This information was recommended by the CHMP on 24 September 2009. It has been sent to the European Commission for the adoption of a formal decision applicable in all European Union Member States.

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:

3.75 micrograms**

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

* 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

This pandemic influenza vaccine has been authorised based on data obtained with a version containing H5N1 antigen supplemented with data obtained with a vaccine containing H1N1 antigen. The Clinical Particulars section will be updated in accordance with emerging additional data.

There is currently very limited clinical experience with an investigational formulation of Pandemrix (H1N1) containing a higher amount of antigen (see section 5.1) in healthy adults aged 18-60 years and no clinical experience in the elderly, in children or in adolescents. The decision to use Pandemrix (H1N1) in each age group defined below should take into account the extent of the clinical data
available with a version of the vaccine containing H5N1 antigen and the disease characteristics of the current influenza pandemic.

The dose recommendations are based on:
• safety and immunogenicity data available on the administration of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) at 0 and 21 days to adults, including the elderly, and on the administration of the adult dose and half of the adult dose at 0 and 21 days to children aged from 3-9 years
• very limited immunogenicity data obtained three weeks after administration of a single dose of an investigational formulation of Pandemrix (H1N1) to healthy adults aged 18-60 years.

See sections 4.8 and 5.1.

Posology

Adults aged 18-60 years:
One dose of 0.5 ml at an elected date.
A second dose of vaccine should preferably be given. There should be an interval of at least three weeks between the first and second dose.
However, preliminary immunogenicity data obtained at three weeks after administration of an investigational formulation of Pandemrix (H1N1) to a limited number of healthy adults aged 18-60 years suggest that a single dose may be sufficient in this age group. See section 5.1.

Elderly (>60 years)
One dose of 0.5 ml at an elected date.
A second dose of vaccine should be given after an interval of at least three weeks. See section 5.1.

Children and adolescents aged 10-17 years
If vaccination is considered to be necessary, consideration may be given to dosing 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. See sections 4.8 and 5.1.

Children aged 3-9 years
If vaccination is considered to be necessary, the available data suggest that administration of 0.25 ml of vaccine (i.e. half of the adult dose) at an elected date and a second dose administered at least three weeks later may be sufficient.
There are very limited safety and immunogenicity data available on the administration of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) and on administration of half a dose of the same vaccine (i.e. 1.875 µg HA and half the amount of AS03 adjuvant in 0.25 ml ) at 0 and 21 days in this age group.
See sections 4.8 and 5.1.

Children aged from 6 months to 3 years
If vaccination is considered to be necessary, consideration may be given to dosing in accordance with the recommendation in children aged 3-9 years. See sections 4.8 and 5.1.

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

For further information, see sections 4.4, 4.8 and 5.1.

It is recommended that subjects who receive a first dose of Pandemrix, 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 Pandemix 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 is very limited experience in children between 3 and 9 years of age and no experience in children less than 3 years of age or in children and adolescents between 10 and 17 years. See sections 4.2, 4.8 and 5.1.

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

There are no data on co-administration of Pandemrix with other vaccines. However, 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.

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:

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>3-5 years</th>
<th>6-9 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Half dose</td>
<td>Full dose</td>
</tr>
<tr>
<td>Induration</td>
<td>9.9%</td>
<td>18.6%</td>
</tr>
<tr>
<td>Pain</td>
<td>48.5%</td>
<td>62.9%</td>
</tr>
<tr>
<td>Redness</td>
<td>10.9%</td>
<td>19.6%</td>
</tr>
<tr>
<td>Swelling</td>
<td>11.9%</td>
<td>24.7%</td>
</tr>
<tr>
<td>Fever (&gt;38°C)</td>
<td>2.0%</td>
<td>6.2%</td>
</tr>
<tr>
<td></td>
<td>- per-dose frequency</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td>- per-subject frequency</td>
<td>3.9%</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>7.9%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Irritability</td>
<td>7.9%</td>
<td>18.6%</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>6.9%</td>
<td>16.5%</td>
</tr>
<tr>
<td>Shivering</td>
<td>1.0%</td>
<td>12.4%</td>
</tr>
</tbody>
</table>

NA=not available

• Post-marketing surveillance

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

Uncommon:
Generalised skin reactions including urticaria

Rare:
Neuralgia, convulsions, transient thrombocytopenia.
Allergic reactions, in rare cases leading to shock, have been reported.
Very rare:
Vasculitis with transient renal involvement.
Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

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.

