each withdrawal.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
rue de l'Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/664/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 March 2011

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

Name and address of the manufacturer of the biological active substance

IB Biomedical Corporation of Quebec doing business as
GlaxoSmithKline Biologicals North America
2323 du parc Technologique Blvd.
Saint-Foy, Quebec,
Canada G1P 4R8

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut
B-1330 Rixensart
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

Pumarix can only be marketed when there is an official WHO/EU declaration of an influenza pandemic, on the condition that the Marketing Authorisation Holder for Pumarix takes due account of the officially declared pandemic strain.

- ***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

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

The MAH shall perform the studies and pharmacovigilance activities detailed in the Pharmacovigilance Plan and requested as specific obligations.

Risk Management plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

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

In addition, an updated RMP should be submitted:

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

PSURs

Outside of the pandemic period, the normal PSUR periodicity and format will be maintained, with a specific review of AESI and possible adverse events related to adjuvants. This should include data from ongoing studies, or actual use if applicable, of the 'mock-up' strains and any safety data relevant to the adjuvant system.

During a pandemic situation (Phase 6 of the WHO global Influenza preparedness plan), bi-weekly "simplified PSUR" accompanied by a summary of vaccine distribution will be provided according to the cRMP guidance (Doc. Ref. EMEA/32706/2007 for 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, duration a pandemic, resources needed for an in-depth evaluation of Periodic Safety Update Reports in the format as defined in Volume 9a of the Rules Governing Medicinal Product in the European Union may not be adequate for a rapid identification of a new safety issue.
> In consequence, as soon as the pandemic is declared (Phase 6 of the WHO global Influenza preparedness plan) and the pandemic vaccine is used, the MAH shall submit periodic safety update reports with periodicity and format defined as follows:

Frequency of submission

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

When it has been agreed by the CHMP that the S-PSUR is no longer necessary, a full PSUR covering the period since the data lock point of the last routine PSUR will be submitted within a time frame to be agreed with the Rapporteur.

Format

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

1. Fatal and/or life-threatening reactions – for each Preferred Term (PT), including the proportion of fatal reports
2. Adverse Events of Special Interest (PTs)
3. Serious unexpected reactions (PTs)
4. All events occurring in the following age groups: 6-23 months, 2-8 years, 8-17 years, 18-60 years, >60 years
5. All events occurring in pregnant women
6. All events reported by patients that have been entered into the database by data-lock point

7. A cumulative overview of all events reported during the period, stratified according to type of reporter (patient or health care professional), seriousness, expectedness, and whether spontaneous or solicited.

Presentation of data will take into consideration the following recommendations:

- Serious expected reactions will be reviewed by the MAH as part of their signal detection procedures and will only form part of the report if an issue of concern arises.
- All tables will be based on number of events (presented on PT level, sorted by System Organ Class (SOC)) and not number of cases.
- Tables 1 to 4 will be based on events reported from healthcare professionals only.
- In Tables 1 to 5, numbers will be provided for events received during the reporting period and cumulatively.
- All tables will be based on generic and not product-specific data. Product-specific data can be evaluated during signal work-up.
- A measure of relative reporting rate of signals for each reported PT should be provided if possible (e.g. Proportional reporting ratio (PRR), Information Component (IC) or the Empirical Bayesian Geometric Mean (EBMG)); this is not mandatory as all MAHs do not yet have this capability.
- No line listings are required – these can be provided in signal evaluation reports as necessary.

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

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

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

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

Not applicable.

- **SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
During the pandemic, the applicant will conduct a surveillance on the safety of the vaccine during pregnancy using dedicated registry.	Protocol of the registry will be submitted as part of RMP, during the pandemic
During the pandemic, the applicant will conduct a prospective cohort study as identified in the Pharmacovigilance plan.	Depending on and after implementation of vaccine strain, when first pandemic will take place.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK CONTAINING 1 PACK OF 50 VIALS OF SUSPENSION AND 2 PACKS OF 25 VIALS OF EMULSION

1. NAME OF THE MEDICINAL PRODUCT

Pumarix suspension and emulsion for emulsion for injection.
Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After mixing, 1 dose (0.5 ml) contains:

Split influenza virus inactivated, containing antigen equivalent to:

A/Indonesia/05/2005 (H5N1) like strain used (PR8-IBCDC-RG2) 3.75 micrograms*

AS03 adjuvant composed of squalene, DL-α-tocopherol and polysorbate 80

* haemagglutinin

3. LIST OF EXCIPIENTS

Thiomersal
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension and emulsion for emulsion for injection

50 vials: suspension (antigen)
50 vials: emulsion (adjuvant)

The volume after mixing 1 vial of suspension (2.5 ml) with 1 vial of emulsion (2.5 ml) corresponds to **10 doses** of vaccine (5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet 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

Suspension and emulsion to be mixed before administration

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a 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 regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/664/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 50 VIALS OF SUSPENSION (ANTIGEN)

1. NAME OF THE MEDICINAL PRODUCT

Suspension for emulsion for injection for Pumarix
Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Split influenza virus, inactivated, containing antigen* equivalent to:
3.75 micrograms haemagglutinin/dose
*Antigen: A/Indonesia/5/2005 (H5N1) like strain used (PR8-IBCDC-RG2)

3. LIST OF EXCIPIENTS

Excipients: Thiomersal, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Antigen suspension for injection
50 vials: suspension
2.5 ml/vial.
After mixing with adjuvant emulsion: **10 doses** of 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet 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

Suspension to be exclusively mixed with adjuvant emulsion before administration

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Storage in a 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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Biologicals, Rixensart - Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/664/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 25 VIALS OF EMULSION (ADJUVANT)

1. NAME OF THE MEDICINAL PRODUCT

Emulsion for emulsion for injection for Pumarix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Content: AS03 adjuvant composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Adjuvant emulsion for injection
25 vials: emulsion
2.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet 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

Emulsion to be exclusively mixed with antigen suspension before administration

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Storage in a 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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Biologicals, Rixensart - Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/664/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SUSPENSION VIAL

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

Antigen suspension for Pumarix
Pandemic influenza vaccine
A/Indonesia/5/2005 (H5N1) like strain used (PR8-IBCDC-RG2)
I.M.

2. METHOD OF ADMINISTRATION

Mix with adjuvant emulsion before use

3. EXPIRY DATE

EXP
After mixing: Use within 24 hours and do not store above 30°C.
Date and time of mixing:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml
After mixing with adjuvant emulsion: 10 doses of 0.5 ml

6. OTHER

Storage (2ºC-8ºC), do not freeze, protect from light

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

EMULSION VIAL

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

Adjuvant emulsion for Pumarix
I.M.

2. METHOD OF ADMINISTRATION

Mix into Antigen suspension before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml

6. OTHER

Storage (2ºC-8ºC), do not freeze, protect from light

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Pumarix suspension and emulsion for emulsion for injection
Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)

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.
- This vaccine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Pumarix is and what it is used for

What Pumarix is and what it is used for
Pumarix is a vaccine for use in adults from 18 years old to prevent pandemic flu (influenza).

Pandemic flu is a type of influenza that happens at intervals that vary from less than 10 years to many decades. It spreads rapidly around the world. The signs of pandemic flu are similar to those of ordinary flu but may be more serious.

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

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

2. What you need to know before you are given Pumarix

Pumarix should not be given:

- if you have previously had a sudden life-threatening allergic reaction to any ingredient of this vaccine (listed in section 6) or to anything else that may be present in very small amounts, such as: egg and chicken protein, ovalbumin, formaldehyde or sodium deoxycholate.
  - 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, you may still be given the vaccine. This is as long as medical treatment is available straight away, in case you have an allergic reaction.

Do not have Pumarix if any of the above apply to you.
If you are not sure, talk to your doctor or nurse before having this vaccine.

Warnings and precautions

Talk to your doctor or nurse before you are given Pumarix:

- if you have had any allergic reaction other than a sudden life-threatening allergic reaction to any ingredient contained in this vaccine (listed in section 6) or to thiomersal, to egg and chicken protein, ovalbumin, formaldehyde or to sodium deoxycholate.
- if you have a serious 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 a problem, but your doctor will advise whether you could still be vaccinated with Pumarix.
- if you have problems with your immune system, since your response to the vaccine may then be poor.
- if you are having a blood test to look for evidence of infection with certain viruses. In the first few weeks after vaccination with Pumarix the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently been given Pumarix.
- if you have a bleeding problem or you bruise easily.

