**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<br>N=1,488 | Day 180<br>N=353 | Day 42<br>N=479 | Day 180<br>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<br>N=145 | Day 42<br>N=145 | Day 180<br>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<br>N=145 | Day 42<br>N=145 | Day 180<br>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

12 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)

EU/1/10/624/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23/03/2010

## 10. DATE OF REVISION OF THE TEXT

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

# ANNEX II

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

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

**C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER**

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

Name and address of the manufacturer of the biological active substance

IB Biomedical Corporation of Quebec doing business as
GlaxoSmithKline Biologicals North America
2323 du parc Technologique Blvd.
Saint-Foy, Quebec,
Canada G1P 4R8

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut
B-1330 Rixensart
Belgium

## B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- The Applicant/MAH shall agree with Member States to measures facilitating the identification and traceability of the A/H1N1 pandemic vaccine administered to each patient, in order to minimise medication errors and aid patients and health care professionals to report adverse reactions. The MAH should check regarding the possible confounding layouts with other pandemic vaccine supplied in EU.

- The Applicant/MAH shall agree with Member States on mechanisms allowing patients and health care professionals to have continuous access to updated information regarding Arepanrix.

- The Applicant/MAH shall agree with Member Sates on the provision of a targeted communication to healthcare professionals which should address the following:

    - The correct way to prepare the vaccine prior to administration.

    - Adverse events to be prioritised for reporting, i.e. fatal and life-threatening adverse reactions, unexpected severe adverse reactions, adverse events of special interest (AESI).

    - The minimal data elements to be transmitted in individual case safety reports in order to facilitate the evaluation and the identification of the vaccine administered to each subject, including the invented name, the vaccine manufacturer and the batch number.

- If a specific notification system has been put in place, how to report adverse reactions.

- **OTHER CONDITIONS**

*Official batch release*: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

*Pharmacovigilance system*
The MAH must ensure that the system of pharmacovigilance, as described in version 3.05 (dated September 2009) presented in Module 1.8.1 of the marketing authorisation application, is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

PSUR submission during the influenza pandemic:

During a pandemic situation, the frequency of submission of periodic safety update reports specified in Article 24 of Regulation (EC) No 726/2004 will not be adequate for the safety monitoring of a pandemic vaccine for which high levels of exposure are expected within a short period of time. Such situation requires rapid notification of safety information that may have the greatest implications for benefit-risk balance in a pandemic. Prompt analysis of cumulative safety information, in light of the extent of exposure, will be crucial for regulatory decisions and protection of the population to be vaccinated. The MAH shall submit on a monthly basis a simplified periodic safety update report with the timelines, format and content as defined in the CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009) and any subsequent update.

*Risk Management Plan*
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4 (dated January 2010) of the Risk Management Plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.



## C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Applicant/Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the continuous reassessment of the benefit/risk profile.

| Area | Description | Due Date |
|---|---|---|
| Quality | The Applicant/MAH commits not to release lots prepared using the extended formulation/fill process until the relevant validation data have been submitted and approved (RR#7Q5) | 31-January-2010 |
| Quality | The Applicant/MAH commits to set a maximum decrease of 20% of HA content for the Drug Substance and to review when data for H1N1 become available. (Arise from Q1 RR#13) | 26-February-2010 |
| Clinical | The Applicant/MAH commits to provide abridged report for the following study performed in children | |

