

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After mixing, 1 dose (0.5 ml) contains:

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

A/VietNam/1194/2004 (H5N1) like strain used (NIBRG-14) 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 (10.68 milligrams), DL- α -tocopherol (11.86 milligrams) and polysorbate 80 (4.85 milligrams)

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

Excipients: It 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. Pandemic influenza vaccine should be used in accordance with official guidance (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Posology

Adults from the age of 18 to 60 years: 1 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.

There is no experience in children and adults above 60 years of age.

For further information, see section 5.1.

Method of administration

Immunisation should be carried out by intramuscular injection.

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. However, in a pandemic situation, it may be appropriate to give the vaccine, provided that facilities for resuscitation are immediately available in case of need.

See section 4.4.

4.4 Special warnings and precautions for use

Caution is needed when 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.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Pandemrix should not be given at the same time as other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

No data have been generated in pregnant women with Pandemrix or with any other vaccine that contains the AS03 adjuvant

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).

Healthcare providers need to assess the benefits and potential risks of administering the vaccine to pregnant women taking into consideration official recommendations.

Pandemrix may be used during lactation.

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 operate machinery.

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).

The incidence of adverse reactions has been evaluated in approximately 5,000 subjects 18 years old and above who received formulations containing at least 3.75 microgram HA/AS03.

Adverse reactions reported are listed according to the following frequency:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ 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

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

Psychiatric disorders

Uncommon: insomnia

- Post-marketing surveillance

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

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

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

Immune response against vaccine strain contained in Pandemrix (A/Vietnam/1194/2004 (H5N1)):

In a consistency study, more than 900 subjects aged 18-60 years received Pandemrix following a 0, 21 days schedule.

Twenty-one days after the first and second dose of the vaccine, the seroprotection rates, seroconversion rates and seroconversion factors for anti-haemagglutinin (anti-HA) antibody were as follows:

anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate*†	44.5%	94.3%
Seroconversion rate†	42.5%	93.7%
Seroconversion factor†	4.1	39.8

* anti-HA \geq 1:40

† seroprotection rate : proportion of subjects with haemagglutination inhibition (HI) titre \geq 1:40; seroconversion rate: proportion of subjects who were 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; seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

Twenty-one days after administration of the second dose, 96.0% of subjects had a 4-fold increase in serum neutralising antibody titres.

A neutralising antibody titre of at least 1:80 was achieved in 97.8% of subjects at day 42.

In a dose finding study in subjects aged 18-60 years, 50 subjects received a dose of 3.75 micrograms HA/AS03 in a volume of 1 ml at 0 and 21 days. The seroprotection rates, seroconversion rates and seroconversion factors for anti-haemagglutinin (anti-HA) antibody at day 42 (post dose 2) and day 180 (persistence) were as follows:

anti-HA antibody	Day 42	Day 180
Seroprotection rate*†	84%	54%
Seroconversion rate†	82%	52%
Seroconversion factor†	27.9	4.4

* anti-HA \geq 1:40

† seroprotection rate : proportion of subjects with haemagglutination inhibition (HI) titre \geq 1:40; 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; 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 85.7% of subjects at day 42 and 72% at day 180.

Cross-reactive immune response against variants of A/Vietnam/1194/2004 (H5N1):

In the consistency study the seroprotection rate, seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody against A/Indonesia/5/2005 at 21 days after the second dose were as follows:

anti-HA antibody	A/Indonesia/5/2005 N = 924
Seroprotection rate*†	50.2%
Seroconversion rate†	50.2%
Seroconversion factor†	4.9

* anti-HA \geq 1:40

† seroprotection rate : proportion of subjects with haemagglutination inhibition (HI) titre \geq 1:40; 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; 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 obtained in 91.4% of subjects at day 42.

In the dose finding study the seroprotection rate, seroconversion rate and seroconversion factor against H5N1 drift variants 21 days after the second dose were as follows:

anti-HA antibody	A/Indonesia/5/2005 N = 50	A/Anhui/01/2005 N = 20	A/Turkey/Turkey/1/2005 N = 20
Seroprotection rate*†	20.0%	35.0%	60.0%
Seroconversion rate†	20.0%	35.0%	60.0%
Seroconversion factor†	2.0	3.4	4.7

* anti-HA \geq 1:40

† seroprotection rate : proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$; 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; seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

Twenty one days after the second dose, a 4-fold increase in serum neutralising antibody titres was obtained in 77.1% of subjects against the A/Indonesia/5/2005 strain, in 75.0% of subjects against A/Anhui/01/2005 and in 85.0% of subjects against A/Turkey/Turkey/1/2005.

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 reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, female fertility, embryo-foetal 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

18 months.

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

Vial A: multidose vial containing the antigen (suspension),

Vial B: multidose vial containing the adjuvant (emulsion).

