ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pandemrix suspension and emulsion for emulsion for injection.
Pandemic influenza vaccine (H1N1)v (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/California/7/2009 (H1N1)v-like strain (X-179A)	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.

Excipients: the vaccine contains 5 micrograms thiomersal

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Suspension and emulsion for emulsion for injection.
The suspension is a colourless light opalescent liquid.
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

The dose recommendations take into account available data from on-going clinical studies in healthy subjects who received a single dose of Pandemrix (H1N1) and from clinical studies in healthy subjects who received two doses of a version of Pandemrix containing HA derived from A/Vietnam/1194/2004 (H5N1).

In some age groups there are limited data (adults aged 60-79 years), very limited data (adults aged 80 years and older, children aged 6 months to 9 years) or no data (children aged less than 6 months or from 10-17 years) with one or both versions of Pandemrix as detailed in sections 4.4, 4.8 and 5.1.

Adults aged 18 years and older:
One dose of 0.5 ml at an elected date.
Immunogenicity data obtained at three weeks after administration of Pandemrix (H1N1) in clinical studies suggest that a single dose may be sufficient.
If a second dose is administered there should be an interval of at least three weeks between the first and the second dose.

Children and adolescents aged 10-17 years
Dosing may be in accordance with the recommendations for adults. However, the choice of dose for this age group should take into account the available data on safety and immunogenicity in adults and in children aged from 3-9 years.

Children aged from 6 months to 9 years
One dose of 0.25 ml at an elected date.
Preliminary immunogenicity data obtained in a limited number of children aged 6-35 months show that there is a further immune response to a second dose of 0.25 ml administered after an interval of three weeks.

The use of a second dose should take into consideration the information provided in sections 4.4, 4.8 and 5.1.

Children aged less than 6 months
Vaccination is not currently recommended in this age group.

It is recommended that subjects who receive a first dose of Pandemrix should complete the vaccination course with Pandemrix (see section 4.4).

Method of administration

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

4.3 Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate and sodium deoxycholate) of this vaccine. If vaccination is considered to be necessary, facilities for resuscitation should be immediately available in case of need.

See section 4.4 for Special warnings and special precautions for use.

4.4 Special warnings and precautions for use

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

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

There are no safety and immunogenicity data available from clinical studies with Pandemrix (H1N1) in children and adolescents aged from 3-17 years or in children aged less than 6 months. There are very limited data available from a clinical study with Pandemrix (H1N1) in healthy children aged from 6 to 35 months and limited data from a study with a version of Pandemrix containing H5N1 antigens in children aged from 3 to 9 years.

Very limited data in children aged 6 to 35 months (N=51) who received two doses of 0.25 ml (half of the adult dose) with an interval of 3 weeks between doses indicate an increase in the rates of injection site reactions and general symptoms (see section 4.8). In particular rates of fever (axillary temperature ≥38°C) may increase considerably after 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) after each vaccination.
There are limited data available from clinical studies with Pandemrix (H1N1) in adults aged over 60 years and very limited data with Pandemrix (H1N1) or with a version of the vaccine containing H5N1 antigens in adults aged over 80 years.

There are no safety, immunogenicity or efficacy data to support interchangeability of Pandemrix with other H1N1 pandemic vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

Data obtained on co-administration of Pandemrix H1N1 with non-adjuvanted seasonal influenza vaccine (Fluarix, a split virion vaccine) in healthy adults aged over 60 years did not suggest any significant interference in the immune response to Pandemrix H1N1. The immune response to Fluarix was satisfactory.
Co-administration was not associated with higher rates of local or systemic reactions compared to administration of Pandemrix alone.
Therefore the data indicate that Pandemrix may be co-administered with non-adjuvanted seasonal influenza vaccines (with injections made into opposite limbs).

There are no data on co-administration of Pandemrix 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 Pregnancy and lactation

There are currently no data available on the use of Pandemrix in pregnancy. Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or fetal or neonatal toxicity.

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

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

Pandemrix may be used in lactating women.

