ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After mixing, 1 dose (0.5 ml) contains:

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

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

* propagated in eggs
** haemagglutinin

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

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

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

Excipients: the vaccine contains 5 micrograms thiomersal

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Suspension and emulsion for emulsion for injection.
The suspension is a translucent to off white opalescent suspension, which may sediment slightly.
The emulsion is a whitish homogeneous liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation (see sections 4.2 and 5.1).

Pandemic influenza vaccine should be used in accordance with Official Guidance.

4.2 Posology and method of administration

Posology

The dose recommendations take into account available data from:

- Ongoing clinical studies in healthy subjects who received a single dose of Arepanrix (H1N1)
- Clinical studies in healthy subjects (including elderly subjects) who received two doses of a version of Arepanrix containing 3.75 µg HA derived from A/Indonesia/05/2005 (H5N1)

And also from:

- On-going clinical studies in healthy subjects who received a single dose or two doses of an AS03-containing vaccine containing HA from H1N1v manufactured using a different process
- Clinical studies in healthy subjects who received two doses of an AS03-containing vaccine containing HA from H5N1 manufactured using a different process.

In some age groups there are limited clinical study data (adults aged 60-79 years and children aged 10 to 17 years), very limited clinical study data (adults aged 80 years and older, children aged 6 months to 9 years) or no data (children aged less than 6 months) with an AS03-containing vaccine containing HA from H5N1 or from H1N1v manufactured using a different process as detailed in sections 4.4, 4.8 and 5.1.

Adults aged 18-60 years:
One dose of 0.5 ml at an elected date.
Immunogenicity data obtained at three weeks after administration of Arepanrix (H1N1) in clinical studies suggest that a single dose may be sufficient.
If a second dose is administered there should be an interval of at least three weeks between the first and the second dose.

Elderly (>60 years)
One dose of 0.5 ml at an elected date.
Immunogenicity data obtained at three weeks after administration of an AS03-containing vaccine containing HA from H1N1v manufactured using a different process in clinical studies suggest that a single dose may be sufficient.
If a second dose is administered there should be an interval of at least three weeks between the first and the second dose.

Children and adolescents aged 10-17 years
Immunogenicity data obtained at three weeks after administration of an AS03-containing vaccine containing HA from H1N1v manufactured using a different process in clinical studies suggest that dosing may be in accordance with the recommendations for adults.

Children aged from 6 months to 9 years
One dose of 0.25 ml at an elected date.
Preliminary immunogenicity data obtained with an AS03-containing vaccine containing HA from H1N1v manufactured using a different process in a limited number of children aged 6-35 months show that there is a further immune response to a second dose of 0.25 ml administered after an interval of three weeks.

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

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

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

Method of administration

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

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

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

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

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

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

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

There are no safety and immunogenicity data available from clinical studies with Arepanrix or with an AS03-containing vaccine containing HA from H1N1v manufactured using a different process in children aged less than 6 months. There are limited data available from a clinical study with an AS03-containing vaccine containing HA from H1N1v manufactured using a different process in healthy children aged from 10 to 17 years, very limited data with the AS03-containing vaccine containing HA from H1N1v manufactured using a different process in healthy children aged from 6 to 35 months and limited data from a study with a version of an AS03-containing vaccine containing HA from H5N1 manufactured using a different process in children aged from 3 to 9 years.

Very limited data with an AS03-containing vaccine containing HA from H1N1v manufactured using a different process in children aged 6 to 35 months (N=51) who received two doses of 0.25 ml (half of the adult dose) with an interval of 3 weeks between doses indicate an increase in the rates of injection site reactions and general symptoms (see section 4.8). In particular rates of fever (axillary temperature ≥38°C) may increase considerably after the second dose. Therefore, monitoring of temperature and measures to lower the fever (such as antipyretic medication as seems clinically necessary) are recommended in young children (e.g. up to approximately 6 years of age) after each vaccination.