| | | |
|---|---|---|
| | Study Q-Pan H1N1-003 (6 months-8 yrs, Dose finding,)<br><br>- abridged report for post dose 1 Wave 1 immuno data, solicited and unsolicited symptoms, SAEs )<br><br>- abridged report for post dose 2 Waves 1 and 2 (immuno data, solicited and unsolicited symptoms, SAEs ) | 05 March 2010<br><br>04 June 2010 |
| Clinical | The Applicant/MAH commits to provide abridged report for the following study performed in adults:<br>Study Q-Pan H1N1-001 abridged report for post dose 1 and post dose 2 (≥ 18 yrs, Dose finding, adjuvanted vaccine vs plain) | 30 April 2010 |
| Clinical | The Applicant/MAH commits to provide abridged report for the following study performed in adults<br>Study Q-Pan H1N1-019 (18-60 yrs, TIV effect and co-administration)<br><br>- abridged report for post dose 3 (immuno & solicited and unsolicited symptoms, SAEs) | 04 June 2010 |
| Clinical | The Applicant/MAH commits to provide abridged report for the following study performed in children<br>Study Q-Pan H1N1-031 (9-17 yrs, Safety/ Immunogenicity)<br>- abridged report for post dose 1 & post dose 2 (immuno & solicited and unsolicited symptoms, SAEs ) | 04 June 2010 |
| Clinical | The Applicant/MAH commits to provide abridged report for the following study performed in children<br>Study Q-Pan H1N1-032 (2-5 months, Safety/ Immunogenicity)<br>- abridged report for post dose 1 & post dose 2 (immuno & solicited and unsolicited symptoms, SAEs ) | 08 July 2010 (pending on enrolment of subjects and data availability) |
| Pharmacovigilance | The Applicant/MAH will support one prospective and one retrospective cohort safety study with Arepanrix, in at least 9,000 patients, in accordance with the protocols submitted with the Risk Management Plan. Interim and final results will be submitted one week after being available. | Timelines described in the RMP<br><br>*Prospective cohort*: initiated 23 Oct 2009; First endpoints available in Feb 2010<br>*Retrospective cohort*: to be initiated in Feb 2010; Preliminary analysis in April |
| Pharmacovigilance | The Applicant/MAH commits to provide the results of a study in a pregnancy registry conducted with Arepanrix. | Results, including all preliminary analysis, |

| | | |
|---|---|---|
| | | have to be provided in the (simplified) PSUR |
| Pharmacovigilance | The Applicant/MAH commits to support an effectiveness study with Arepanrix ongoing and submit the results one week after being available. | Results submitted 1 week after being available.<br><br>Study initiated in October 2009; Final report foreseen in April 2010 |
| Pharmacovigilance | The Applicant/MAH commits to support a Post-authorisation study in immunocompromised subjects (adults with HIV) being conducted by PCIRN (Public Health Agency of Canada - Canadian Institutes of Health Research Influenza Research Network) and provide the final result | Updated status and available results, including all preliminary analysis, have to be provided in the (simplified) PSUR |
| Pharmacovigilance | The Applicant/MAH commits to establish the mechanisms to promptly investigate issues affecting the benefit-risk balance of the vaccine.<br><br>The MAH should provide an inventory of all valuable database ready to be use to promptly investigate issues affecting the benefit-risk balance of the vaccine. Details regarding databases (e.g., data sources, characteristics of the data, potential analysis) need to be reported. | The characteristics and the validity of these sources is to be agreed with EMEA within 1 month of the Commission Decision granting the Marketing Authorisation in order to conduct additional studies for emerging benefit-risk evaluation. |

**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

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

After mixing, 1 dose (0.5 ml) contains:

Split influenza virus inactivated, containing antigen equivalent to:

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

AS03 adjuvant composed of squalene, DL-α-tocopherol and polysorbate 80

* haemagglutinin



## 3. LIST OF EXCIPIENTS

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

## 4. PHARMACEUTICAL FORM AND CONTENTS

Suspension and emulsion for emulsion for injection

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

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

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet before use

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

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Suspension and emulsion to be mixed before administration

## 8. EXPIRY DATE

EXP:

## 9. SPECIAL STORAGE CONDITIONS

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

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

Dispose of in accordance with local regulations

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/624/001

## 13. BATCH NUMBER

Lot:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**PACK OF 50 VIALS OF SUSPENSION (ANTIGEN)**

## 1. NAME OF THE MEDICINAL PRODUCT

Suspension for emulsion for injection for Arepanrix
Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Split influenza virus, inactivated, containing antigen* equivalent to:
3.75 micrograms haemagglutinin/dose
*Antigen: A/California/7/2009 (H1N1)v-like strain (X-179A)

## 3. LIST OF EXCIPIENTS

Excipients: Thiomersal, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

Antigen suspension for injection
50 vials: suspension
2.5 ml per vial.
After mixing with adjuvant emulsion: **10 doses** of 0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet before use

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

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Suspension to be exclusively mixed with adjuvant emulsion before administration

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Biologicals, Rixensart - Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/624/001

## 13. BATCH NUMBER

Lot:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**PACK OF 25 VIALS OF EMULSION (ADJUVANT)**

## 1. NAME OF THE MEDICINAL PRODUCT

Emulsion for emulsion for injection for Arepanrix

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

Adjuvant emulsion for injection
25 vials: emulsion
2.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet before use

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

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Emulsion to be exclusively mixed with antigen suspension before administration

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Biologicals, Rixensart - Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/624/001

## 13. BATCH NUMBER

Lot:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**SUSPENSION VIAL**

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

Antigen suspension for Arepanrix
Pandemic influenza vaccine
A/California/7/2009 (H1N1)v-like strain (X-179A)
I.M.