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

- Clinical trials

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).

Adults

Clinical studies have evaluated the incidence of adverse reactions listed below in approximately 5,000 subjects 18 years old and above who received formulations containing A/Vietnam/1194/2004 (H5N1) strain with at least 3.75 microgram HA/AS03.

A clinical study evaluated the reactogenicity of the first dose of Pandemrix (H1N1) in healthy adults aged 18-60 (N=120) and above 60 years (N=120). The frequency of adverse reactions was similar between age groups, except for redness (more common in subjects aged >60 years) and shivering and sweating (more common in subjects aged 18-60 years).

The frequency of adverse reactions observed with Pandemrix (H1N1) was similar to that reported below, except that redness and fever were reported at lower rates and shivering and sweating were reported at higher rates with Pandemrix (H1N1) in subjects aged 18-60 years.

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)

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

Blood and lymphatic system disorders
Common: lymphadenopathy

Psychiatric disorders
Uncommon: insomnia

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

Gastrointestinal disorders
Uncommon: gastro-intestinal symptoms (such as diarrhoea, vomiting, abdominal pain, nausea)

Skin and subcutaneous tissue disorders
Common: ecchymosis at the injection site, sweating increased
Uncommon: pruritus, rash

Musculoskeletal and connective tissue disorders
Very common: arthralgia, myalgia

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

Children aged 3-9 years

A clinical study evaluated the reactogenicity in children 3 to 5 and 6 to 9 years of age who received either a full or a half dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1).

The per-dose frequency of adverse reactions observed in the groups of children who received a full dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) was higher than that observed in the groups of children who received half of the dose, except for redness in the 6-9 years of age group. The per-dose frequency of the following 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

Children aged 6-35 months

A clinical study evaluated the reactogenicity in children aged 6 to 35 months who received half the adult dose (i.e. 0.25 ml) following a 0, 21 days schedule. After the second dose, an increase in injection site reactions and general symptoms was observed overall in the 6 to 35 months age group, particularly in rates of axillary fever (≥38°C). The overall per-dose frequency of the following adverse reactions was as follows:

Adverse reactions	Post dose 1	Post dose 2
Pain	31.4%	41.2%
Redness	19.6%	29.4%
Swelling	15.7%	23.5%
Fever (≥38°C) axillary	5.9%	43.1%
Fever (≥39°C) axillary	0.0%	3.9%
Drowsiness	7.8%	35.3%
Irritability	21.6%	37.3%
Loss of appetite	9.8%	39.2%

- Post-marketing surveillance

Pandemrix H1N1v

In addition to the adverse reactions reported in the clinical trials, the following have been reported during post-marketing experience with Pandemrix H1N1v:

Immune system disorders
Anaphylaxis, allergic reactions

Nervous system disorders
Febrile convulsions

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

Interpandemic trivalent vaccines

From Post-marketing surveillance with interpandemic trivalent vaccines, the following adverse reactions have also been reported:

Rare:
Neuralgia, transient thrombocytopenia.

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

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.

This medicinal product has been authorised under "Exceptional Circumstances". The European Medicines Agency (EMEA) will regularly review any new information which may become available and this SPC will be updated as necessary.

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.

Clinical studies with Pandemrix (H1N1) currently provide:

- Limited safety and immunogenicity data obtained three weeks after administration of a single dose of Pandemrix (H1N1) to healthy adults aged 18-79 years.
- Very limited safety and immunogenicity data obtained three weeks after administration of a single dose of Pandemrix (H1N1) to healthy adults aged over 80 years.
- Very limited safety and immunogenicity data obtained three weeks after a single administration of half the adult dose (i.e. 0.25 ml) of Pandemrix (H1N1) to healthy children aged 6-35 months.

Clinical studies in which a version of Pandemrix containing HA derived from A/Vietnam/1194/2004 (H5N1) was administered at day 0 and at day 21 provide:

- Safety and immunogenicity data in healthy adults, including the elderly
- Limited safety and immunogenicity data in healthy children aged from 3-9 years who received 0.5 ml or 0.25 ml (i.e. half the adult dose).

