

PRODUCT INFORMATION LEAFLET

**AREPANRIX™ H1N1**

AS03-Adjuvanted H1N1 Pandemic Influenza Vaccine

Emulsion for Injection

ATC Code J07BB02

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**Health Canada has authorized the sale of Arepanrix™ H1N1 based on limited clinical testing in humans under the provision of an Interim Order (IO) issued on October 13, 2009.** The authorization is based on the Health Canada review of the available data on quality, safety and immunogenicity, and given the current pandemic threat and its risk to human health, Health Canada considers that the benefit/risk profile of the Arepanrix™ H1N1 vaccine is favourable for active immunization against the H1N1 2009 influenza strain in an officially declared pandemic situation.

As part of the authorization for sale for Arepanrix™ H1N1, Health Canada has requested the sponsor agree to post-market commitments. Adherence to these commitments, as well as updates to information on quality, non-clinical, and clinical data will be continuously monitored by Health Canada and the Public Health Agency of Canada.

THIS LEAFLET WILL BE UPDATED ACCORDINGLY.

PLEASE CONSULT THE HEALTH CANADA WEBSITE FOR THE MOST UP-TO-DATE INFORMATION FOR THIS PRODUCT:

<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/legislation/interimorders-arretesurgence/index-eng.php>

<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/legislation/interimorders-arretesurgence/index-fra.php>

RECOMMENDATIONS MADE BY THE PUBLIC HEALTH AGENCY OF CANADA SHOULD ALSO BE TAKEN INTO CONSIDERATION.

**TABLE OF CONTENTS**

	<b>PAGE</b>
1.0 PHARMACEUTICAL FORM .....	4
2.0 QUALITATIVE AND QUANTITATIVE COMPOSITION .....	4
3.0 CLINICAL PARTICULARS .....	5
Indications .....	5
Dosage and Administration .....	5
Contraindications .....	6
Warnings and Precautions .....	6
Interactions .....	7
Effects on Ability to Drive and Use Machines .....	8
Adverse Reactions .....	8
Clinical trials .....	9
Overdose .....	14
4.0 PHARMACOLOGICAL PROPERTIES.....	15
Pharmacodynamics.....	15
Pharmacokinetics.....	18
Pre-clinical Safety Data.....	18
5.0 PHARMACEUTICAL PARTICULARS.....	19
List of Excipients .....	19
Incompatibilities.....	19
Shelf Life .....	19
Special Precautions for Storage.....	19
Nature and Contents of Container .....	19
Instructions for Use/Handling .....	20
CONSUMER INFORMATION .....	22

## 1.0 PHARMACEUTICAL FORM

Arepanrix™ H1N1 (AS03-adjuvanted H1N1 pandemic influenza vaccine) is a two-component vaccine consisting of an H1N1 immunizing antigen (as a suspension), and an AS03 adjuvant (as an oil-in-water emulsion).

The H1N1 antigen is a sterile, colorless to slightly opalescent suspension that may sediment slightly in a 10mL vial. The antigen is prepared from virus grown in the allantoic cavity of embryonated hen's eggs. The virus is inactivated with ultraviolet light treatment followed by formaldehyde treatment, purified by centrifugation and disrupted with sodium deoxycholate.

The AS03 adjuvant system is a sterile, homogenized, whitish emulsion composed of DL- $\alpha$ -tocopherol, squalene and polysorbate 80 in a 3mL vial.

Immediately prior to use, the full contents of the AS03 vial is withdrawn and added to the antigen vial (mix ratio 1:1). The mixed final product for administration is an emulsion, containing enough product for 10 doses.