This section describes the clinical experience with the mock-up vaccines following a two-dose administration and with an investigational formulation of Pandemrix (H1N1) after a single dose in healthy adults aged 18-60 years.

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 have evaluated the immunogenicity of different formulations of AS03-adjuvanted and non-adjuvanted vaccines (A/H5N1) in subjects aged 3-9 years, 18-60 years and >60 years following a 0, 21 day schedule. The majority of these subjects had no detectable anti-haemagglutinin (anti-HA) antibody to the H5N1 strains tested before vaccination.

Immune response to an investigational formulation of Pandemrix (H1N1) in adults aged 18-60 years

In a clinical study that evaluated the immunogenicity of AS03-adjuvanted vaccine containing 5.25 µg HA derived from A/California/7/2009 (H1N1)v-like in healthy subjects aged 18-60 years the anti-HA antibody responses were as follows:

<table>
<thead>
<tr>
<th>anti-HA antibody</th>
<th>Immune response to A/California/7/2009 (H1N1)v-like</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21 days after 1st dose</td>
</tr>
<tr>
<td></td>
<td>N=62</td>
</tr>
<tr>
<td>Seroprotection rate¹</td>
<td>98.4%</td>
</tr>
<tr>
<td>Seroconversion rate²</td>
<td>98.4%</td>
</tr>
<tr>
<td>Seroconversion factor³</td>
<td>41.4</td>
</tr>
</tbody>
</table>

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.
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:

<table>
<thead>
<tr>
<th>anti-HA antibody</th>
<th>Immune response to A/Vietnam/1194/2004</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0, 21 days schedule</td>
</tr>
<tr>
<td></td>
<td>21 days after 1st dose N=925</td>
</tr>
<tr>
<td>Seroprotection rate(^1)</td>
<td>44.5%</td>
</tr>
<tr>
<td>Seroconversion rate(^2)</td>
<td>42.5%</td>
</tr>
<tr>
<td>Seroconversion factor(^3)</td>
<td>4.1</td>
</tr>
</tbody>
</table>

\(^1\) seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre \(\geq 1:40\);
\(^2\) seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of \(\geq 1:40\), 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 \(\geq 1:40\)) 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:

<table>
<thead>
<tr>
<th>anti-HA antibody</th>
<th>Immune response to A/Vietnam/1194/2004 (D42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61 to 70 years</td>
</tr>
<tr>
<td>Seroprotection rate(^1)</td>
<td>84.6%</td>
</tr>
<tr>
<td>Seroconversion rate(^2)</td>
<td>74.7%</td>
</tr>
<tr>
<td>Seroconversion factor(^3)</td>
<td>11.8</td>
</tr>
</tbody>
</table>

\(^1\) seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre \(\geq 1:40\);
\(^2\) seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of \(\geq 1:40\), 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 double 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:

<table>
<thead>
<tr>
<th>anti-HA antibody</th>
<th>Immune response to A/Vietnam/1194/2004</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 to 5 years</td>
</tr>
<tr>
<td></td>
<td>Day 42</td>
</tr>
<tr>
<td>Half dose</td>
<td>N=49</td>
</tr>
<tr>
<td>Full dose</td>
<td>N=50</td>
</tr>
<tr>
<td>Seroprotection rate(^1)</td>
<td>95.9% 100%</td>
</tr>
<tr>
<td>Seroconversion rate(^2)</td>
<td>95.9% 100%</td>
</tr>
<tr>
<td>Seroconversion factor(^3)</td>
<td>78.5 191.3</td>
</tr>
</tbody>
</table>

\(^1\)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:

<table>
<thead>
<tr>
<th>Serum neutralising antibody</th>
<th>Immune response to A/Vietnam/1194/2004</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21 days after 2(^{nd}) dose</td>
</tr>
<tr>
<td></td>
<td>3 to 5 years</td>
</tr>
<tr>
<td></td>
<td>6 to 9 years</td>
</tr>
<tr>
<td>Half dose</td>
<td>N=47</td>
</tr>
<tr>
<td>Full dose</td>
<td>N=42</td>
</tr>
<tr>
<td>Half dose</td>
<td>N=42</td>
</tr>
<tr>
<td>Full dose</td>
<td>N=42</td>
</tr>
<tr>
<td>GMT(^1)</td>
<td>1044.4 4578.3</td>
</tr>
<tr>
<td>Seroconversion rate(^2)</td>
<td>95.6% 97.4%</td>
</tr>
</tbody>
</table>

\(^1\)GMT: geometric mean titre.  
\(^2\)Seroconversion rate: proportion of subjects with a titre of at least 1:80 at day 42.
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:

<table>
<thead>
<tr>
<th>anti-HA antibody</th>
<th>Immune response to A/Indonesia/05/2005</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 21</td>
</tr>
<tr>
<td></td>
<td>N=140</td>
</tr>
<tr>
<td>Seroprotection rate</td>
<td>45.7%</td>
</tr>
<tr>
<td>Seroconversion rate</td>
<td>45.7%</td>
</tr>
<tr>
<td>Seroconversion factor</td>
<td>4.7</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>anti-HA antibody</th>
<th>A/Indonesia/5/2005</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0, 21 days schedule</td>
</tr>
<tr>
<td></td>
<td>21 days after 2nd dose</td>
</tr>
<tr>
<td></td>
<td>N = 924</td>
</tr>
<tr>
<td>Seroprotection rate</td>
<td>50.2%</td>
</tr>
<tr>
<td>Seroconversion rate</td>
<td>50.2%</td>
</tr>
<tr>
<td>Seroconversion factor</td>
<td>4.9</td>
</tr>
</tbody>
</table>

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 against 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:

<table>
<thead>
<tr>
<th>anti-HA antibody</th>
<th>Immune response to A/Indonesia/5/2005</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 to 5 years</td>
</tr>
<tr>
<td></td>
<td>Day 42</td>
</tr>
<tr>
<td>Half dose N=49</td>
<td></td>
</tr>
<tr>
<td>Full dose N=44</td>
<td></td>
</tr>
<tr>
<td>Half dose N=50</td>
<td>71.4%</td>
</tr>
<tr>
<td>Full dose N=29</td>
<td></td>
</tr>
<tr>
<td>Half dose N=43</td>
<td>74.4%</td>
</tr>
<tr>
<td>Full dose N=44</td>
<td></td>
</tr>
<tr>
<td>Half dose N=44</td>
<td>71.4%</td>
</tr>
<tr>
<td>Full dose N=43</td>
<td></td>
</tr>
<tr>
<td>Half dose N=44</td>
<td>4.5%</td>
</tr>
<tr>
<td>Full dose N=41</td>
<td></td>
</tr>
</tbody>
</table>

1seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
2seroconversion 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;
3seroconversion 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.

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.

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:

<table>
<thead>
<tr>
<th>anti-HA antibody</th>
<th>Against A/Vietnam 21 days after boosting with A/Vietnam N=46</th>
<th>Against A/Indonesia 21 days after boosting with A/Indonesia N=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroprotection rate¹</td>
<td>89.6% 91.3% 98.1% 93.9%</td>
<td>87.5% 82.6% 98.1% 91.8%</td>
</tr>
<tr>
<td>Booster seroconversion rate²</td>
<td>29.2 11.5 55.3 45.6</td>
<td></td>
</tr>
</tbody>
</table>

¹seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
²booster 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;
³booster 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.

Information from non-clinical studies:

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 (Na₂HPO₄)
- Potassium dihydrogen phosphate (KH₂PO₄)
- Potassium chloride (KCl)
- Magnesium chloride (MgCl₂)
- Water for injections

**Emulsion vial:**
- Sodium chloride (NaCl)
- Disodium hydrogen phosphate (Na₂HPO₄)
- Potassium dihydrogen phosphate (KH₂PO₄)
- 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 (10 x 0.25 ml doses) with a stopper (butyl rubber).
- two packs of 25 vials (type I glass) of 2.5 ml emulsion (10 x 0.25 ml doses) 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 and suspension should be allowed to reach room temperature, shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.
2. The vaccine is mixed by withdrawing the contents of the vial containing the emulsion by means of a syringe and by adding it to the vial containing the suspension.
3. After the addition of the emulsion to the suspension, 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 Pandemrix (5 ml) after mixing corresponds to 10 doses of vaccine.
5. The vial should be shaken prior to each administration.
6. Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection.
7. The needle used for withdrawal must be replaced by a needle suitable for intramuscular injection.
8. After mixing, use the vaccine within 24 hours and do not store above 25°C.