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 (Vial B) by means of a syringe and by adding it to the vial containing the suspension (Vial A).
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.

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)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

Not applicable

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version V01 (dated June 2006) presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version RMPv3 (dated 31 January 2008) 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.

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

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

PSURs

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 risk-benefit balance in a pandemic. Prompt analysis of cumulative safety information, in light of extent of exposure, will be crucial for regulatory decisions and protection of the population to be vaccinated. In addition, during a pandemic, resources needed for an in-depth evaluation of Periodic Safety Update Reports in the format as defined in Volume 9a of the Rules Governing Medicinal Product in the European Union may not be adequate for a rapid identification of a new safety issue.

In consequence, as soon as the pandemic is declared (Phase 6 of the WHO global Influenza preparedness plan) and the pandemic vaccine is used, the MAH shall submit periodic safety update reports with periodicity and format defined as follows:

Frequency of submission

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

Format

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

1. Fatal and/or life-threatening reactions – for each Preferred Term (PT), including the proportion of fatal reports
2. Adverse Events of Special Interest (PTs)
3. Serious unexpected reactions (PTs)
4. All events occurring in the following age groups: 6-23 months, 2-8 years, 8-17 years, 18-60 years, >60 years
All events occurring in pregnant women
5. All events reported by patients that have been entered into the database by data-lock point
6. A cumulative overview of all events reported during the period, stratified according to type of reporter (patient or health care professional), seriousness, expectedness, and whether spontaneous or solicited.

Presentation of data will take into consideration the following recommendations:

- Serious expected reactions will be reviewed by the MAH as part of their signal detection procedures and will only form part of the report if an issue of concern arises.
- All tables will be based on number of events (presented on PT level, sorted by System Organ Class [SOC]) and not number of cases.
- Tables 1 to 4 will be based on events reported from healthcare professionals only.
- In Tables 1 to 5, numbers will be provided for events received during the reporting period and cumulatively.
- All tables will be based on generic and not product-specific data. Product-specific data can be evaluated during signal work-up.
- No line listings are required – these can be provided in signal evaluation reports as necessary.

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

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

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

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.

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 annual reassessment of the benefit/risk profile.

Clinical	During the pandemic, the applicant will collect clinical safety and effectiveness data of the pandemic vaccine and submit this information to the CHMP for evaluation.	Depending on and after implementation of vaccine when first pandemic will take place.
Pharmacovigilance	During the pandemic, the applicant will conduct a prospective cohort study as identified in the Pharmacovigilance plan.	Depending on and after implementation of vaccine when first pandemic will take place.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

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

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After mixing, 1 dose (0.5 ml) contains:

Split influenza virus inactivated, containing antigen equivalent to:

A/VietNam/1194/2004 (H5N1) like strain used (NIBRG-14) 3.75 micrograms*

AS03 adjuvant composed of squalene (10.68 milligrams), DL- α -tocopherol (11.86 milligrams) and polysorbate 80 (4.85 milligrams)

* 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

25 vials x 2: emulsion

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: MM/YYYY

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

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

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**

1. NAME OF THE MEDICINAL PRODUCT

Pandemrix suspension for emulsion for injection
Pandemic influenza vaccine (H5N1)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Split influenza virus, inactivated, containing antigen equivalent to
A/VietNam/1194/2004 (H5N1) like strain used (NIBRG-14) 3.75 micrograms*

* 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 for emulsion for injection
50 vials: suspension

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 emulsion before administration

8. EXPIRY DATE

EXP: MM/YYYY

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/0/00/000/000

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**

1. NAME OF THE MEDICINAL PRODUCT

Emulsion for emulsion for injection for Pandemrix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

AS03 adjuvant composed of squalene (10.68 milligrams), DL- α -tocopherol (11.86 milligrams) and polysorbate 80 (4.85 milligrams)

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Emulsion for emulsion for injection
25 vials: emulsion

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 suspension before administration

8. EXPIRY DATE

EXP: MM/YYYY

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/0/00/000/000

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

Vial A
Pandemrix suspension for emulsion for injection

IM

2. METHOD OF ADMINISTRATION

To be mixed with Vial B before administration

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

10 doses (2.5 ml)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
EMULSION VIAL

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

Vial B
Emulsion for emulsion for injection for Pandemrix

IM

2. METHOD OF ADMINISTRATION

To be mixed with Vial A before administration

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses (2.5 ml)

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you start receiving this vaccine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for you. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Pandemrix is and what it is used for
2. Before you receive Pandemrix
3. How Pandemrix is given
4. Possible side effects
5. How to store Pandemrix
6. Further information

1. WHAT PANDEMRIX IS AND WHAT IT IS USED FOR

Pandemrix is a vaccine for use in adults aged 18 to 60 years to prevent pandemic influenza (flu).