Immune response to Pandemrix (H1N1)

Adults aged 18-60 years

In two clinical studies (D-Pan H1N1-007 and D-Pan H1N1-008) that evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like in healthy subjects aged 18-60 years the anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like			
	D-Pan H1N1-007		D-Pan H1N1-008	
	Total enrolled subjects N=61 [95% CI]	Seronegative subjects prior to vaccination N=40 [95% CI]	Total enrolled subjects N=120 [95% CI]	Seronegative subjects prior to vaccination N=76 [95% CI]
Seroprotection rate[1]	100% [94.1;100]	100% [91.2;100]	97.5% [92.9;99.5]	96.1% [88.9;99.2]
Seroconversion rate[2]	96.7% [88.7;99.6]	100% [91.2;100]	95.0% [89.4;98.1]	96.1% [88.9;99.2]
Seroconversion factor[3]	43.3 [31.8;59.0]	56.7 [39.9;80.5]	42.15 [33.43.53.16]	50.73 [37.84;68.02]

[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.

Elderly (>60 years)

Study D-Pan H1N1-008 also evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like in healthy subjects (N=120) aged >60 years (stratified in ranges from 61 to 70, 71 to 80 and > 80 years of age). The anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like					
	61-70 years		71-80 years		>80 years	
	Total enrolled subjects N=75 [95% CI]	Seronegative subjects prior to vaccination N=43 [95% CI]	Total enrolled subjects N=40 [95% CI]	Seronegative subjects prior to vaccination N=23 [95% CI]	Total enrolled subjects N=5 [95% CI]	Seronegative subjects prior to vaccination N=3 [95% CI]
Seroprotection rate[1]	88.0% [78.4;94.4]	81.4% [66.6;91.6]	87.5% [73.2;95.8]	82.6% [61.2;95.0]	80.0% [28.4;99.5]	66.7% [9.4;99.2]
Seroconversion rate[2]	80.0% [69.2;88.4]	81.4% [66.6;91.6]	77.5% [61.5;89.2]	82.6% [61.2;95.0]	80.0% [28.4;99.5]	66.7% [9.4;99.2]
Seroconversion factor[3]	13.5 [10.3;17.7]	20.3 [13.94;28.78]	13.5 [8.6;21.1]	20.67 [11.58;36.88]	18.4 [4.3;78.1]	17.95 [0.55;582.25]

[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.

Children aged 6-35 months

Another clinical study evaluated the immunogenicity of a half adult dose (i.e. 0.25 ml) of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like in healthy children 6 months to 35 months of age (stratified in ranges from 6 to 11, 12 to 23 and 24-35 months of age. The anti-HA antibody responses 21 days after a first and a second half dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like						
	6-11 months			12-23 months[4]		24-35 months[4]	
	Post dose 1	Post dose 2	Post dose 1	Post dose 1	Post dose 2	Post dose 1	Post dose 2
	Total enrolled subjects [95% CI]		Seronegative subjects prior to vaccination [95% CI]	Total enrolled subjects [95% CI]		Total enrolled subjects [95% CI]	
	N=17	N = 17	N=14	N=17	N= 16	N=16	N= 17
Seroprotection rate[1]	100% [80.5; 100]	100% [80.5; 100]	100% [76.8;100]	100% [80.5; 100]	100% [79.4; 100]	100% [79.4; 100]	100% [80.5; 100]
Seroconversion rate[2]	94.1% [71.3; 99.9]	100% [80.5; 100]	100% [76.8;100]	100% [80.5; 100]	100% [79.4; 100]	100% [79.4; 100]	100% [80.5; 100]
Seroconversion factor[3]	44.4 [24.1; 81.5]	221.9 [102.6; 480.2]	70.67 [51.91; 96.20]	76.9 [55.7; 106.1]	378.0 [282.0; 506.7]	53.8 [40.7; 71.1]	409.1 [320.7; 521.9]

[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.
[4]all subjects seronegative prior to vaccination

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

Analysis of a subset of 36 subjects aged 6 months to 35 months old showed that 80.6 % had a 4 fold increase in serum neutralising antibodies 21 days after the first dose (66.7 % in 12 subjects aged 6 to 11 months old, 91.7 % in 12 subjects aged 12 to 23 months old and 83.3 % in 12 subjects aged 24 to 35 months old).