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 States 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 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 RMPv5 (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 AUTHORITY 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.

<table>
<thead>
<tr>
<th>Clinical</th>
<th>The MAH commits to provide abridged reports for the following studies performed in adults:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety and Immunogenicity data:</td>
</tr>
<tr>
<td></td>
<td>Study D-Pan H1N1-021</td>
</tr>
<tr>
<td></td>
<td>The MAH commits to provide the D21 neutralising antibodies data from study D-Pan H1N1-021</td>
</tr>
<tr>
<td></td>
<td>Study D-Pan H1N1-007</td>
</tr>
<tr>
<td></td>
<td>-post dose 1</td>
</tr>
<tr>
<td></td>
<td>-post dose 2</td>
</tr>
<tr>
<td></td>
<td>06 November 2009</td>
</tr>
<tr>
<td></td>
<td>14 October 2009</td>
</tr>
<tr>
<td></td>
<td>14 October 2009</td>
</tr>
<tr>
<td></td>
<td>04 December 2009</td>
</tr>
</tbody>
</table>
| Study D-Pan H1N1-008 | 06 November 2009  
| - post dose 1  
| - post dose 2  
| Study D-Pan H1N1-020 | 04 December 2009  
| - post dose 1  
| - post dose 2  
| Study D-Pan H1N1-018 | 06 November 2009  
| - post dose 1  
| - post dose 2  
| Study D-Pan H1N1-022 | 09 April 2010  
| Study D-Pan H1N1-017 | 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 (half dose data)  
  - post dose 2 (half dose data)  
  - 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  
  06 November 2009  
  08 January 2010  
  04 December 2009  
  08 January 2010  
  05 March 2010  
  09 July 2010

### Clinical

The MAH commits to submit the protocol and provide the results of the effectiveness studies carried out in accordance with the study protocols published by ECDC. Protocol to be submitted on 15 October 2009. Results of studies 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:

\[ 3.75 \, \text{micrograms}^* \]

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

AS03 adjuvant composed of squalene, DL-\(\alpha\)-tocopherol and polysorbate 80

* haemagglutinin

3. LIST OF EXCIPIENTS

Polysorbate 80
Octoxynol 10
Thiomersal
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na\(_2\)HPO\(_4\))
Potassium dihydrogen phosphate (KH\(_2\)PO\(_4\))
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 vaccine (5 ml)

1 dose = 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 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
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
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 (2°C-8°C), do not freeze, protect from light
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EMULSION VIAL</td>
<td></td>
</tr>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
<td></td>
</tr>
<tr>
<td>Adjuvant emulsion for Pandemrix</td>
<td>I.M.</td>
</tr>
<tr>
<td><strong>2. METHOD OF ADMINISTRATION</strong></td>
<td></td>
</tr>
<tr>
<td>Mix into Antigen suspension before use</td>
<td></td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
<td></td>
</tr>
<tr>
<td>EXP</td>
<td></td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
<td></td>
</tr>
<tr>
<td>Lot</td>
<td></td>
</tr>
<tr>
<td><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
<td></td>
</tr>
<tr>
<td>2.5 ml</td>
<td></td>
</tr>
<tr>
<td><strong>6. OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>Storage (2ºC-8ºC), do not freeze, protect from light</td>
<td></td>
</tr>
</tbody>
</table>
B. PACKAGE 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.

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.

There is no information on administration of the vaccine 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).

**Adults, including the elderly**

A dose (0.5 ml) of the vaccine will be given.

A second dose of 0.5 ml vaccine may be given after an interval of at least three weeks.

**Children and adolescents 10-17 years of age**

If it is considered that you need to be vaccinated, you may receive two doses of 0.5 ml vaccine given at least three weeks apart.