## 2.0 QUALITATIVE AND QUANTITATIVE COMPOSITION

After combining and mixing the two components, 0.5mL of the resultant emulsion is withdrawn into a syringe for intramuscular injection. The final composition of each vaccine component per 0.5mL dose is as follows:

### Antigen:

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

A/California/7/2009 (H1N1)v-like strain (X-179A) 3.75 $\mu$ g HA\*\* per 0.5mL dose

\* isolated from virus propagated in eggs

\*\* HA = haemagglutinin

Preservative content is 5 $\mu$ g Thimerosal USP per 0.5mL dose or 2.5 micrograms organic mercury (Hg) per 0.5mL dose

### Adjuvant:

DL- $\alpha$ -tocopherol 11.86 milligrams/0.5mL dose

Squalene 10.69 milligrams/0.5mL dose,

Polysorbate 80 4.86 milligrams/0.5mL dose

The suspension and emulsion vials, once mixed, form a multidose vaccine in a vial. See section *Nature and Contents of Container* for the number of doses per vial.

For a full list of excipients, see section *List of Excipients* under 5.0.

### 3.0 CLINICAL PARTICULARS

#### Indications

Arepanrix™ H1N1 Vaccine is indicated for active immunization against H1N1 influenza strain in an officially declared pandemic situation.

(see section 2.0 *Qualitative and Quantitative Composition*).

#### Dosage and Administration

There is currently limited clinical experience with Arepanrix™ H1N1, and limited clinical experience with an investigational formulation of another AS03-adjuvanted vaccine containing the same or a slightly higher amount of antigen derived from A/California/7/2009 (H1N1) (see section *Pharmacodynamics*) in healthy adults aged 18-60 years and no clinical experience yet in the elderly, in children or in adolescents. The decision to use Arepanrix™ H1N1 in each age group defined below should take into account the extent of the clinical data available with a version of the vaccine containing H5N1 antigen and the disease characteristics of the current influenza pandemic.

The dose recommendations are based on:

- safety and immunogenicity data available on the administration of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/5/2005 (H5N1) (Arepanrix™ H5N1) at 0 and 21 days to adults, including the elderly
- safety and immunogenicity data available on the administration of the adult dose and half of the adult dose to children aged from 3-9 years with another AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) at 0 and 21 days
- limited immunogenicity data from 2 studies obtained three weeks after administration of a single dose of an investigational formulation of another AS03-adjuvanted H1N1 vaccine containing either 5.25 µg or 3.75 µg HA derived from A/California/7/2009 (H1N1) (Pandemrix™) to healthy adults aged 18-60 years. See section *Pharmacodynamics*.

#### Adults aged 18-60 years:

One dose of 0.5mL at an elected date.

The need for a second dose is currently unknown. However, preliminary immunogenicity data obtained at three weeks after administration of an investigational formulation of another AS03-adjuvanted H1N1 vaccine containing either 5.25 µg or 3.75 µg HA derived from A/California/7/2009 (H1N1) (Pandemrix™) to a limited number of healthy adults aged 18-60 years suggest that a single dose may be sufficient in this age group. See section *Pharmacodynamics*.

If a second dose is needed, it should be given after an interval of at least three weeks.

Elderly (>60 years):

No clinical data are available for Arepanrix™ H1N1 in this age group. One dose of 0.5mL at an elected date may be considered.

The need for a second dose of vaccine is unknown. If a second dose is needed, it should be given after an interval of at least three weeks. See section *Pharmacodynamics*.

Children and adolescents aged 10-17 years:

No clinical data are available for any influenza vaccines with AS03 in this age group. Consideration may be given to dosing in accordance with recommendations for adults.

Children aged 3-9 years:

Based on limited clinical data available for AS03-adjuvanted H5N1 vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 in this age group, 0.25mL of vaccine (i.e. half of the adult dose) at an elected date and a second dose administered at least three weeks later may be considered sufficient. See section *Pharmacodynamics*.

Children aged from 6-35 months:

No clinical data are available for influenza vaccines with AS03 in this age group. Consideration may be given to dosing in accordance with the recommendation in children aged 3-9 years.

Children aged less than 6 months:

Vaccination is not currently recommended in this age group.

For further information, see section *Pharmacodynamics*.

Method of administration:

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

### **Contraindications**

History of an anaphylactic reaction (i.e. life-threatening) to any of the constituents or trace residues of this vaccine.

See also section *Warnings and Precautions*.