Immune response against A/Vietnam/1194/2004 (H5N1):

Adults aged 18-60 years

In clinical studies that evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 the anti-HA antibody responses were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004				
	0, 21 days schedule		0, 6 months schedule		
	21 days after 1st dose N=925	21 days after 2nd dose N=924	21 days after 1st dose N=55	7 days after 2nd dose N=47	21 days after 2nd dose N=48
Seroprotection rate[1]	44.5%	94.3%	38.2%	89.4%	89.6%
Seroconversion rate[2]	42.5%	93.7%	38.2%	89.4%	89.6%
Seroconversion factor[3]	4.1	39.8	3.1	38.2	54.2

[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.

After two doses given 21 days or 6 months apart, 96.0% of subjects had a 4-fold increase in serum neutralising antibody titres and 98-100% had a titre of at least 1:80.

Follow up of 50 subjects who had received two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 at 0 and 21 days showed that 84% were seroprotected (HI titre ≥1:40) at day 42 compared with 54% at day 180. A 4-fold increase in serum neutralising antibody titres from day 0 was observed in 85.7% at day 42 and 72% at day 180.

Elderly (>60 years)

In another clinical study, 152 subjects aged > 60 years (stratified in ranges from 61 to 70, 71 to 80 and > 80 years of age) received either a single or a double dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) at 0 and 21 days. At day 42, the anti-HA antibody responses were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004 (D42)		
	61 to 70 years	71 to 80 years	>80 years

	Single dose N=91	Double dose N=92	Single dose N=48	Double dose N=43	Single dose N=13	Double dose N=10
Seroprotection rate[1]	84.6%	97.8%	87.5%	93.0%	61.5%	90.0%
Seroconversion rate[2]	74.7%	90.2%	77.1%	93.0%	38.5%	50.0%
Seroconversion factor[3]	11.8	26.5	13.7	22.4	3.8	7.7

[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.

Although an adequate immune response was achieved at day 42 following two administrations of a single dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1), a higher response was observed following two administrations of a double dose of vaccine.

Very limited data in seronegative subjects >80 years of age (N=5) showed that no subject achieved seroprotection following two administrations of a single dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1). However, following two administrations of a double dose of vaccine, the seroprotection rate at day 42 was 75%.

The day 180 seroprotection rates in subjects aged >60 years were 52.9% for those who had received two single doses and 69.5% for those who had received two doubles doses at day 0 and day 21.

In addition, 44.8% and 56.1% of subjects in respective dose groups had a 4-fold increase in serum neutralising antibody titres from day 0 to day 42 and 96.6% and 100% of subjects had a titre of at least 1:80 at day 42.

Children aged 3 to 9 years

In another clinical study, 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 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

Immune response against A/Indonesia/05/2005 (H5N1)

In a clinical study in which two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 were administered on days 0 and 21 to 140 subjects aged 18-60 years, the anti-HA antibody responses were as follows:

anti-HA antibody	Immune response to A/Indonesia/05/2005		
	Day 21 N=140	Day 42 N=140	Day 180 N=138
Seroprotection rate[1]	45.7%	96.4%	49.3%
Seroconversion rate[2]	45.7%	96.4%	48.6%
Seroconversion factor[3]	4.7	95.3	5.2

[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.

A 4-fold increase in serum neutralising antibody titres was observed in 79.2% of subjects twenty-one days after the first dose, 95.8% twenty-one days after the second dose and 87.5% six months after the second dose.

In a second study, 49 subjects aged 18-60 years received two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 on days 0 and 21. At day 42, the anti-HA antibody seroconversion rate was 98%, all subjects were seroprotected and the seroconversion factor was 88.6. In addition, all subjects had neutralising antibody titres of at least 1:80.