Pandemic flu is a type of influenza that occurs at intervals that vary from less than 10 years to many decades. It spreads rapidly around the world. The symptoms of pandemic flu are similar to those of ordinary flu but are usually more severe.

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

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

2. BEFORE YOU RECEIVE PANDEMRIX

Pandemrix should not be given:

- 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.

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 will advise whether you can still be vaccinated with Pandemrix.

- if you have problems with your immune system, since your response to the vaccine may then be poor.
- if you are having a blood test to look for evidence of infection with certain viruses. In the first few weeks after vaccination with Pandemrix the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently received Pandemrix.

Using other medicines or vaccines

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

Pandemrix is not intended to be given at the same time as other vaccines. However, if this cannot be avoided, the other vaccine will be injected into the other arm. Any side effects that occur may be more severe.

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

Pregnancy and breast-feeding

There is no information on the use of Pandemrix in pregnant women. Your doctor needs to assess the benefits and potential risks of giving you the vaccine if you are pregnant. Please tell your doctor if you are/may be pregnant or intend to become pregnant.

Pandemrix may be given while you are 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

Thiomersal (preservative) is present in this product, and it is possible that you may experience an allergic reaction.

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

You will receive two doses of Pandemrix. The second dose should be given after an interval of at least three weeks after the first dose.

The doctor or nurse will give Pandemrix as an injection into your upper arm muscle.

The vaccine should never be given into a vein or into the skin.

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

4. POSSIBLE SIDE EFFECTS

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

- ◆ Very common (these may occur with 1 in 10 doses or more of the vaccine):
 - Headache

- Tiredness
 - Pain, redness, swelling or a hard lump at the injection site
 - Fever
 - Aching muscles, joint pain
- ◆ Common (these may occur with up to 1 in 10 doses of the vaccine):
 - Warmth, itching or bruising at the injection site
 - Increased sweating, shivering, flu-like symptoms
 - Swollen glands in the neck, armpit or groin
 - ◆ Uncommon (these may occur with up to 1 in 100 doses of the vaccine):
 - Tingling or numbness of the hands or feet
 - Sleepiness
 - Dizziness
 - Diarrhoea, vomiting, stomach pain, feeling sick
 - Itching, rash
 - Generally feeling unwell
 - Sleeplessness

These reactions usually disappear within 1-2 days without treatment.

Other side effects which have occurred in the days or weeks after vaccination with ordinary flu vaccines include:

- ◆ Uncommon (these may occur with up to 1 in 100 doses of the vaccine):
 - Generalised skin reactions including urticaria (hives)
- ◆ Rare (these may occur with up to 1 in 1,000 doses of the vaccine):
 - Severe stabbing or throbbing pain along one or more nerves
 - Fits
 - Low blood platelet count which can result in bleeding or bruising
 - Allergic reactions leading to a dangerous decrease of blood pressure, which, if untreated, may lead to collapse, coma and death
- ◆ Very rare (these may occur with up to 1 in 10,000 doses of the vaccine):
 - Narrowing or blockage of blood vessels with kidney problems
 - Temporary inflammation of the brain and nerves causing pain, weakness and paralysis that may spread across the body.

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

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:**
After mixing, one dose (0.5 ml) contains 3.75 micrograms of haemagglutinin from the following influenza virus strain:

A/Vietnam/1194/2004 (H5N1)
- **Adjuvant:**
The emulsion vial contains an ‘adjuvant’ (AS03). This compound contains squalene (10.68 milligrams), DL- α -tocopherol (11.86 milligrams) and polysorbate 80 (4.85 milligrams). Adjuvants are used to improve the body’s response to the vaccine.
- **Other ingredients:**
The other ingredients are: 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

What Pandemrix looks like and contents of the pack

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

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.

Marketing Authorisation Holder and Manufacturer

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

For any information about this medicinal product, 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

Danmark

GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
info@glaxosmithkline.dk

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) 1 39 17 84 44
diam@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 89 95 01

Latvija

GlaxoSmithKline Latvia SIA
Tel: + 371 7312687

Malta

GlaxoSmithKline Malta
Tel: + 356 21 238131

Nederland

GlaxoSmithKline BV
Tel: + 31 (0)30 69 38 100
nlinfo@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 49 10 33 11
repcia.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

Lietuva

GlaxoSmithKline Lietuva UAB

Tel. +370 5 264 90 00

info.lt@gsk.com

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

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

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

Pandemrix consists of two containers:

Vial A: multidose vial containing the antigen (suspension),

Vial B: multidose vial containing the adjuvant (emulsion).

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 (Vial B) by means of a syringe and by adding it to the vial containing the suspension (Vial A).
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.

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