ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Adjupanrix 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 (10.69 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.

Excipient with known effect
The vaccine contains 5 micrograms thiomersal (see section 4.4).

For the 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 to yellowish homogeneous milky liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation.

Adjupanrix should be used in accordance with official guidance.

4.2 Posology and method of administration

Posology

Persons not previously vaccinated with Prepandrix

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 and up to twelve months after the first dose for maximum efficacy.

Based on very limited data, adults aged >80 years may require a double dose of Adjupanrix 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).

Persons previously vaccinated with one or two doses of Prepandrix containing HA derived from a different clade of the same influenza subtype as the pandemic influenza virus:

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

Paediatric population

There are limited safety and immunogenicity data available on the administration of Adjupanrix and on administration of half a dose of the vaccine (i.e. 1.875 µg HA and half the amount of AS03 adjuvant) at 0 and 21 days in children aged 3 to 9 years.

Currently available data are described in section 4.4, 4.8 and 5.1 but no recommendation on a posology can be made.

For further information, see sections 4.4, 4.8 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 preferably into the deltoid muscle or anterolateral thigh (depending on the muscle mass).

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

4.3 Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (egg and chicken protein, ovalbumin, formaldehyde, 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 listed in section 6.1, 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.

Adjupanrix should under no circumstances be administered intravascularly. There are no data with Adjupanrix using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleedings.

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

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

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

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

Epidemiological studies relating to another AS03-adjuvanted vaccine (Pandemrix H1N1, also manufactured in the same facility as Adjupanrix), in several European countries have indicated an increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated individuals. In children/adolescents (aged up to 20 years), these studies have indicated an additional 1.4 to 8 cases in 100,000 vaccinated subjects. Available epidemiological data in adults aged over 20 years have indicated approximately 1 additional case per 100,000 vaccinated subjects. These data suggest that the excess risk tends to decline with increasing age at vaccination. There is currently no evidence to indicate that Adjupanrix may be associated with a risk of narcolepsy.

Paediatric population

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

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

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

Breast-feeding

Adjupanrix may be used in lactating women.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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.

List of adverse reactions
Adverse reactions reported are listed according to the following frequency:

Frequencies are reported as:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

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

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

Paediatric population

A clinical study (D-H5N1-009) evaluated the reactogenicity in children 3 to 5 and 6 to 9 years of age who received either two adult (i.e. 0.5 ml) doses or two half adult (i.e. 0.25 ml) doses (21 days apart) of Adjupanrix.

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

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

NA=not available

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

- Post-marketing surveillance

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

AS03-containing vaccines containing 3.75 µg HA derived from A/California/7/2009 (H1N1)

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

Immune system disorders
Anaphylaxis, allergic reactions

Nervous system disorders
Febrile convulsions

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

Interpandemic trivalent vaccines

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

Rare:
Neuralgia, transient thrombocytopenia.

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

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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code: J07BB02.

Pharmacodynamic effects

This section describes the clinical experience with the pandemic preparedness vaccines.

Pandemic preparedness 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 pandemic preparedness vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with pandemic preparedness vaccines are relevant for the pandemic vaccines.

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 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 (D-Pan-H5N1-002)		0, 6 months schedule (D-Pan-H5N1-012)		
	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.

Subjects of D-Pan-H5N1-002 were followed up for persistence of the immune response. The seroprotection rates 6, 12, 24 and 36 months after the first dose were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004			
	6 months after the 1st dose N=256	12 months after the 1st dose N=559	24 months after the 1st dose N=411	36 months after the 1st dose N=387
Seroprotection rate[1]	40.2%	23.4%	16.3%	16.3%

[1] seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40

Older (>60 years)

In another clinical study (D-Pan-H5N1-010), 297 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 rate 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%.
Subjects of D-Pan-H5N1-010 were followed up for persistence of the immune response. The seroprotection rates 6, 12 and 24 months after vaccination were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004					
	6 months after vaccination		12 months after vaccination		24 months after vaccination	
	Single dose (N=140)	Double dose (N=131)	Single dose (N=86)	Double dose (N=81)	Single dose (N=86)	Double dose (N=81)
Seroprotection rate[1]	52.9%	69.5%	45.3%	44.4%	37.2%	30.9%

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40

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.