Cross-reactive immune responses elicited by AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1):

Adults aged 18-60 years

Anti-HA responses against A/Indonesia/5/2005 following administration of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 were as follows:

anti-HA antibody	A/Indonesia/5/2005		
	0, 21 days schedule	0, 6 months schedule	
	21 days after 2nd dose N = 924	7 days after 2nd dose N = 47	21 days after 2nd dose N = 48
Seroprotection rate[1]	50.2%	74.5%	83.3%
Seroconversion rate[2]	50.2%	74.5%	83.3%
Seroconversion factor[3]	4.9	12.9	18.5

[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.

A 4-fold increase in serum neutralising antibodyagainst A/Indonesia/5/2005 was achieved in >90% of subjects after two doses regardless of the schedule. After two doses administered 6 months apart all subjects had a titre of at least 1:80.

In a different study in 50 subjects the anti-HA antibody seroprotection rates 21 days after the second dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 were 20% against A/Indonesia/5/2005, 35% against A/Anhui/01/2005 and 60% against A/Turkey/Turkey/1/2005.

Elderly (>60 years)

In 152 subjects aged > 60 years the anti-HA antibody seroprotection and seroconversion rates against A/Indonesia/5/2005 at day 42 after two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 were 23% and the seroconversion factor was 2.7. Neutralising antibody titres of at least 1:40 or at least 1:80 were achieved in 87% and 67%, respectively, of the 87 subjects tested.

Children aged 3 to 9 years

In the subjects aged 3 to 5 and 6 to 9 years old who received two doses of either a full or a half dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1), the anti-HA antibody responses at day 42 (N=179) and six months after the second dose (N=164) were as follows:

anti-HA antibody	Immune response to A/Indonesia/5/2005							
	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]	71.4%	95.5%	6.0%	69.0%	74.4%	79.1%	4.5%	61.0%
Seroconversion rate[2]	71.4%	95.5%	6.0%	69.0%	74.4%	79.1%	2.4%	61.0%
Seroconversion factor[3]	10.7	33.6	1.4	8.5	12.2	18.5	1.2	7.4

[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.

Furthermore, in the group of children that received a half dose of vaccine, the rate of subjects with a titre of neutralising antibodies above 1:80 remained high up to 12 months after the first dose: in the 3-5 years old group, 97.8% at day 42, 89.6% at month 6 and 87.2% at month 12 and in the 6-9 years old group, 97.6% at day 42, 90.0% at month 6 and 82.9% at month 12.

<u>One dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 administered after one or two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004.</u>

In a clinical study, 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.

<u>Information from non-clinical studies:</u>

The ability to induce protection against homologous and heterologous vaccine strains was assessed non-clinically using ferret challenge models.

In each experiment, four groups of six ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). Doses of 15, 5, 1.7 or 0.6 micrograms of HA were tested in the homologous challenge experiment, and doses of 15, 7.5, 3.8 or 1.75 micrograms of HA were tested in the heterologous challenge experiment. Control

groups included ferrets immunized with adjuvant alone, non-adjuvanted vaccine (15 micrograms HA) or phosphate buffered saline solution. Ferrets were vaccinated on days 0 and 21 and challenged by the intra-tracheal route on day 49 with a lethal dose of either H5N1/A/Vietnam/1194/04 or heterologous H5N1/A/Indonesia/5/05. Of the animals receiving adjuvanted vaccine, 87% and 96% were protected against the lethal homologous or heterologous challenge, respectively. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with the mock-up vaccine using a H5N1 vaccine strain 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:
Polysorbate 80
Octoxynol 10
Thiomersal
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Magnesium chloride ($MgCl_2$)
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

2 years.
After mixing, the vaccine should be used within 24 hours. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°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.