### **Warnings and Precautions**

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 and to residues.

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, immunization shall be postponed in patients with severe febrile illness or acute infection.

Arepanrix™ H1N1 should under no circumstances be administered intravascularly or intradermally.

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 *Pharmacodynamics*).

#### Pediatric:

There is very limited experience with AS03-adjuvanted H5N1 vaccine in children between 3 and 9 years of age, and no experience in children less than 3 years of age or in children and adolescents between 10 and 17 years of age. See sections *Dosage and Administration*, *Adverse Reactions* and *Pharmacodynamics*.

#### Pregnancy and Lactation

No data have been generated in pregnant women with Arepanrix™ H1N1 nor with the prototype AS03 adjuvanted H5N1 vaccine. Data from vaccinations with seasonal trivalent influenza vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine.

CONSIDERATION SHOULD BE TAKEN OF ANY RECOMMENDATIONS MADE BY THE PUBLIC HEALTH AGENCY OF CANADA.

Animal studies have not demonstrated harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see also the section *Non-clinical information*).

No data have been generated in breast-feeding women.

### **Interactions**

No data are available on the concomitant administration of Arepanrix™ H1N1 with other vaccines, including seasonal trivalent influenza vaccines. Such data are in development, and this document will be amended to include them as soon as available. However, if co-administration with another vaccine is indicated, immunization 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 antibodies to HIV-1, Hepatitis C, and especially HTLV-1. These transient false-positive results may be due to cross-reactive IgM elicited by the vaccine. For this reason, a definitive diagnosis of HIV-1, Hepatitis C, or HTLV-1 infection

requires a positive result from a virus-specific confirmatory test (e.g, Western Blot or immunoblot).

### Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

### Adverse Reactions

#### H1N1 Studies:

Preliminary reactogenicity (solicited local and general adverse events reported within 7 days of vaccination) are provided for 2 studies which evaluated the safety of another AS03-adjuvanted vaccine containing HA derived from A/California/7/2009 (H1N1)v-like (Pandemrix™) in healthy subjects aged 18-60 years. In one study, the vaccine contained a higher amount of antigen (5.25 µg HA). In both studies, a group of subjects received the vaccine without the AS03 adjuvant. Solicited local and general symptoms were generally reported more frequently in the H1N1+AS03 group compared to the H1N1 group. Pain at the injection site was the most frequently reported solicited adverse events (AE). The frequency of 'related' Grade 3 symptoms was low and did not exceed 1.6%.

#### **D-Pan H1N1-021 (Day 0 to Day 6 solicited adverse events following a single dose of 5.25µg HA + AS03 H1N1 vaccine [Pandemrix™] versus a single dose of 21 µg HA unadjuvanted H1N1 vaccine) - Adverse Events with a causal relationship**

<b>Adverse reactions</b>	<b>H1N1/AS03 N=63</b>	<b>H1N1 N=66</b>
<b>Pain</b>	88.9%	59.1%
<b>Redness</b>	31.7%	4.5%
<b>Swelling</b>	30.2%	1.5%
<b>Fatigue</b>	15.9%	10.6%
<b>Headache</b>	14.3%	7.6%
<b>Arthralgia</b>	14.3%	3.0%
<b>Myalgia</b>	15.9%	4.5%
<b>Shivering</b>	3.2%	4.5%
<b>Sweating</b>	6.3%	4.5%
<b>Fever</b>	0.0%	0.0%

**D-Pan H1N1-007 (Day 0 to Day 6 solicited adverse events following a single dose of 3.75 µg HA + AS03 vaccine [Pandemrix™] versus a single dose of 15 µg HA unadjuvanted H1N1 vaccine) - Adverse Events with a causal relationship**

<b>Adverse reactions</b>	<b>H1N1/AS03 N=62</b>	<b>H1N1 N=62</b>
<b>Pain</b>	90.3%	37.1%
<b>Redness</b>	1.6%	0.0%
<b>Swelling</b>	6.5%	0.0%
<b>Fatigue</b>	32.3%	25.8%
<b>Headache</b>	14.3%	7.6%
<b>Arthralgia</b>	11.3%	4.8%
<b>Myalgia</b>	33.9%	8.1%
<b>Shivering</b>	8.1%	3.2%
<b>Sweating</b>	9.7%	8.1%
<b>Fever</b>	0.0%	0.0%

A total of four serious adverse events (SAEs) have been reported with the H1N1 studies. Three of them were considered by the investigators to be unrelated to the study vaccine. One reported case of hypersensitivity was considered by the investigator to be related to vaccination.