There are limited data available from clinical studies with an AS03-containing vaccine containing HA from H1N1v manufactured using a different process in adults aged over 60 years and very limited data in adults aged over 80 years.

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

4.5 Interaction with other medicinal products and other forms of interaction

Data obtained on co-administration of an AS03-containing vaccine containing HA from H1N1v manufactured using a different process with non-adjuvanted seasonal influenza vaccine (Fluarix, a split virion vaccine) in healthy adults aged over 60 years did not suggest any significant interference in the immune response to the AS03-containing vaccine containing HA from H1N1v. The immune response to Fluarix was satisfactory. Co-administration was not associated with higher rates of local or systemic reactions compared to administration of the AS03-containing vaccine containing HA from H1N1v alone.
Therefore the data indicate that Arepanrix may be co-administered with non-adjuvanted seasonal influenza vaccines (with injections made into opposite limbs).

Data obtained on the administration of a non-adjuvanted seasonal influenza vaccine (Fluarix, a split virion vaccine) three weeks before a dose of an AS03-containing vaccine containing HA from H1N1v manufactured using a different process in healthy adults over 60 years of age, did not suggest any significant interference in the immune response to the AS03-containing vaccine containing HA from H1N1v. Therefore the data indicate that Arepanrix may be administered three weeks after the administration of non-adjuvanted seasonal influenza vaccines.

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

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

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

4.6 Pregnancy and lactation

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

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

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

Arepanrix may be used in lactating women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

- Clinical trials

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)

Clinical studies have evaluated the incidence of adverse reactions in approximately 4,500 subjects 18 years old and above who received a version of Arepanrix containing 3.75 microgram HA derived from A/Indonesia/5/2005 (H5N1).

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

Blood and lymphatic system disorders
Uncommon: lymphadenopathy

Psychiatric disorders
Uncommon: insomnia

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

Ear and labyrinth disorders
Uncommon: vertigo

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea

Gastrointestinal disorders
Common: nausea, diarrhoea
Uncommon: abdominal pain, vomiting, dyspepsia, stomach discomfort

Skin and subcutaneous tissue disorders
Common: sweating
Uncommon: pruritus, rash

Musculoskeletal and connective tissue disorders
Very common: joint pain, muscle aches
Uncommon: back pain, musculoskeletal stiffness, neck pain, muscle spasms, pain in extremity

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

Additional data on reactogenicity are available from clinical studies in healthy subjects of various age groups from 6 months of age upwards who received an AS03-containing vaccine containing HA from H1N1v manufactured using a different process. The available data are as follows:

Adults

In a clinical study that evaluated the reactogenicity of the first 0.5 ml dose of an AS03-containing vaccine containing HA from H1N1v manufactured using a different process in healthy adults aged 18-60 (N=120) and above 60 years (N=120) the frequency of adverse reactions was similar between age groups, except for redness (more common in subjects aged >60 years) and shivering and sweating (more common in subjects aged 18-60 years).

In a clinical study that evaluated reactogenicity in healthy adults aged 18-60 years who received two 0.5 ml doses (21 days apart) of an AS03-containing vaccine containing HA from H1N1v manufactured using a different process, there were higher rates of most general solicited symptoms (such as fatigue, headache, arthralgia, shivering, sweating and fever) after the second dose compared to the first dose.

Children aged 10-17 years

In a clinical study that evaluated the reactogenicity in children 10 to 17 years of age who received two 0.5 ml doses (21 days apart) of an AS03-containing vaccine containing HA from H1N1v manufactured using a different process, there was no increase in reactogenicity after the second dose compared to the first dose. Gastro-intestinal symptoms and shivering were reported at higher rates compared to the rates reported from studies with AS03-containing vaccine containing HA from H5N1 manufactured using a different process.