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

Fainting can occur following, or even before, any needle injection. Therefore tell the doctor or nurse if you fainted with a previous injection.

Children:
If your child receives the vaccine, you should be aware that the side effects may be more intense after the second dose, especially temperature over 38°C. Therefore monitoring of temperature and measures to lower the temperature (such as giving paracetamol or other medicines that lower fever) after each dose are recommended.

Other medicines and Pumarix
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines or have recently received any other vaccine.

In particular, please tell your doctor or nurse if you are having any treatments (such as corticosteroid treatments or chemotherapy for cancer) that affect the immune system. Pumarix can still be given but your response to the vaccine may be poor.

Pumarix is not intended to be given at the same time as some other vaccines. However, if this needs to happen, the other vaccine will be injected into the other arm. Any side effects that happen may be more serious.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you receive this vaccine.

Driving and using machines
Some effects listed in Section 4 “Possible side effects” may affect your ability to drive or use tools or machines. It is best to see how Pumarix affects you before you try these activities.

Pumarix contains thiomersal
Pumarix contains thiomersal as a preservative and it is possible that you may experience an allergic reaction. Tell your doctor if you have any known allergies.

Pumarix contains sodium and potassium
Pumarix contains less than 1 mmol sodium (23 mg) and less than 1 mmol of potassium (39 mg) per dose. It is essentially sodium- and potassium-free.

3. How Pumarix is given

- Adults from 18 years onwards: you will receive two doses of Pumarix. The second dose should be given after an interval of at least three weeks after the first dose.

If you have previously received one or two doses of a similar H5N1 AS03-containing vaccine

- Adults from 18 years onwards: you will receive one dose of Pumarix.

Use in children
There is limited information available on the use of vaccine very similar to Pumarix (but manufactured in a different facility) to children aged from 3-9 years who received either two adult doses or two half adult doses given three weeks apart. There is no information available on use in children aged less than 3 years or aged from 10-17 years.

Your doctor or nurse will give you Pumarix.
- They will give Pumarix as an injection into a muscle
- This will usually be in the upper arm.

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

4. Possible side effects

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

Allergic reactions
Allergic reactions which may cause you to have dangerously low blood pressure. If this is not treated it may lead to shock. Your doctors know that this might happen and will have emergency treatment ready to use.

Other side effects:

Very common: may affect more than 1 in 10 people
- Pain where the injection was given
- Headache
- Feeling tired
- Aching muscles, joint pain

Common: may affect up to 1 in 10 people
- Redness and swelling where the injection was given
- Fever
- Sweating
- Shivering
- Diarrhoea, feeling sick

Uncommon: may affect up to 1 in 100 people
- Reactions where the injection was given such as bruising, a hard lump, itching, warmth
- Swollen glands in your neck
- Feeling dizzy
- Generally feeling unwell
- Unusual weakness

- Being sick, stomach pain, acid indigestion
- Not being able to sleep
- Tingling or numbness of the hands or feet
- Shortness of breath
- Pain in the chest
- Itching, rash
- Pain in the back or neck, stiff muscles, muscle spasms, pain in your leg or hand

Additional side effects in children

When a dose of 0.5 ml of a similar vaccine was given to children aged 3-9 years, fever occurred more often than when half of this dose (0.25 ml of vaccine) was given. Also fever occurred more often in children aged 6-9 years compared to the children aged 3-5 years. There was no increase after the second dose whether the children received half of the adult or the adult dose, except for some side effects which were higher after the second dose, particularly for rates of fever in < 6 years old children.

In other clinical studies where children 6 months to 17 years received a similar vaccine containing A/Indonesia/05/2005, increases in the frequency of some side effects (including injection site pain, redness and fever) were seen after the second dose in children aged less than 6 years.

The side effects listed below have happened with H1N1 AS03-containing vaccines. They may also happen with Pumarix. If any of the side effects below occur, please tell your doctor or nurse immediately:

- Allergic reactions leading to a dangerously low blood pressure. If this is not treated, it may lead to shock. Your doctors will know that this might happen and will have emergency treatment ready to use
- Fits
- Generalised skin reactions including urticaria (hives)

The side effects listed below have happened in the days or weeks after vaccination with vaccines given routinely every year to prevent flu. They may also happen with Pumarix. If any of the side effects below occur, please tell your doctor or nurse immediately:

Rare: may affect up to 1 in 1,000 people
- Serious stabbing or throbbing pain along one or more of your nerves
- Low blood platelet count. This can cause bleeding or bruising.