**H5N1 Studies:**

**Clinical trials**

Adverse reactions from clinical trials conducted using the mock-up vaccine are listed below.

**Adults:**

Clinical studies have evaluated the incidence of adverse reactions listed below in approximately 3,500 subjects 18 years old and above who received Influenza Virus Vaccine containing A/Indonesia/05/2005 (Arepanrix™ H5N1) with at least 3.75 µg HA/AS03.

The reactogenicity of vaccination was solicited by collecting adverse events using standardized forms for 7 consecutive days following vaccination with Arepanrix™ H5N1 or placebo (i.e., Day 0 to Day 6). The average frequencies of solicited local and general adverse events reported within 7 days after each vaccination dose are presented below:

**Percentage of Doses Followed by Solicited Local or General Adverse Events Within 7 Days of Any Vaccination With Arepanrix™ H5N1 (Total Vaccinated Cohort\*)**

	<b>AREPANRIX™ H5N1</b>	<b>Placebo</b>
<b>Local</b>	<b>N=6647 doses</b>	<b>N=2209 doses</b>
Pain	73.1	12.0
Swelling	6.7	0.4
Redness	5.25	0.4
<b>General</b>	<b>N=6639 doses</b>	<b>N=2210 doses</b>
Muscle Aches	33.3	11.8
Headache	23.4	17.6
Fatigue	23.3	14.1
Joint Pain	16.4	7.4
Shivering	9.8	6.0
Sweating	6.3	4.4
Fever, $\geq 38.0$ °C	2.4	1.9

\* Total Vaccinated Cohort = all subjects who received at least one dose of vaccine and for whom any safety data were available.

Pain at the injection site was the most commonly reported solicited local symptom in both Arepanrix™ H5N1 and placebo groups and was reported at a 6-fold higher frequency (i.e. following 73% of doses) in the Arepanrix™ H5N1 group. Despite the high incidence of injection site pain, the incidence of severe pain was low, with reports occurring after 2.7% of Arepanrix™ H5N1 doses and 0.4% of placebo doses. Overall, severe solicited or unsolicited adverse events of any type occurred in the 7 days after 6.4 to 7.0% of Arepanrix™ H5N1 doses and 3.6% of placebo doses. The most common severe solicited adverse event was local injection site pain; all severe general solicited adverse events occurred after <2% of doses.

Other/Additional adverse reactions reported are listed according to the following frequency classification:

Very common ( $\geq 1/10$ )

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

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

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders

Common: lymphadenopathy

Psychiatric disorders

Uncommon: insomnia

Nervous system disorders

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: pruritus

Uncommon: rash

Musculoskeletal and connective tissue disorders

Uncommon: back pain, musculoskeletal stiffness, neck pain, muscle spasms, pain in extremity

General disorders and administration site conditions

Common: injection site reactions (such as bruising, pruritus, warmth)