Children aged 3-9 years

In a clinical study that evaluated reactogenicity in children 3 to 5 and 6 to 9 years of age who received a single half adult (i.e. 0.25 ml) dose of an AS03-containing vaccine containing HA from H1N1 manufactured using a different process, the frequency of the following adverse reactions was as shown in the table:

Adverse reactions	3-5 years	6-9 years
Pain	60.0%	63.1%
Redness	26.7%	23.1%
Swelling	21.7%	23.1%
Shivering	13.3%	10.8%
Sweating	10.0%	6.2%
Fever >38°C	10.0%	4.6%
Fever >39°C	1.7%	0.0%
Diarrhoea	5.0%	NA
Drowsiness	23.3%	NA
Irritability	20.0%	NA
Loss of appetite	20.0%	NA
Arthralgia	NA	15.4%
Myalgia	NA	16.9%
Fatigue	NA	27.7%
Gastrointestinal	NA	13.8%
Headache	NA	21.5%

NA= not available

No data are available at present on reactogenicity after a second half adult (i.e. 0.25 ml) dose of an AS03-containing vaccine containing HA from H1N1 manufactured using a different process in children aged 3 to 9 years. However, in another clinical study which evaluated reactogenicity in children 3 to 9 years who received two adult (i.e. 0.5 ml) doses (21 days apart) of an AS03-containing vaccine containing HA from H1N1 manufactured using a different process there was an increase in injection site reactions and general symptoms after the second dose compared to the first dose.

Children aged 6-35 months

In a clinical study that evaluated reactogenicity in children aged 6 to 35 months who received two half adult (i.e. 0.25 ml) doses (21 days apart) of an AS03-containing vaccine containing HA from H1N1v manufactured using a different process there was an increase in injection site reactions and general symptoms after the second dose compared to the first dose particularly in rates of axillary fever (≥38°C). The per-dose frequency of the following adverse reactions was as shown in the table:

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

Reactogenicity was also evaluated in healthy adults aged 18-60 years who received a first 0.5 ml dose of either Arepanrix (H1N1) (N=167) or an AS03-containing vaccine containing HA from H1N1v manufactured using a different process (N=167). The frequency of adverse reactions was similar between the two groups.

- Post-marketing surveillance

AS03-containing vaccine containing HA from H1N1v manufactured using a different process

In addition to the adverse reactions reported in the clinical trials, the following have been reported during post-marketing experience with an AS03-containing vaccine containing HA from H1N1v manufactured using a different process:

Immune system disorders
Anaphylaxis, allergic reactions

Nervous system disorders
Febrile convulsions

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

Interpandemic trivalent vaccines

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

Rare:
Neuralgia, transient thrombocytopenia.

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

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see section 4.4).

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB02.

This medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency (EMEA) will review any new information on this medicine and this SPC will be updated as necessary.

A clinical study with Arepanrix (H1N1) provides limited safety and immunogenicity data obtained up to three weeks after administration of a single 0.5 ml dose to healthy adults aged 18-60 years.

Clinical studies with an AS03-containing vaccine containing HA from H1N1v manufactured using a different process currently provide:

- Limited safety and immunogenicity data obtained three weeks after administration of a single dose to healthy adults aged 18-79 years.
- Limited safety and immunogenicity data obtained after administration of two doses to healthy adults aged 18-60 years.
- Very limited safety and immunogenicity data obtained three weeks after administration of a single dose to healthy adults aged over 80 years.
- Limited immunogenicity data obtained three weeks after administration of a single dose of 0.25 ml or 0.5 ml to healthy children aged 10-17 years.
- Limited safety data obtained after administration of 0.25 ml or two doses of 0.5 ml to healthy children aged 10-17 years.
- Very limited safety and immunogenicity data obtained three weeks after a single administration of half the adult dose (i.e. 0.25 ml) to healthy children aged 3-9 years.
- Very limited safety and immunogenicity data obtained three weeks after a single administration of half the adult dose (i.e. 0.25 ml) to healthy children aged 6-35 months.