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

Pandemrix 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 allowed to reach room temperature; each vial should be shaken 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.
2. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a syringe and by adding it to the vial containing the antigen.
3. 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.
4. The volume of the Pandemrix vial after mixing is at least 5 ml. The vaccine should be administered in accordance with the recommended posology (see section 4.2).
5. 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.
6. Each vaccine dose of 0.5 ml (full dose) or 0.25 ml (half dose) is withdrawn into a syringe for injection and administered intramuscularly.
7. 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 not exceeding 25°C. If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature before each withdrawal.

Any unused 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/1/08/452/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20/05/2008

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer(s) of the biological active substance

GlaxoSmithKline Biologicals
Branch of SmithKline Beecham Pharma GmbH & Co. KG
Zirkustraße 40, D-01069 Dresden
Germany

Name and address of the manufacturer(s) responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

Medicinal product subject to medical prescription.

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

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

- The MAH shall agree with Member States to measures facilitating the identification and traceability of the A/H1N1 pandemic vaccine administered to each patient, in order to minimise medication errors and aid patients and health care professionals to report adverse reactions. This may include the provision by the MAH of stickers with invented name and batch number with each pack of the vaccine.

- The MAH shall agree with Member States on mechanisms allowing patients and health care professionals to have continuous access to updated information regarding Pandemrix.

- The MAH shall agree with Member Sates on the provision of a targeted communication to healthcare professionals which should address the following:

    - The correct way to prepare the vaccine prior to administration.

    - Adverse events to be prioritised for reporting, i.e. fatal and life-threatening adverse reactions, unexpected severe adverse reactions, adverse events of special interest (AESI).

    - The minimal data elements to be transmitted in individual case safety reports in order to facilitate the evaluation and the identification of the vaccine administered to each subject, including the invented name, the vaccine manufacturer and the batch number.

    - If a specific notification system has been put in place, how to report adverse reactions.

- **OTHER CONDITIONS**

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

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 3.4 (dated 4 September 2009) presented in Module 1.8.1 of the marketing authorisation application, is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

PSUR submission during the influenza pandemic:

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

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version RMPv2 (dated September 2009) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

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

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

Clinical	The MAH commits to provide abridged reports for the following studies performed in adults: Safety and Immunogenicity data: The MAH commits to provide the D21 neutralising antibodies data from study D-Pan H1N1-021 Study D-Pan H1N1-007 -post dose 2 Study D-Pan H1N1-008 -post dose 2	 04 December 2009 04 December 2009 05 February 2010

	Study D-Pan H1N1-020 - post dose 1 - post dose 2 Study D-Pan H1N1-018 - post dose 2 Study D-Pan H1N1-022 Study D-Pan H1N1-017	 04 December 2009 05 February 2010 05 February 2010 09 April 2010 05 March 2010
Clinical	The MAH commits to provide abridged reports for the following studies performed in children: Safety and Immunogenicity data: Study D-Pan H1N1-009 - - post dose 1 (full dose data) - post dose 2 (full dose data) - post dose 2 (full and half dose cleaned data) Study D-Pan H1N1-010 -post dose 1 -post dose 2 Study D-Pan H1N1-023 Study D-Pan H1N1-012	 08 January 201008 January 2010 05 March 2010 04 December 2009 05 March 2010 05 March 2010 09 July 2010
Clinical	The MAH commits to provide the results of the effectiveness study.	Results of study to be provided within two weeks of availability.
Pharmacovigilance	The MAH will conduct a prospective cohort safety study in at least 9,000 patients, in different age groups, including immunocompromised subjects, in accordance with the protocol submitted with the Risk Management Plan. Observed-to-Expected analyses will be performed.	Interim and final results will be submitted in accordance with the protocol.
Pharmacovigilance	The MAH commits to provide the details of the design and to provide the results of a study in a pregnancy registry.	Details to be submitted within one month of Commission Decision granting the Variation. Results to be provided in the simplified PSUR.
Pharmacovigilance	The MAH commits to establish the mechanism to promptly investigate issues affecting the benefit-risk balance of the vaccine.	Agree with EMEA on design of additional studies for emerging benefit-risk evaluation within 1 month of the Commission Decision granting the Variation.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PACK CONTAINING 1 PACK OF 50 VIALS OF SUSPENSION AND 2 PACKS OF 25 VIALS OF EMULSION