**Children 3-9 years of age**

If it is considered that your child needs to be vaccinated, he/she may receive one dose of 0.25 ml vaccine and a second dose of 0.25 ml at least three weeks later.

**Children aged from 6 months to 3 years of age**
If it is considered that your child needs to be vaccinated, he/she may receive one dose of 0.25 ml vaccine and a second dose of 0.25 ml at least three weeks later.

**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.

In the clinical studies with a similar vaccine, most side effects were mild in nature and short term. The side-effects are generally similar to those related to the seasonal flu vaccine.

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 in clinical studies in adults, including the elderly and in children aged from 3-9 years:

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

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.

**Uncommon**
- Generalised skin reactions including urticaria (hives)

**Rare**
- 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.
- Fits
- 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) for 10 doses
- two packs containing 25 vials of 2.5 ml emulsion (adjuvant) for 10 doses

**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:

**België/Belgique/Belgien**
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

**Luxembourg/Luxemburg**
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

**България**
ГлаксоСмитКлайн ЕООД
Тел.: + 359 2 953 10 34

**Magyarország**
GlaxoSmithKline Kft.
Tel.: + 36-1-2255300

**Česká republika**
GlaxoSmithKline s.r.o.
Tel: + 420 2 22 00 11 11
gsk.czmail@gsk.com

**Malta**
GlaxoSmithKline Malta
Tel: + 356 21 238131

**Danmark**
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
dk-info@gsk.com

**Nederland**
GlaxoSmithKline BV
Tel: + 31 (0)30 69 38 100
nlinfo@gsk.com
Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel: + 49 (0)89 360448701
produkt.info@gsk.com

Eesti
GlaxoSmithKline Eesti OÜ
Tel: +372 667 6900
estonia@gsk.com

Ελλάδα
GlaxoSmithKline A.E.B.E
Τηλ.: + 30 210 68 82 100

España
GlaxoSmithKline, S.A.
Tel: + 34 902 202 700
es-ci@gsk.com

France
Laboratoire GlaxoSmithKline
Tél: + 33 (0) 800 00 12 12
grippeA@gsk.com

Ireland
GlaxoSmithKline (Ireland) Ltd
Tel: + 353 (0)1 4955000

Ísland
GlaxoSmithKline ehf.
Sími: +354-530 3700

Italia
GlaxoSmithKline S.p.A.
Tel:+ 39 04 59 21 81 11

Κύπρος
GlaxoSmithKline Cyprus Ltd
Τηλ.: + 357 22 39 70 00

Latvija
GlaxoSmithKline Latvia SIA
Tel: + 371 67312687
lv-epasts@gsk.com

Lietuva
GlaxoSmithKline Lietuva UAB
Tel. +370 5 264 90 00
info.lt@gsk.com

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

Österreich
GlaxoSmithKline Pharma GmbH.
Tel: + 43 1 970 75-0
at.info@gsk.com

Polska
GSK Commercial Sp. z o.o.
Tel.: + 48 (22) 576 9000

Portugal
GlaxoSmithKline, Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România
GlaxoSmithKline (GSK) SRL
Tel: + 40 (0)21 3028 208

Slovenija
GlaxoSmithKline d.o.o.
Tel: + 386 (0) 1 280 25 00
medical.x.si@gsk.com

Slovenská republika
GlaxoSmithKline Slovakia s.r.o.
Tel: + 421 (0)2 48 26 11 11
recepcia.sk@gsk.com

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 10 30 30 30
Finland.tuoteinfo@gsk.com

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom
GlaxoSmithKline UK
Tel: + 44 (0)808 100 9997
customercontactuk@gsk.com

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) website: [http://www.emea.europa.eu/](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 and suspension should be allowed to reach room temperature, shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.
2. The vaccine is mixed by withdrawing the contents of the vial containing the emulsion (adjuvant) by means of a syringe and by adding it to the vial containing the suspension (antigen).
3. After the addition of the emulsion to the suspension, 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 Pandemrix (5 ml) after mixing corresponds to 10 doses of vaccine.
5. The vial should be shaken prior to each administration.
6. Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection.
7. The needle used for withdrawal must be replaced by a needle suitable for intramuscular injection.
8. After mixing, use the vaccine within 24 hours and do not store above 25°C.

The vaccine should not be administered intravascularly.

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