Clinical studies with a version of Arepanrix containing 3.75 µg HA derived from A/Indonesia/05/2005 (H5N1) provide additional safety and immunogenicity data in healthy adults, including the elderly.

Immune response to Arepanrix (H1N1) in adults aged 18-60 years:

In a clinical study that evaluated immunogenicity in healthy subjects aged 18-60 years who received either Arepanrix (H1N1) (N=167) or an AS03-containing vaccine containing HA from H1N1v manufactured using a different process (N=167), the anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like	
	Arepanrix (H1N1) N=164)	AS03-containing vaccine containing HA from H1N1v manufactured using a different process N=164
Seroprotection rate[1]	100%	97.6%
Seroconversion rate[2]	97.6%	93.9%
Seroconversion	41.5	32.0

factor[3]		

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

Immune response to an AS03-containing vaccine containing HA from H1N1v manufactured using a different process:

Adults aged 18-60 years

In two clinical studies (D-Pan H1N1-007 and D-Pan H1N1-008) that evaluated immunogenicity in healthy subjects aged 18-60 years the anti-HA antibody responses were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like					
	D-Pan H1N1-007				D-Pan H1N1-008	
	21 days after 1st dose		21 days after 2nd dose		21 days after 1st dose	
	Total enrolled subjects N=60 [95% CI]	Seronegative subjects prior to vaccination N=40 [95% CI]	Total enrolled subjects N=59 [95% CI]	Seronegative subjects prior to vaccination N=37 [95% CI]	Total enrolled subjects N=120 [95% CI]	Seronegative subjects prior to vaccination N=76 [95% CI]
Seroprotection rate[1]	100% [94.0;100]	100% [90.5;100]	100% [93.9;100]	100% [90.5;100]	97.5% [92.9;99.5]	96.1% [88.9;99.2]
Seroconversion rate[2]	98.3% [91.1;100]	100% [90.5;100]	98.3% [90.9;100]	100% [90.5;100]	95.0% [89.4;98.1]	96.1% [88.9;99.2]
Seroconversion factor[3]	38.1	47.0	72.9	113.3	42.15 [33.43.53.16]	50.73 [37.84;68.02]

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

Elderly (>60 years)

Study D-Pan H1N1-008 evaluated immunogenicity in healthy subjects (N=120) aged >60 years (stratified in ranges from 61 to 70, 71 to 80 and > 80 years of age). The anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like					
	61-70 years		71-80 years		>80 years	
	Total enrolled subjects N=75 [95% CI]	Seronegative subjects prior to vaccination N=43 [95% CI]	Total enrolled subjects N=40 [95% CI]	Seronegative subjects prior to vaccination N=23 [95% CI]	Total enrolled subjects N=5 [95% CI]	Seronegative subjects prior to vaccination N=3 [95% CI]

Seroprotection rate[1]	88.0% [78.4;94.4]	81.4% [66.6;91.6]	87.5% [73.2;95.8]	82.6% [61.2;95.0]	80.0% [28.4;99.5]	66.7% [9.4;99.2]
Seroconversion rate[2]	80.0% [69.2;88.4]	81.4% [66.6;91.6]	77.5% [61.5;89.2]	82.6% [61.2;95.0]	80.0% [28.4;99.5]	66.7% [9.4;99.2]
Seroconversion factor[3]	13.5 [10.3;17.7]	20.3 [13.94;28.78]	13.5 [8.6;21.1]	20.67 [11.58;36.88]	18.4 [4.3;78.1]	17.95 [0.55;582.25]

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

Children aged 10-17 years

Two clinical studies evaluated the immunogenicity of a half (0.25 ml) dose and a full (0.5 ml) adult dose in healthy children 10 to 17 years of age. The anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like			
	Half dose		Full dose	
	Total enrolled subjects N=58 [95% CI]	Seronegative subjects prior to vaccination N=38 [95% CI]	Total enrolled subjects N=97 [95% CI]	Seronegative subjects prior to vaccination N=61 [95% CI]
Seroprotection rate[1]	98.3% [90.8;100]	97.4% [86.2;99.9]	100% [96.3;100]	100% [94.1;100]
Seroconversion rate[2]	96.6% [88.1;99.6]	97.4% [86.2;99.9]	96.9% [91.2;99.4]	100% [94.1;100]
Seroconversion factor[3]	46.7 [34.8;62.5]	67.0 [49.1;91.3]	69.0 [52.9;68.4]	95.8 [78.0;117.7]

[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.