Twelve and twenty-four months after vaccination, the neutralising antibody titres were as follows:

Serum neutralising antibody	Immune response to A/Vietnam/1194/2004			
	12 months after vaccination		24 months after vaccination	
	Single dose N=51	Double dose N=54	Single dose N=49	Double dose N=54
GMT[1]	274.8	272.0	391.0	382.8
Seroconversion rate[2]	27.5%	27.8%	36.7%	40.7%
≥1:80[3]	82.4%	90.7%	91.8%	100%

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

Paediatric population

Children aged 3 to 9 years

In a clinical study (D-Pan-H5N1-009), children aged 3 to 5 and 6 to 9 years old received two doses of either a full (0.5 ml) or a half dose (0.25 ml) of an AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) at 0 and 21 days. At day 42, the anti-HA antibody responses were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004			
	3 to 5 years		6 to 9 years	
	Half dose N=49	Full dose N=44	Half dose N=43	Full dose N=43
Seroprotection rate[1]	95.9%	100%	100%	100%
Seroconversion rate[2]	95.9%	100%	100%	100%
Seroconversion factor[3]	78.5	191.3	108.1	176.7

[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.

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

Subjects of D-Pan-H5N1-009 were followed up for persistence of the immune response. The seroprotection rates 6, 12 and 24 months after vaccination were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004 3-5 years					
	6 months after vaccination		12 months after vaccination		24 months after vaccination	
	Half dose (N=50)	Full dose (N=29)	Half dose (N=47)	Full dose (N=27)	Half dose (N=27)	Full dose (N=26)
Seroprotection rate[1]	56.0%	82.8%	38.3%	48.1%	38.3%	73.1%

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40

anti-HA antibody	Immune response to A/Vietnam/1194/2004 6-9 years					
	6 months after vaccination		12 months after vaccination		24 months after vaccination	
	Half dose (N=44)	Full dose (N=41)	Half dose (N=37)	Full dose (N=35)	Half dose (N=37)	Full dose (N=34)
Seroprotection rate[1]	63.6%	78.0%	24.3%	62.9%	24.3%	67.6%

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40

At day 42, and after 6, 12 and 24 months the neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Vietnam/1194/2004				
	3-5 years				
	21 days after 2nd dose		6 months after vaccination	12 months after vaccination	24 months after vaccination
	Half dose N=47	Full dose N=42	Half dose N=49	Half dose N=47	Half dose N=47
GMT[1]	1044.4	4578.3	781.2	238.9	302.5
Seroconversion rate[2]	95.6%	97.4%	87.2%	82.2%	80.0%
≥1:80[3]	100%	100%	100%	93.6%	95.7%

[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

Serum neutralising antibody	Immune response to A/Vietnam/1194/2004				
	6-9 years				
	21 days after 2nd dose		6 months after vaccination	12 months after vaccination	24 months after vaccination
	Half dose N=42	Full dose N=42	Half dose N=40	Half dose N=36	Half dose N=38
GMT[1]	1155.1	3032.5	756.1	179.4	234.5
Seroconversion rate[2]	100%	100%	95.0%	67.6%	63.9%

≥1:80[3]	100%	100%	100%	86.1%	97.4%

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

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

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

In a clinical study (Q-Pan-H5N1-001) in which two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 were administered on days 0 and 21 to 140 subjects aged 18-60 years, the anti-HA antibody responses were as follows:

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

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

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

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

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

Adults aged 18-60 years

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

anti-HA antibody	A/Indonesia/5/2005		
	0, 21 days schedule (D-Pan-H5N1-002)	0, 6 months schedule (D-Pan-H5N1-012)	
	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

* anti-HA ≥1:40

[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.

Subjects from study D-Pan-H5N1-002 were followed up for persistence of anti-HA antibodies against A/Indonesia/5/2005. The seroprotection rates were 2.2%, 4.7%, 2.4% and 7.8% at months 6, 12, 24 and 36, respectively.

