ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg suspension and emulsion for emulsion for injection.
Prepandemic 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

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

Active immunisation against H5N1 subtype of Influenza A virus.
This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of vaccine prepared from A/VietNam/1194/2004 NIBRG-14 (H5N1) (see section 5.1).

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg should be used in accordance with official guidance.

4.2 Posology and method of administration

Posology

Adults from the age of 18 years:
One dose of 0.5 ml at an elected date.
A second dose of 0.5 ml should be given after an interval of at least three weeks.

Based on very limited data, adults aged >80 years may require a double dose of Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg on an elected date and again after an interval of at least three weeks in order to achieve an immune response (see section 5.1).

A complete vaccination course with Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg consists of two doses. However, in the event of an officially declared influenza pandemic, persons previously vaccinated with one or two doses of Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg that contained HA antigen derived from a different clade of the same influenza subtype as the pandemic influenza strain may receive a single dose of Pandemrix instead of two doses that are required in previously unvaccinated individuals.

There is no experience in children.

For further information, see sections 4.4 and 5.1.

Method of administration

Immunisation should be carried out by intramuscular injection.

If a double dose is given, the injections should be given into opposite limbs.

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. See sections 4.4, 4.8 and 6.1.

Acute severe febrile illness. Immunisation should be postponed.

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.

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg should under no circumstances be administered intravascularly or intradermally.

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).

4.5 Interaction with other medicinal products and other forms of interaction

The vaccine should not usually be given at the same time as other vaccines. However, if co-administration with another vaccine is considered to be essential, the vaccines should be injected into 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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg 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, embryonic/fetal 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.

There are no data regarding the use of Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg during lactation. The potential benefits to the mother and risks to the infant should be considered before administering Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg 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

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 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

- Post-marketing surveillance

No post-marketing surveillance data are available following Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg 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

Immune response againstA/Vietnam/1194/2004 :

In clinical studies that evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 in subjects aged 18-60 years the anti-haemagglutinin (anti-HA) antibody responses were as follows:

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

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

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

Follow up of 50 subjects aged 18-60 years who had received two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 at 0 and 21 days showed that 84% were seroprotected (HI titre ≥1:40) at day 42 compared with 54% at day 180. A 4-fold increase in serum neutralising antibody titres from day 0 was observed in 85.7% at day 42 and 72% at day 180.

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

anti-HA antibody	Immune response to A/Vietnam/1194/2004 (D42)					
	61 to 70 years		71 to 80 years		>80 years	
	Single dose N=91	Double dose N=92	Single dose N=48	Double dose N=43	Single dose N=13	Double dose N=10
Seroprotection rate[1]	84.6%	97.8%	87.5%	93.0%	61.5%	90.0%
Seroconversion rate[2]	74.7%	90.2%	77.1%	93.0%	38.5%	50.0%
Seroconversion factor[3]	11.8	26.5	13.7	22.4	3.8	7.7

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

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

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

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

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

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

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

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

A 4-fold increase in serum neutralising 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 aged 18-60 years 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.

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.

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:

anti-HA antibody	Against A/Vietnam 21 days after boosting with A/Vietnam	Against A/Indonesia 21 days after boosting with A/Indonesia

	N=46		N=49	
	After one priming dose	After two priming doses	After one priming dose	After two priming doses
Seroprotection rate[1]	89.6%	91.3%	98.1%	93.9%
Booster seroconversion rate[2]	87.5%	82.6%	98.1%	91.8%
Booster factor[3]	29.2	11.5	55.3	45.6

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

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

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

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-fetal and postnatal toxicity (up to the end of the lactation period).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Suspension vial:
Polysorbate 80
Octoxynol 10
Thiomersal
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Magnesium chloride ($MgCl_2$)
Water for injections

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

For adjuvants, see section 2.

6.2 Incompatibilities

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

6.3 Shelf-life

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

6.4 Special precautions for storage

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

6.5 Nature and contents of container

One pack containing:
- one pack of 50 vials (type I glass) of 2.5 ml suspension (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

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg 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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg (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)

EU/1/08/478/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26/09/2008

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

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

Name and address of the manufacturer 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 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.