Children aged 3 to 9 years

In a clinical study in which children aged 3 to 9 years old received a half adult dose (0.25 ml) of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like the anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like			
	3-5 years		6-9 years	
	Total enrolled subjects N=30 [95% CI]	Seronegative subjects prior to vaccination N=27 [95% CI]	Total enrolled subjects N=30 [95% CI]	Seronegative subjects prior to vaccination N=29 [95% CI]
Seroprotection rate[1]	100% [88.4;100]	100% [87.2;100]	100% [88.4;100]	100% [88.1;100]

Seroconversion rate[2]	100% [88.4;100]	100% [87.2;100]	100% [88.4;100]	100% [88.1;100]
Seroconversion factor[3]	32.4 [25.4;41.2]	36.4 [29.1;45.4]	36.3 [28.0;47.2]	37.4 [28.7;48.7]

[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.

Children aged 6-35 months

In a clinical study in healthy children 6 months to 35 months of age (stratified in ranges from 6 to 11, 12 to 23 and 24-35 months of age) the anti-HA antibody responses 21 days after a first and a second half adult dose (i.e. 0.25 ml) were as follows:

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

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

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

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

Immune response to a version of Arepanrix containing 3.75 µg HA derived from A/Indonesia/05/2005 (H5N1):

Three clinical studies have evaluated the immunogenicity of a version of Arepanrix containing 3.75 µg HA derived from A/Indonesia/05/2005 (H5N1) in subjects from the age of 18 years onwards following a 0, 21 days schedule.

In a consistency study, the anti-haemagglutinin (anti-HA) antibody responses twenty-one days and six months after the second dose were as follows:

anti-HA antibody	Immune response to A/Indonesia/5/2005			
	18-60 years		>60 years	
	Day 42 N=1,488	Day 180 N=353	Day 42 N=479	Day 180 N=104
Seroprotection rate[1]	91%	62%	76.8%	63.5%
Seroconversion rate[2]	91%	62%	76.4%	62.5%
Seroconversion factor[3]	51.4	7.4	17.2	7.8

[1]seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40);
[2]seroconversion rate (i.e. 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 (i.e. ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty-one days after the second dose, a 4-fold increase in serum neutralising antibody against A/Indonesia/5/2005 was achieved in 94.4% of subjects aged 18-60 years and in 80.4% of subjects over 60 years of age.

In another clinical study, the anti-haemagglutinin (anti-HA) antibody responses in subjects aged 18-64 years were as follows:

anti-HA antibody	Immune response to A/Indonesia/5/2005		
	Day 21 N=145	Day 42 N=145	Day 180 N=141
Seroprotection rate[1]	42.1%	97.2%	54.6%
Seroconversion rate[2]	42.1%	97.2%	54.6%
Seroconversion factor[3]	4.5	92.9	5.6

[1]seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40);
[2]seroconversion rate (i.e. 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 (i.e. ratio of the post-vaccination GMT and the pre-vaccination GMT)

A 4-fold increase in serum neutralising antibody titres against A/Indonesia/5/2005 was achieved in 76.6% of subjects at day 21, 97.9% at day 42 and 91.5% at day 180.

Cross-reactive immune responses elicited by a version of Arepanrix containing 3.75 µg HA derived from A/Indonesia/05/2005 (H5N1):

In the consistency study, a 4-fold increase in serum neutralising antibody against A/Vietnam/1194/2004 was at day 42 achieved in 65.5% of subjects aged 18-60 years and in 24.1% of subjects over 60 years of age.