1. NAME OF THE MEDICINAL PRODUCT

Pandemrix suspension and emulsion for emulsion for injection.
Pandemic influenza vaccine (H1N1) (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:

3.75 micrograms*
A/California/7/2009 (H1N1)v-like strain (X-179A)

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

* haemagglutinin

3. LIST OF EXCIPIENTS

Polysorbate 80
Octoxynol 10
Thiomersal
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Magnesium chloride ($MgCl_2$)
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 0.5 ml vaccine

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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/1/08/452/001

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 Pandemrix
Pandemic influenza vaccine (H1N1) (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/California/7/2009 (H1N1)v-like strain (X-179A)

3. LIST OF EXCIPIENTS

Excipients:
Polysorbate 80
Octoxynol 10
Thiomersal
Sodium chloride
Disodium hydrogen phosphate
Potassium dihydrogen phosphate
Potassium chloride
Magnesium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Antigen suspension for injection
50 vials: suspension
2.5 ml per 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Biologicals, Rixensart - Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/452/001

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 Pandemrix

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Biologicals, Rixensart - Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/452/001

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 Pandemrix
Pandemic influenza vaccine
A/California/7/2009 (H1N1)v-like strain (X-179A)
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 25°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 Pandemrix
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

Pandemrix suspension and emulsion for emulsion for injection
Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted)

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

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

In this leaflet:

1. What Pandemrix is and what it is used for

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

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

2. Before you receive Pandemrix

You should not receive Pandemrix:

- if you have previously had a sudden life-threatening allergic reaction to any ingredient of Pandemrix (these are listed at the end of the leaflet) or to any of the substances that may be present in trace amounts as follows: egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate (antibiotic) 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, it may be appropriate for you to have the vaccine provided that appropriate medical treatment is immediately available in case of an allergic reaction.

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

Take special care with Pandemrix:

- if you have had any allergic reaction other than a sudden life-threatening allergic reaction to any ingredient contained in the vaccine, to thiomersal, to egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate (antibiotic) or to sodium deoxycholate. (see section 6. Further information).

- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be a problem, but your doctor or nurse will advise whether you could still be vaccinated with Pandemrix,
- if you are having a blood test to look for evidence of infection with certain viruses. In the first few weeks after vaccination with Pandemrix the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently been given Pandemrix.

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

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

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

Pandemrix can be given at the same time as seasonal influenza vaccines that do not contain an adjuvant. There is no information on administration of Pandemrix with other vaccines. However, if this cannot be avoided, the vaccines should be injected into separate limbs. In such cases, you should be aware that the side effects may be more intense.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant, think you may be pregnant, plan to become pregnant. You should discuss with your doctor whether you should receive Pandemrix.
The vaccine may be used during breast-feeding.

Driving and using machines
Some effects mentioned under section 4. "Possible side effects" may affect the ability to drive or use machines.

Important information about some of the ingredients of Pandemrix
This vaccine 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.

This medicinal product contains less than 1 mmol sodium (23 mg) and less than 1 mmol of potassium (39 mg) per dose, i.e. essentially sodium- and potassium-free.

3. How Pandemrix is given

Your doctor or nurse will administer the vaccine in accordance with official recommendations.

The vaccine will be injected into a muscle (usually in the upper arm).

<u>Adults, including the elderly and children from the age of 10 years onwards</u>
A dose (0.5 ml) of the vaccine will be given.
Clinical data suggest that a single dose may be sufficient.
If a second dose is administered there should be an interval of at least three weeks between the first and second dose.

<u>Children from 6 months to 9 years of age</u>
A dose (0.25 ml) of the vaccine will be given.
If a second dose of 0.25 ml is given this will be administered at least three weeks after the first dose.

Children aged less than 6 months of age
Vaccination is currently not recommended in this age group.