- **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 V03 (dated 19 November 2007) 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 RMPv6 (dated March 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.

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

Outside of the pandemic period, the normal PSUR periodicity and format will be maintained.

PSUR submission when Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg is used 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, duration a pandemic, resources needed for an in-depth evaluation of Periodic Safety Update Reports in the format as defined in Volume 9a of the Rules Governing Medicinal Product in the European Union may not be adequate for a rapid identification of a new safety issue.

In consequence, as soon as the pandemic is declared (Phase 6 of the WHO global Influenza preparedness plan) and the prepandemic vaccine is used, the MAH shall submit more frequent simplified periodic safety update reports with a format and a periodicity defined in the "CHMP Recommendations for the Core Risk Management Plan for Influenza Vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context" (EMEA/49993/2008), and any subsequent update.

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.

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

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg suspension and emulsion for emulsion for injection
Prepandemic 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 (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 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/1/08/478/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 50 VIALS OF SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg suspension for emulsion for injection
Prepandemic 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/1/08/478/001

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

1. NAME OF THE MEDICINAL PRODUCT

Emulsion for emulsion for injection for Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

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Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/478/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS SUSPENSION VIAL

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

Vial A
Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg 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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg
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

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg suspension and emulsion for emulsion for injection
Prepandemic 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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg is and what it is used for

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg is a vaccine for use in adults from 18 years old. It is intended to be given before or during the next influenza (flu) pandemic to prevent flu caused by the H5N1 type of the virus. 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, Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg may not fully protect all persons who are vaccinated.

2. Before you receive Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg should not be given:

- if you have previously had a sudden life-threatening allergic reaction to any ingredient of Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg (these are listed at the end of this 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.

- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will 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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg.

Do not have Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before having this vaccine.

Take special care with Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg:

- 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 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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently received Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg.

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.

There are no data on the use of Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg given at the same time as other vaccines. Therefore, Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg 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, Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg 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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg in pregnant or breast-feeding women. Your doctor needs to assess the benefits and potential risks of giving you the vaccine if you are pregnant or breast-feeding. Please tell your doctor if you are/may be pregnant or intend to become pregnant, or if you are breast-feeding and follow his advice.

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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg

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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg is given

You will receive two doses of Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg. The second dose should be given after an interval of at least three weeks.

If you are older than 80 years of age, you may receive two double injections of Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg. The first two injections should be given at the elected date and the two other injections should preferably be given 3 weeks after.

The doctor or nurse will give Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg as an injection into your upper arm muscle. The vaccine should never be given into a vein or into the skin. The double injections will be given in opposite arms.

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

4. Possible side effects

Like all medicines, Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg can cause side effects, although not everybody gets them.

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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg.

Very rare (these may occur with up to 1 in 10,000 doses of the vaccine):
- Temporary inflammation of the brain and nerves causing pain, weakness and paralysis that may spread across the body.
- Narrowing or blockage of blood vessels with kidney problems

Rare (these may occur with up to 1 in 1,000 doses of the vaccine):
- Allergic reactions leading to a dangerous decrease of blood pressure, which, if untreated, may lead to collapse, coma and death
- Fits
- Severe stabbing or throbbing pain along one or more nerves
- Low blood platelet count which can result in bleeding or bruising

Uncommon (these may occur with up to 1 in 100 doses of the vaccine):
- Generalised skin reactions including urticaria (hives)

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

The side effects listed below have occurred with Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg in clinical studies:

Very common (these may occur with more than 1 in 10 doses of the vaccine):
- Tiredness
- Headache
- 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
- Dizziness
- Sleepiness
- Sleeplessness
- Diarrhoea, vomiting, stomach pain, feeling sick
- Itching, rash
- Generally feeling unwell

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

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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg

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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg 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 (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams). Adjuvants are used to improve the body's response to the vaccine.

- Other ingredients:
  The other ingredients are: 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

What Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg looks like and contents of the pack

One pack of Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg consists of:
- one pack containing 50 vials of 2.5 ml suspension (active substance) 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 medicine, please contact the local representative of the Marketing Authorisation Holder:

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

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

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

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg 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 Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals 3.75 µg (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.