In a different study (D-Pan-H5N1-007) 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.

Older (>60 years)

In 297 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.

Subjects from study D-Pan-H5N1-010 who received a single dose were followed-up for persistence of anti-HA antibodies against A/Indonesia/5/2005. The seroprotection rates were 16.3% and 4.7% at months 12 and 24, respectively. Seroconversion rates for neutralising antibodies against A/Indonesia/5/2005 were 15.7% and 12.2% for months 12 and 24, respectively. The percentage of subjects reaching neutralising antibody titres of >1/80 were 54.9% and 44.9% at months 12 and 24, respectively.

Paediatric population

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 were as follows:

anti-HA antibody	Immune response to A/Indonesia/5/2005			
	3 to 5 years		6 to 9 years	
	Half dose N=49	Full dose N=44	Half dose N=43	Full dose N=43
Seroprotection rate[1]	71.4%	95.5%	74.4%	79.1%
Seroconversion rate[2]	71.4%	95.5%	74.4%	79.1%
Seroconversion factor[3]	10.7	33.6	12.2	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.

Subjects of D-Pan-H5N1-009 were followed up for persistence of the immune response. The seroprotection rate at month 6, 12 and 24 were as follows:

anti-HA antibody	Immune response to A/Indonesia/5/2005					
	3 to 5 years					
	Month 6		Month 12		Month 24	
	Half dose N=49	Full dose N=27	Half dose N=47	Full dose N=27	Half dose N=47	Full dose N=26
Seroprotection rate[1]	6.1%	70.4%	36.2%	44.4%	10.6%	53.8%

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40

anti-HA antibody	Immune response to A/Indonesia/5/2005					
	6 to 9 years					
	Month 6		Month 12		Month 24	
	Half dose N=42	Full dose N=34	Half dose N=36	Full dose N=35	Half dose N=37	Full dose N=34
Seroprotection rate[1]	4.8%	64.7%	19.4%	42.9%	10.8%	29.4%

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40

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 24 months after the first dose. The neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Indonesia/5/2005							
	3 to 5 years				6 to 9 years			
	Day 42 N=46	Month 6 N=48	Month 12 N=47	Month 24 N=47	Day 42 N=42	Month 6 N=40	Month 12 N=35	Month 24 N=38
GMT[1]	331.4	242.1	177.7	188.5	412.1	208.4	128.1	146.0
Seropositivity rate[2]	95.6%	93.0%	97.9%	97.9%	97.2%	97.3%	94.4%	97.4%
≥1:80[3]	75.6%	72.1%	85.1%	80.9%	88.9%	70.3%	86.1%	81.6%

[1] Geometric Mean Titre
[2] % of subjects with titre ≥1:28
[3] % of subjects reaching a serum neutralising antibody titre of at least 1:80

Cross-reactive immune response elicited by AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 (H5N1)

After two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 administered on days 0 and 21 to 140 subjects aged 18-60 years, the anti-HA antibody responses to A/Vietnam/1194/2004 were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004	
	Day 21 N=140	Day 42 N=140
Seroprotection rate[1]	15%	59.3%
Seroconversion rate[2]	12.1%	56.4%
Seroconversion factor[3]	1.7	6.1

[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.

At day 180, the seroprotection rate was 13%.

A 4-fold increase in serum neutralising antibody titres against A/Vietnam was obtained in 49% of subjects twenty-one days after the first dose, 67.3% twenty-one days after the second dose and 44.9% six months after the second dose.