## 2. METHOD OF ADMINISTRATION

Mix with adjuvant emulsion before use

## 3. EXPIRY DATE

EXP
After mixing: Use within 24 hours and do not store above 25ºC.
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 Arepanrix
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**

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

**For the most up-to-date information please consult the website of the European Medicines Agency (EMEA): http://www.emea.europa.eu/.**

**Read all of this leaflet carefully before you receive this vaccine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

**In this leaflet**:




## 1. What Arepanrix is and what it is used for

Arepanrix is a vaccine against a pandemic influenza (flu).

Pandemic flu is a type of influenza that occurs every few decades and which spreads rapidly around the world. The symptoms of pandemic flu are similar to those of ordinary flu but may be more severe.

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

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

## 2. Before you are given Arepanrix

**You should not receive Arepanrix:**

- if you have previously had a sudden life-threatening allergic reaction to any ingredient of Arepanrix (these are listed at the end of the leaflet) or to any of the substances that may be present in trace amounts as follows: egg and chicken protein, ovalbumin, formaldehyde or sodium deoxycholate. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. However, in a pandemic situation, it may be appropriate for you to have the vaccine provided that appropriate medical treatment is immediately available in case of an allergic reaction.

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

**Take special care with Arepanrix:**

- if you have had any allergic reaction other than a sudden life-threatening allergic reaction to any

ingredient contained in the vaccine, to thiomersal, to egg and chicken protein, ovalbumin, formaldehyde or to sodium deoxycholate. (see section 6. Further information).

- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be a problem, but your doctor will advise whether you could still be vaccinated with Arepanrix.
- if you have a poor immune response (as for example because of immunosuppressive therapy, e.g. corticosteroid treatments or chemotherapy for cancer),
- if you are having a blood test to look for evidence of infection with certain viruses. In the first few weeks after vaccination with Arepanrix the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently been given Arepanrix.

In any of these cases, TELL YOUR DOCTOR OR NURSE, as vaccination may not be recommended, or may need to be delayed.

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.

Please inform your doctor or nurse if you have a bleeding problem or bruise easily.

**Taking other medicines**
Please tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or have recently been given any other vaccine.

Areapanrix can be given at the same time as seasonal influenza vaccines that do not contain an adjuvant.

Persons who have received a seasonal influenza vaccine that does not contain an adjuvant may receive Arepanrix after an interval of at least three weeks.

There is no information on administration of Arepanrix with other vaccines and no information on administration of the AS03-containing vaccine containing HA from H1N1v manufactured using a different process with any other vaccines than non-adjuvanted seasonal influenza vaccine. However, if this cannot be avoided, the vaccines should be injected into separate limbs. In such cases, you should be aware that the side effects may be more intense.

**Pregnancy and breast-feeding**
Tell your doctor if you are pregnant, think you may be pregnant, plan to become pregnant. You should discuss with your doctor whether you should receive Arepanrix.
The vaccine may be used during breast-feeding.

**Driving and using machines**
Some effects mentioned under section 4. “Possible side effects” may affect the ability to drive or use machines.

**Important information about some of the ingredients of Arepanrix**
This vaccine contains thiomersal as a preservative and it is possible that you may experience an allergic reaction. Tell your doctor if you have any known allergies.

This medicinal product contains less than 1 mmol sodium (23 mg) and less than 1 mmol of potassium (39 mg) per dose, i.e. essentially sodium- and potassium-free.

## 3. How Arepanrix is given

Your doctor or nurse will administer the vaccine in accordance with official recommendations.

The vaccine will be injected into a muscle (usually in the upper arm).

Adults including the elderly and children from the age of 10 years onwards:
A dose (0.5 ml) of the vaccine will be given
Clinical data with an AS03-containing vaccine containing HA from H1N1v manufactured using a different process 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 second dose.

Children from 6 months to 9 years of age
A dose (0.25 ml) of the vaccine will be given.
If a second dose of 0.25 ml is given this will be administered at least three weeks after the first dose.

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

When Arepanrix is given for the first dose, it is recommended that Arepanrix (and not another vaccine against H1N1) be given for the complete vaccination course.



## 4. Possible side effects

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

Allergic reactions may occur following vaccination, in rare cases leading to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.