In another clinical study, anti-HA responses against A/Vietnam/1194/2004 following administration of a version of Arepanrix containing 3.75 µg HA derived from A/Indonesia/05/2005 (H5N1) were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004		
	Day 21 N=145	Day 42 N=145	Day 180 N=141
Seroprotection rate[1]	15.2%	64.1%	10.6%
Seroconversion rate[2]	13.1%	62.1%	9.2%
Seroconversion factor[3]	1.9	7.6	1.7

[1]seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40);
[2]seroconversion rate (i.e. 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 (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

A 4-fold increase in serum neutralising antibody against A/Vietnam/1194/2004 was achieved in 44.7% of subjects at day 21, 53.2% at day 42 and 38.3% at day 180.

Information from non-clinical studies:

The ability to induce protection against homologous and heterologous vaccine strains was assessed non-clinically with A/Indonesia/05/05 (H5N1) using ferret challenge models.

- Challenge with a homologous pandemic H5N1 strain (A/Indonesia/5/05)

In this protection experiment, the ferrets (six ferrets/group) were immunized intramuscularly with vaccine candidate containing three different doses of H5N1 antigen (7.5, 3.8 and 1.9 µg of HA antigen) adjuvanted with the standard dose or half dose of AS03. Control groups included ferrets immunized with adjuvant alone and non-adjuvanted vaccine (7.5 micrograms HA). Ferrets immunized with the non adjuvanted H5N1 influenza vaccine were not protected from death and showed similar lung viral loads and degree of viral shedding in the upper respiratory tract as those exhibited by ferrets immunized with the adjuvant alone. Conversely the combination of a range of doses of H5N1 antigen with AS03 adjuvant was able to protect against mortality and to reduce lung virus loads and viral shedding after intra-tracheal challenge with a homologous wild type H5N1 virus. Serological testing indicated a direct correlation between vaccines induced HI and neutralising antibody titres in protected animals compared to antigen and adjuvant controls.

- Challenge with a heterologous pandemic H5N1 strain (A/Hong Kong/156/97)

In this protection experiment, the ferrets (six ferrets/group) were immunized intramuscularly with vaccine candidate containing four different doses of H5N1 antigen (3.75, 1.5, 0.6 and 0.24 µg of HA antigen) adjuvanted with half dose of AS03. In addition, one group of six ferrets were immunized with vaccine candidate containing 3.75 µg H5N1 + full dose of AS03 and one control group included ferrets immunized with non-adjuvanted vaccine (3.75 micrograms HA). The results of this heterologous challenge study indicate 80.7%-100% protection in all adjuvanted candidate vaccines compared to 43% protection with the non adjuvanted vaccine, showing the benefit of AS03 adjuvantation.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with a version of Arepanrix containing 3.75 µg HA derived from A/Indonesia/05/2005 (H5N1) 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:
Thiomersal
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Water for injections

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

For adjuvants, see section 2.

6.2 Incompatibilities

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

6.3 Shelf-life

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

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

Arepanrix 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. Whitish sediments may be observed in the suspension vial; these sediments are part of the normal physical appearance of the suspension. The emulsion presents as a whitish appearance.
2. Each vial should be shaken and inspected visually for any foreign particulate matter (other than the white sediments described above) and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
3. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a syringe and by adding it to the vial containing the antigen.
4. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish emulsion. In the event of other variation being observed, discard the vaccine.
5. The volume of the Arepanrix vial after mixing is at least 5 ml. The vaccine should be administered in accordance with the recommended posology (see section 4.2).
6. 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.
7. Each vaccine dose of 0.5 ml (full dose) or 0.25 ml (half dose) is withdrawn into a syringe for injection and administered intramuscularly.
8. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2°C – 8°C) or at room temperature not exceeding 25°C. If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature before each withdrawal.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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/.