Alternative schedules
An extended dosing interval was investigated in study D-H5N1-012 in which a group of subjects 18-60 years of age received two doses of Adjupanrix 6 months or 12 months apart. Twenty-one days after the second dose, the seroprotection rate and the vaccine response rate against A/Vietnam/1194/2004 in subjects who received the vaccine 6 months apart were 89.6% and 95.7%, respectively. Twenty-one days after the second dose, the seroprotection rate and the vaccine response rate in subjects who received the vaccine 12 months apart were 92.0% and 100%, respectively.
In this study, cross-reactive immune responses against A/Indonesia/5/2005 were also observed. Twenty-one days after the second dose, the seroprotection rate and the vaccine response rate in subjects who received the vaccine 6 months apart were 83.3% and 100%, respectively. Twenty-one days after the second dose, the seroprotection rate and the vaccine response rate in subjects who received the vaccine 12 months apart were 84.0% and 100%, respectively.

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

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

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

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

In another clinical study (D-Pan-H5N1-015), 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.

In another clinical study (D-Pan-H5N1-038), 387 subjects aged 18-60 years received 1 dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/5/2005 36 months after they had received two doses of A/Vietnam/1194/2004. The seroprotection rate, booster seroconversion rate and booster factor against A/Indonesia/5/2005 21 days after booster vaccination was 100%, 99.7% and 123.8, respectively.

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 immunised 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.

This medicinal product has been authorised under 'exceptional circumstances'.
This means that for scientific reasons it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

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

5 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.

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

6.5 Nature and contents of container

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

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

6.6 Special precautions for disposal and other handling

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

Prior to administration, the two components should be mixed.

Instructions for mixing and administration of the vaccine:

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

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/578/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 October 2009
Date of latest renewal: 18 July 2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

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

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

Name and address of the manufacturer of the biological active substance

Sächsisches Serumwerk Dresden
Branch of GlaxoSmithKline Biologicals
Zirkusstraße 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 OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

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

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

During a pandemic situation, the resources must be concentrated on a timely and effective monitoring of the safety profile of the influenza vaccines used during the pandemic. Moreover, a 6-monthly cycle may be too long to allow assessment of the safety of a vaccine for which high levels of exposure are expected within a short period of time. Therefore, 6-monthly or annual PSURs falling within the pandemic period will be replaced by monthly “simplified PSURs” (S-PSUR) accompanied by a summary of vaccine distribution.

Frequency of submission

- The clock should start from the first Monday after shipment of the first batch of vaccine.

- First data-lock point is 30 days later.
- S-PSUR submission to the Rapporteur and CHMP members on Day 45.
- Rapporteur's assessment report is circulated to CHMP members on Day 50.
- CHMP report is circulated to the vaccine manufacturer on Day 55.
- Reporting to be monthly for the first 6 months.
- Periodicity should be reviewed by the MAH and the (Co-)Rapporteur at 6 monthly intervals.

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

Format of the simplified PSUR

Only spontaneously reported data should be included in the PSUR. The report should include the following Tables of aggregate data (using the pre-defined templates attached in Annex 2).

1. An overview for all spontaneous cases per country, stratified according to type of report (medically confirmed or non-medically confirmed) and seriousness, for the period covered by the report and cumulatively.

2. An overview for all spontaneous adverse reactions by SOC, High Level Term (HLT) and Preferred Term (PT), stratified according to type of report (medically confirmed or non-medically confirmed) and including the number of fatal reports, for the period covered by the report and cumulatively.

3. Adverse Events of Special Interest stratified according to type of report (medically confirmed or non-medically confirmed). AESIs will be defined as follows:

   - Neuritis: PT "Neuritis"
   - Convulsion: narrow SMQ "Convulsions"
   - Anaphylaxis: narrow SMQ "Anaphylactic reaction" and narrow SMQ "Angioedema"
   - Encephalitis: narrow SMQ "Non-infectious encephalitis"
   - Vasculitis: narrow SMQ "Vasculitis"
   - Guillain-Barré syndrome: narrow SMQ "Guillain-Barré syndrome"
   - Demyelination: narrow SMQ "Demyelination" (as GBS is also included in this SMQ, there will be an overlap in the number of cases for these two categories).
   - Bell's palsy: PT "Bell's palsy"
   - Vaccination failure: PT "Vaccination failure".

4. Serious unlisted adverse reactions (SOC, HLT, PTs) stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

5. All spontaneous adverse reactions by age group, per SOC, HLT and PT, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively. The following age groups will be used: < 2 years, 2-8 years, ≥ 9 years.