Uncommon: asthenia, chest pain, malaise

**Serious Adverse Events in Adults**

An integrated summary of safety was developed based on the first 9,873 adults to receive Arepanrix™ H5N1 or a closely similar product, Pandemrix™ H5N1, containing influenza antigen made in Germany combined with the AS03 adjuvant system. These trials enrolled adults 18 year of age or older, and included elderly subjects with pre-existing chronic medical conditions. In the primary analysis, which compared six months of safety follow-up in 7,224 recipients of Arepanrix™ H5N1 or Pandemrix™ H5N1 to a similar follow-up in 2,408 recipients of seasonal influenza vaccine or placebo, serious adverse events occurred in 1.6% of Arepanrix™ H5N1 or Pandemrix™ H5N1 recipients (95% Confidence interval 1.3 to 1.9%) versus 1.3% of seasonal influenza vaccine recipients (95% Confidence interval 0.7 to 2.0%) and 1.8% of placebo recipients (95% Confidence interval 1.1 to 2.8%). None of the serious adverse events was considered related to the study drugs by the investigators. Among Arepanrix™ H5N1 or Pandemrix™ H5N1 recipients, five (<0.1%) had fatal serious adverse events, including two instances of ovarian carcinoma, a metastatic malignancy of unspecified type, a myocardial infarction, and exacerbation of diabetes mellitus and hepatic cirrhosis. Among placebo recipients, three (0.1%) sustained fatal serious adverse events one instance of brain neoplasm, one instance of cardiomegaly secondary to chronic obstructive pulmonary disease, and one instance of bilateral pneumonia. During six months of follow-up for the entire group of 9,873 Arepanrix™ or Pandemrix™ H5N1 recipients, 7 (<0.1%) reported an Adverse Event of Special Interest as defined by EMEA. Four subjects reported facial palsy (Bell's palsy) at intervals ranging from hours to 135 days after vaccine exposure; all of these resolved spontaneously and completely. A 45 year old male had an anaphylactic reaction to food six (6) days after first exposure to H5N/AS03 vaccine, and a 25 year old white female had a single episode of convulsions

35 days after the second dose. None of these Adverse Events of Special Interest was assessed as treatment-related by the investigators. One 48 year old female had “neuritis” with onset almost immediately after injection. Symptoms were localized entirely to the injected arm and compatible with a perineural injection injury; the problem resolved spontaneously. Eleven of 9,873 (0.1%) Arepanrix™ or Pandemrix™ H5N1 recipients were reported to have potential immune-mediated diseases. Diagnoses included two instances of psoriasis, four instances of polymyalgia rheumatica (all in 59 to 84 year-old women, three of whom had symptoms antedating vaccine), and one instance each of Grave’s disease, uveitis, scleroderma, isolated IVth nerve palsy, and erythema nodosum. None of these was assessed as a serious adverse event or as related to the investigational vaccine by the investigators.

**Children aged 3-9 years:**

A clinical study evaluated the reactogenicity in children 3 to 5 and 6 to 9 years of age who received either a full or a half dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1).

The per-dose frequency of adverse reactions observed in the groups of children who received a full dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) was higher than that observed in the groups of children who received half of the dose, except for redness in the 6-9 years of age group. The per-dose frequency of specifically-solicited adverse events in the 7 days after each dose is illustrated in the following table. Grade 3 (severe) events of all types, solicited or unsolicited, in the 7 days after each dose, occurred following 9.3% of Arepanrix™ H5N1 doses and 2.8% of Fluarix™ control doses.

**Reactogenicity in children 3 to 5 and 6 to 9 years of age (full or a half dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) versus Fluarix™) - Adverse Events with a causal relationship**

Adverse reactions	3-5 years				6-9 years			
	Half dose N=101	Fluarix N=35	Full dose N=97	Fluarix N=34	Half dose N=100	Fluarix N=36	Full dose N=98	Fluarix N=36
Induration	9.9%	2.9 %	18.6%	0 %	12.0%	22.2%	12.2%	2.8%
Pain	48.5%	28.6%	62.9%	23.5 %	68.0%	58.3%	73.5%	61.1%
Redness	10.9%	5.7 %	19.6%	8.8 %	13.0%	16.7%	6.1%	2.8 %
Swelling	11.9%	2.9 %	24.7%	5.9 %	14.0%	19.4%	20.4%	8.3 %
Fever (>38°C)	2.0%	0%	6.2%	0%	2.0%	2.8%	10.2%	0%
Fever (>39°C)								
- per-dose frequency	2.0%	0%	5.2%	0%	0%	2.8%	7.1%	0%
- per-subject frequency	3.9%	0%	10.2%	0%	0%	5.6%	14.3%	0%
Drowsiness	7.9%	2.9 %	13.4%	2.9 %	NA	NA	NA	NA
Irritability	7.9%	2.9 %	18.6%	0 %	NA	NA	NA	NA
Loss of appetite	6.9%	2.9 %	16.5%	2.9 %	NA	NA	NA	NA
Shivering	1.0%	0 %	12.4%	2.9 %	4.0%	5.6 %	14.3%	11.1 %