Very rare: may affect up to 1 in 10,000 people
- Inflammation of your blood vessels (vasculitis). This can cause skin rashes, joint pain and kidney problems
- Problems with your brain and nerves such as inflammation of the central nervous system (encephalomyelitis), inflammation of nerves (neuritis) or a type of paralysis known as 'Guillain-Barré Syndrome'.

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

5. How to store Pumarix

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

Before the vaccine is mixed:
Do not use the suspension and the emulsion after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

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

After the vaccine is mixed:
After mixing, use the vaccine within 24 hours and do not store above 30°C.

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 protect the environment.

6. Contents of the pack and other information

What Pumarix contains

- **Active substance:**
  Split influenza virus, inactivated, containing antigen* equivalent to:

  A/H5N1/Indonesia/5/2005 like strain used (PR8-IBCDC-RG2)3.75 micrograms** per 0.5 ml dose

  *propagated in eggs
  **expressed in microgram haemagglutinin

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

- **Adjuvant:**
  The vaccine contains an 'adjuvant' AS03. This adjuvant contains squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams). Adjuvants are used to improve the body's response to the vaccine.

- **Other ingredients:**
  The other ingredients are: thiomersal, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, water for injections

What Pumarix looks like and contents of the pack

The suspension is a translucent to off white opalescent suspension, which may sediment slightly.
The emulsion is a whitish homogeneous liquid.

Before the vaccine is given, the two parts will be mixed together. The mixed vaccine is a whitish emulsion.

One pack of Pumarix consists of:
- one pack containing 50 vials of 2.5 ml suspension (antigen)
- two packs containing 25 vials of 2.5 ml emulsion (adjuvant)

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.

Rue de l'Institut 89
B-1330 Rixensart
Belgium

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

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This leaflet was last revised in {MM/YYYY}.

This medicine has been authorised under 'exceptional circumstances'.
This means that for scientific reasons it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

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

The following information is intended for healthcare professionals only:

Pumarix consists of two containers:
Suspension: multidose vial containing the antigen,
Emulsion: multidose vial containing the adjuvant.

Prior to administration, the two components should be mixed.

Instructions for mixing and administration of the vaccine:

1. Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should be brought to room temperature (allow a minimum of 15 minutes). Whitish sediments may be observed in the suspension vial; these sediments are part of the normal physical appearance of the suspension. The emulsion presents as a whitish appearance.

2. Each vial should be shaken and inspected visually for any foreign particulate matter (other than the white sediments described above) and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
3. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a 5 ml syringe and by adding it to the vial containing the antigen. It is recommended to equip the syringe with a 23-G needle. However, in the case this needle size would not be available, a 21-G needle might be used. The vial containing the adjuvant should be maintained in upside down position to facilitate the withdrawal of the full content.
4. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish emulsion. In the event of other variation being observed, discard the vaccine.
5. The volume of the Pumarix vial after mixing is at least 5 ml. The vaccine should be administered in accordance with the recommended posology (see section 3. "How Pumarix is given").
6. The vial should be shaken prior to each administration and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
7. Each vaccine dose of 0.5 ml is withdrawn into a 1 ml syringe for injection and administered intramuscularly. It is recommended to equip the syringe with a needle not larger than 23-G.
8. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2°C – 8°C) or at room temperature (25°C – 30°C). If the mixed vaccine is stored in a refrigerator, it should be brought to room temperature (allow a minimum of 15 minutes) before each withdrawal.

The vaccine should not be administered intravascularly.

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

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS RECOMMENDING THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Pumarix, the scientific conclusions of the PRAC are as follows:

In relation to the identified risk of fever in children (<6 years), the PRAC does not agree with the MAH that the EU SmPC contains appropriate information on this safety concern. As an identified risk, an appropriate warning should be included in section 4.4. Moreover section 4.8 should be revised to reflect reactogenicity data from the three paediatric studies D-Pan H5N1-009, -013 and 032.

Therefore, in view of the available data regarding fever in children, the PRAC considered that changes to the product information were warranted.
The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for Pumarix, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance purified antigen fractions of inactivated split virion A/Indonesia/05/2005 (H5N1)/PR8-IBCDC-RG2 is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.