6. All spontaneous adverse reactions (SOC, HLT, PT) occurring in pregnant women, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

The following principles should be followed when compiling the data:

- Except for Table 1, all tables will be based on number of reactions (presented on PT level, sorted by System Organ Class [SOC] and High Level Term [HLT]) and not number of cases.

- All tables will be based on generic and not product-specific data1. Product-specific data can be evaluated during signal work-up.
- "Cumulatively" means since the use of the vaccine; events not reported during the period of interest should not be presented in the tables.
- All non-medically confirmed events are those that have been entered into the database by the data-lock point. Those which have not yet been entered should be reported in the following S-PSUR.
- A line listing of fatal cases will be provided in an Annex.

A short summary should be provided in which validated signals and areas of concern are highlighted, taking into account information arising from the prospective cohort study described in 4.5. In the event of multiple signals, signal work-up may be prioritised and appropriate timelines for submission of a full signal evaluation report should be provided.

Vaccine distribution report

To put the safety report into context, a summary of vaccine distribution should be included and should 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.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

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

Description	Due date
During the pandemic, the applicant will 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.
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.

[1] Based on the assumption that product name will not be provided in a significant proportion of cases.

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

Adjupanrix 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, DL-α-tocopherol and polysorbate 80

* haemagglutinin

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension and emulsion for emulsion for injection

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

The volume after mixing 1 vial of suspension (2.5 ml) with 1 vial of emulsion (2.5 ml) corresponds to **10 doses** of 0.5 ml vaccine

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Suspension and emulsion to be mixed before administration

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/578/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
PACK OF 50 VIALS OF SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT

Suspension for emulsion for injection for Adjupanrix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Suspension to be exclusively mixed with adjuvant emulsion before administration

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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/1/09/578/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
PACK OF 25 VIALS OF EMULSION

1. NAME OF THE MEDICINAL PRODUCT

Emulsion for emulsion for injection for Adjupanrix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients:
Sodium chloride
Disodium hydrogen phosphate
Potassium dihydrogen phosphate
Potassium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Adjuvant emulsion for injection
25 vials: emulsion
2.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Emulsion to be exclusively mixed with antigen suspension before administration

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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/1/09/578/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SUSPENSION VIAL

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

Antigen suspension for
Adjupanrix
A/VietNam/1194/2004 (H5N1) like strain used (NIBRG-14)
I.M.

2. METHOD OF ADMINISTRATION

Mix with adjuvant emulsion before use

3. EXPIRY DATE

EXP
After mixing: Use within 24 hours and do not store above 25°C.
Date and time of mixing:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

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

6. OTHER

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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

EMULSION VIAL

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

Adjuvant emulsion for
Adjupanrix
I.M.

2. METHOD OF ADMINISTRATION

Mix into Antigen suspension before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml

6. OTHER

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

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Adjupanrix 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 because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This vaccine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor.This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Adjupanrix is and what it is used for

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

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

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

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

2. What you need to know before you receive Adjupanrix

Adjupanrix should not be given
- If you have previously had a sudden life-threatening allergic reaction to any ingredient of this vaccine (listed in section 6) or to anything else that may be present in very small amounts, such as: egg and chicken protein, ovalbumin, formaldehyde, 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, you may still be given the vaccine. This is as long as medical treatment is available straight away, in case you have an allergic reaction.

Do not have Adjupanrix if any of the above apply to you.

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

Warning and precautions:

Talk to your doctor or nurse before you are given Adjupanrix

- if you have had any allergic reaction other than a sudden life-threatening allergic reaction to any ingredient of Adjupanrix (listed in section 6) or to thiomersal, to egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate (antibiotic) or to sodium deoxycholate.
- if you have a serious infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be a problem, but your doctor will advise whether you could still be vaccinated with Adjupanrix.
- 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 Adjupanrix the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently received Adjupanrix.
- you have a bleeding problem or you bruise easily.