When Pandemrix is given for the first dose, it is recommended that Pandemrix (and not another vaccine against H1N1) be given for the complete vaccination course.

4. Possible side effects

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

Allergic reactions may occur following vaccination, in rare cases leading to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.

The frequency of possible side effects listed below is defined using the following convention:

Very common (affects more than 1 user in 10)
Common (affects 1 to 10 users in 100)
Uncommon (affects 1 to 10 users in 1,000)
Rare (affects 1 to 10 users in 10,000)
Very rare (affects less than 1 user in 10,000)

The side effects listed below have occurred with Pandemrix (H5N1) in clinical studies in adults, including the elderly and in children aged from 3-9 years. In these clinical studies most side effects were mild in nature and short term. The side-effects are generally similar to those related to seasonal flu vaccines. In children aged 3-9 years fever occurred more often when the adult dose (0.5 ml of vaccine) was given compared to administration of half the adult dose (0.25 ml of vaccine). Also fever occurred more often in children aged 6-9 years compared to the children aged 3-5 years.

These side effects have also been observed with similar frequencies in clinical studies in adults including the elderly with Pandemrix (H1N1), except for redness (uncommon in the adults and common in the elderly) and fever (uncommon in both age groups).

Very common:
- Headache
- Tiredness
- Pain, redness, swelling or a hard lump at the injection site
- Fever
- Aching muscles, joint pain

Common:
- Warmth, itching or bruising at the injection site
- Increased sweating, shivering, flu-like symptoms
- Swollen glands in the neck, armpit or groin

Uncommon:
- Tingling or numbness of the hands or feet
- Sleepiness
- Dizziness
- Diarrhoea, vomiting, stomach pain, feeling sick
- Itching, rash
- Generally feeling unwell
- Sleeplessness

In children aged 6-35 months who received a half of the adult dose (0.25 ml) of Pandemrix (H1N1), fever and irritability occurred more often compared to the children 3-9 years who received a half of the adult dose (0.25 ml) of Pandemrix (H5N1).

In children aged 6-35 months who received two doses of 0.25 ml (half of the adult dose) the side effects after the second dose were more intense, especially fever (≥38°C), which occurred very commonly.

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

The side effects listed below have occurred during post-marketing experience with Pandemrix H1N1 vaccine:

- 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.
- Generalised skin reactions including facial swelling and urticaria (hives)
- Fits due to fever

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

Rare
- Severe stabbing or throbbing pain along one or more nerves
- Low blood platelet count which can result in bleeding or bruising

Very rare
- Vasculitis (inflammation of the 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 a Guillain-Barré Syndrome

If any of these side effects occur, please tell your doctor or nurse immediately.

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

5. How to store Pandemrix

Keep out of the reach and sight 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 - 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 25°C.

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

6. Further information

What Pandemrix contains

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

  A/California/7/2009 (H1N1)v-like strain (X-179A) 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 to stimulate a better response. This adjuvant contains squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams).

- Other ingredients:
  The other ingredients are: polysorbate 80, octoxynol 10, thiomersal, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride, water for injections

What Pandemrix looks like and contents of the pack

Suspension and emulsion for emulsion for injection.
The suspension is a colourless light opalescent liquid.
The emulsion is a whitish homogeneous liquid.

Prior to administration, the two components should be mixed. The mixed vaccine is a whitish emulsion.

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

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

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

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

The following information is intended for medical or healthcare professionals only:

Pandemrix 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 allowed to reach room temperature; each vial should be shaken 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.
2. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a syringe and by adding it to the vial containing the antigen.
3. 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.
4. The volume of the Pandemrix vial after mixing is at least 5 ml. The vaccine should be administered in accordance with the recommended posology (see section 3 "How Pandemrix is given").
5. 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.
6. Each vaccine dose of 0.5 ml (full dose) or 0.25 ml (half dose) is withdrawn into a syringe for injection and administered intramuscularly.
7. 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 not exceeding 25°C. If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature before each withdrawal.

The vaccine should not be administered intravascularly.

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