The frequency of possible side effects listed below is defined using the following convention:

Very common (affects more than 1 user in 10)
Common (affects 1 to 10 users in 100)
Uncommon (affects 1 to 10 users in 1,000)
Rare (affects 1 to 10 users in 10,000)
Very rare (affects less than 1 user in 10,000)

The side effects listed below have occurred with Arepanrix (H5N1) in clinical studies in adults, including the elderly. In these clinical studies most side effects were mild in nature and short term. The side-effects are generally similar to those related to seasonal flu vaccines.

These side effects have also been observed with similar frequencies in clinical studies in adults including the elderly and in children aged 10 to 17 years with a similar vaccine (H1N1), except for redness (uncommon in the adults and common in the elderly) and fever (uncommon in the adults and elderly). Gastro-intestinal symptoms and shivering were at a higher rate in the children 10-17 years of age. In children aged 3-9 years who received a first half adult dose of a similar vaccine (H1N1), the side effects were similar compared to the side effects reported in adults, with the exception of shivering, sweating and gastro-intestinal symptoms which were reported at a higher rate in children aged 3 to 9 years. Additionally, in children aged 3 to 5 years of age, drowsiness, irritability and loss of appetite were reported very commonly.

**Very common:**
- Pain at the injection site

- Headache
- Tiredness
- Aching muscles, joint pain

**Common:**
- Redness and swelling at the injection site
- Fever
- Sweating
- Shivering
- Diarrhoea, feeling sick

**Uncommon:**
- Reactions at the injection site such as bruising, hard lump, itching, warmth
- Swollen glands in the axilla
- Dizziness
- Generally feeling unwell
- Unusual weakness
- Being sick, stomach pain, acid indigestion
- Inability to sleep
- Tingling or numbness of the hands or feet
- Shortness of breath
- Pain in the chest
- Itching, rash
- Pain in the back or neck, stiffness in the muscles, muscle spasms, pain in extremity such as leg or hand

In children aged 6-35 months who received a half of the adult dose (0.25 ml) of a similar vaccine (H1N1), fever and irritability occurred more often compared to the children 3-9 years who received a half of the adult dose (0.25 ml) of a similar vaccine (H5N1).

In children aged 6-35 months who received two doses of 0.25 ml (half of the adult dose) the side effects after the second dose were more intense, especially fever (≥38°C), which occurred very commonly.

These side effects usually disappear within 1 to 2 days without treatment. If they persist, CONSULT YOUR DOCTOR.

The side effects listed below have occurred during post-marketing surveillance with a similar vaccine (H1N1). These side effects may occur with Arepanrix.

- Allergic reactions leading to a dangerous decrease of blood pressure, which, if untreated, may lead to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.
- Generalised skin reactions including facial swelling and urticaria (hives)
- Fits due to fever

The side effects listed below have occurred in the days or weeks after vaccination with vaccines given routinely every year to prevent flu. These side effects may occur with Arepanrix.

**Rare**
- Severe stabbing or throbbing pain along one or more nerves
- Low blood platelet count which can result in bleeding or bruising

**Very rare**

- Vasculitis (inflammation of the blood vessels which can cause skin rashes, joint pain and kidney problems)
- Neurological disorders such as encephalomyelitis (inflammation of the central nervous system), neuritis (inflammation of nerves) and a type of paralysis known a Guillain-Barré Syndrome

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

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

## 5. How to store Arepanrix

Keep out of the reach and sight of children.

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

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

**After the vaccine is mixed:**
After mixing, use the vaccine within 24 hours and do not store above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.



## 6. Further information

**What Arepanrix contains**

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

  A/California/7/2009 (H1N1)v-like strain (X-179A) 3.75 micrograms** per 0.5 ml dose

  *propagated in eggs
  **expressed in microgram haemagglutinin

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

- **Adjuvant:**
  The vaccine contains an 'adjuvant' AS03 to stimulate a better response. This adjuvant contains squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)

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

**What Arepanrix looks like and contents of the pack**

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.

Prior to administration, the two components should be mixed. The mixed vaccine is a whitish emulsion.

One pack of Arepanrix 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**

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

Arepanrix has been authorised under "Conditional Approval".
This means that there is more evidence to come about this medicine.
The European Medicines Agency (EMEA) will regularly review any new information on the medicine and this package leaflet will be updated as necessary.

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

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

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 3 “How Arepanrix is given”).
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.

The vaccine should not be administered intravascularly.

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