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

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

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

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

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

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

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

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

Adjupanrix contains thiomersal
Adjupanrix 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.

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

3. How Adjupanrix is given

If you have not previously received doses of Prepandrix

- From 18 years onwards: you will receive two doses of Adjupanrix. The second dose should be given after an interval of at least three weeks and up to twelve months after the first dose.

- From 80 years onwards: you may receive two double injections of Adjupanrix. The first two injections should be given at the elected date and the two other injections should preferably be given 3 weeks after.

If you have previously received one or two doses of Prepandrix

- From 18 years onwards: you will receive one dose of Adjupanrix.

Use in children

In a clinical study, children 3 to 9 years of age have received either two adult (0.5 ml) or two half adult (0.25 ml) doses. Your doctor will decide the appropriate dose for your child.

Your doctor or nurse will give you Adjupanrix.

- They will give Adjupanrix as an injection into a muscle.
- This will usually be in the upper arm.
- The double injections will be given in opposite arms.

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

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

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

Other side effects:

Very common: may affect more than 1 in 10 people
- Headache
- Feeling tired
- Pain, redness, swelling or a hard lump where the injection was given
- Fever
- Aching muscles, joint pain

Common: may affect less than 1 in 10 people
- Warmth, itching or bruising where the injection was given
- Increased sweating, shivering, flu-like symptoms
- Swollen glands in your neck, armpit or groin

Uncommon: may affect less than 1 in 100 people
- Tingling or numbness of the hands or feet

- Sleepiness
- Feeling dizzy
- Diarrhoea, vomiting, stomach pain, feeling sick
- Itching, rash
- Generally feeling unwell
- Sleeplessness

Additional side effects in children

In a clinical study, children 3 to 9 years of age have received either two adult (0.5 ml) or two half adult (0.25 ml) doses. The frequency of side effects was lower in the group of children who received half of the adult dose. There was no increase after the second dose whether the children received half of the adult or the adult dose, except for some side effects which were higher after the second dose, particularly for rates of fever in < 6 years old children.

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

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

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

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

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

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

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Adjupanrix

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

Before the vaccine is mixed:

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

Store in a refrigerator (2°C - 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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Adjupanrix contains

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

  A/Vietnam/1194/2004 (H5N1) like strain used (NIBRG-14) 3.75 micrograms** per 0.5 ml dose

  *propagated in eggs
  **expressed in microgram haemagglutinin

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

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

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

What Adjupanrix looks like and contents of the pack

The suspension is a colourless light opalescent liquid.
The emulsion is a whitish to yellowish homogeneous milky liquid.

Before the vaccine is given, the two parts will be mixed together. The mixed vaccine is a whitish to yellowish homogeneous milky liquid emulsion.

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

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
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For any information about this medicinal vaccine, please contact the local representative of the Marketing Authorisation Holder:

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

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

Other sources of information

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

The following information is intended for healthcare professionals only:

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

Prior to administration, the two components should be mixed.

Instructions for mixing and administration of the vaccine:

1. Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should be allowed to reach room temperature (for a minimum of 15 minutes); each vial should be shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
2. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a 5 ml syringe and by adding it to the vial containing the antigen. It is recommended to equip the syringe with a 23-G needle. However, in the case this needle size would not be available, a 21-G needle might be used. The vial containing the adjuvant should be maintained in upside down position to facilitate the withdrawal of the full content.
3. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish to yellowish homogeneous milky liquid emulsion. In the event of other variation being observed, discard the vaccine.

4. The volume of the Adjupanrix vial after mixing is at least 5 ml. The vaccine should be administered in accordance with the recommended posology (see section 3 “How Adjupanrix is given”).
5. The vial should be shaken prior to each administration and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
6. Each vaccine dose of 0.5 ml is withdrawn into a 1 ml syringe for injection and administered intramuscularly. It is recommended to equip the syringe with a needle gauge not larger than 23-G.
7. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2°C - 8°C) or at room temperature not exceeding 25°C. If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature (for a minimum of 15 minutes) before each withdrawal.

The vaccine should not be administered intravascularly.

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