NA=not available

**SAEs in children**

In analyzed clinical databases covering a period of 180 days of follow-up, there were no serious adverse events in children 3 to 9 years of age who received A/Vietnam/1194/04/AS03 vaccine at half dose. Among children who received full dose vaccine, one 5 year old male was hospitalized for gastroenteritis 19 days after the second dose, and a 4 year female sustained a traumatic brain injury 54 days after the second vaccine dose. Neither was considered by the investigator to be vaccine-related, and both recovered. One 3 year old female subject in a trial of an H5N1/AS03 containing a different ratio of antigen to adjuvant than that in Arepanrix™ H1N1 received the diagnosis of auto-immune hepatitis approximately one year after receiving a single vaccine dose. This child was subsequently found to have had significant abnormalities of serum transaminases prior to any vaccine exposure. One 5 year old female received the diagnosis of anterior uveitis eight days after receipt of the second full dose of Pandemrix™ H5N1. The event was assessed as possibly related to the vaccine, but also occurred in the setting of an apparent infectious syndrome of tonsillitis and gingivostomatitis.

**Post-marketing surveillance**

From Post-marketing surveillance with seasonal trivalent vaccines (without AS03), the following additional adverse events have been reported:

Blood and lymphatic system disorders

Transient thrombocytopenia.

Immune system disorders

Allergic reactions, in rare cases leading to shock.

Nervous system disorders

Neuralgia, convulsions.

Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

Vascular disorders

Vasculitis with transient renal involvement.

Skin and subcutaneous tissue disorders

Generalised skin reactions including urticaria

**Overdose**

Insufficient data are available

## 4.0 PHARMACOLOGICAL PROPERTIES

### Pharmacodynamics

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB02.

#### **H1N1 Studies:**

Health Canada will regularly review any new information which may become available and this Product Information Leaflet will be updated as necessary. The following data is currently available with the H1N1 pandemic strain.

#### Immune response to an investigational formulation of another AS03-adjuvanted vaccine containing 5.25 µg HA derived from A/California/7/2009 (H1N1) (Pandemrix™) in adults aged 18-60 years

In a clinical study that evaluated the immunogenicity of another AS03-adjuvanted vaccine containing 5.25 µg HA derived from A/California/7/2009 (H1N1)v-like in healthy subjects aged 18-60 years the anti-HA antibody responses post-dose 1 were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like 21 days after 1st dose	
	Non-Adjuvanted H1N1 Vaccine (21 µg HA) N=66	AS03-Adjuvanted H1N1 Vaccine (5.25µg HA) N=62
Seroprotection rate <sup>1</sup>	97.0	98.4%
Seroconversion rate <sup>2</sup>	95.5	98.4%
Seroconversion factor <sup>3</sup>	41.4	41.4

<sup>1</sup> seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre  $\geq 1:40$ ;

<sup>2</sup> seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of  $\geq 1:40$ , or who were seropositive at pre-vaccination and have a 4-fold increase in titre;

<sup>3</sup> seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

#### Immune response to an investigational formulation of another AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1) (Pandemrix™) in adults aged 18-60 years

In a clinical study that evaluated the immunogenicity of another AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like in healthy subjects aged 18-60 years the anti-HA antibody responses post-dose 1 were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like 21 days after 1st dose	
	Non-Adjuvanted H1N1 Vaccine (15µg HA) N=66	AS03-Adjuvanted H1N1 Vaccine (3.75 µg HA) N=61
Seroprotection rate <sup>1</sup>	93.9%	100%
Seroconversion rate <sup>2</sup>	84.8%	96.7%
Seroconversion factor <sup>3</sup>	31.0	43.3

<sup>1</sup> seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre  $\geq 1:40$ ;

<sup>2</sup> seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of  $\geq 1:40$ , or who were seropositive at pre-vaccination and have a 4-fold increase in titre;

<sup>3</sup> seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

### **H5N1 Studies:**

Preliminary data obtained from H1N1 pandemic vaccines suggest that the immunogenicity of the H1N1 vaccines is very different from that of H5N1 vaccines. This section describes the clinical experience with the mock-up vaccines, where clinical studies have been generated with H5N1, another strain with pandemic potential.

#### **Immune response against A/Indonesia/5/2005 (H5N1) in adults (18 years of age, and above):**

Clinical studies have evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/5/2005 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 <sup>1</sup>	91%	62%	76.8%	63.5%
Seroconversion rate <sup>2</sup>	91%	62%	76.4%	62.5%
Seroconversion factor <sup>3</sup>	51.4	7.4	17.2	7.8

<sup>1</sup> seroprotection rate (i.e. proportion of subjects with HI titre  $\geq 1:40$ );

<sup>2</sup> seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of  $\geq 1:40$ , or who were seropositive at pre-vaccination and have a 4-fold increase in titre);

<sup>3</sup> 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.

#### **Immune response against A/Vietnam/1194/2004 (H5N1) strain in children (3 to 9 years of age)**

A clinical study evaluated the immunogenicity and safety in children aged 3 to 9 years old. In this study, 49 children aged 3 to 5 and 49 children aged 6 to 9 years old received two doses of another 3.75 µg HA/AS03 vaccine containing the A/Vietnam/1194/2004 (H5N1) vaccine strain at 0 and 21 days.

The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody in these subjects were as follows:

anti-HA antibody	A/Vietnam/1194/2004			
	Children 3 to 5 years		Children 6 to 9 years	
	21 days after 1st dose N=43	21 days after 2nd dose N=44	21 days after 1st dose N=30	21 days after 2nd dose N=43
Seroprotection rate* <sup>1</sup>	46.5%	100%	56.7%	100%
Seroconversion rate <sup>2</sup>	46.5%	100%	56.7%	100%
Seroconversion factor <sup>3</sup>	5.0	191.3	5.5	176.7

\*anti-HA  $\geq$ 1:40

<sup>1</sup>seroprotection rate (i.e. proportion of subjects with HI titre  $\geq$ 1:40);

<sup>2</sup>seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of  $\geq$ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre);

<sup>3</sup>seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

A 4-fold increase in serum neutralising antibody titres was observed in 97.4% of subjects aged 3 to 5 years and in 100% of subjects aged 6 to 9 years 21 days after the second dose.

The persistence of immunogenicity up to 6 months after the second dose was also evaluated in these children. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 82.8%, 82.8% and 16 in the children aged 3 to 5 years and 78%, 78% and 12.3 in the children aged 6 to 9 years.

#### Information from non-clinical studies

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

- 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 µg HA). Ferrets immunized with the non adjuvanted H5N1 influenza vaccine were not protected from death and showed similar reduced 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.

### **Vaccines Used in Pharmacological Studies**

The Pandemrix™ vaccine is an AS03-adjuvanted H1N1 vaccine containing 5.25 µg or 3.75 µg HA derived from A/California/7/2009 (H1N1) manufactured in Dresden, Germany using a different production process than Arepanrix™ H1N1 (A/California/7/2009).

Another AS03-adjuvanted H5N1 vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1; previously described as Pandemrix™ H5N1) is also manufactured in Dresden, Germany using a similar production process as the Pandemrix™ vaccine (with H1N1 strain).

The Arepanrix™ H5N1 vaccine is an AS03-adjuvanted H5N1 vaccine containing 3.75 µg HA derived from A/Indonesia/5/2005 (H5N1) manufactured in Quebec, Canada using the same production process as the Arepanrix™ H1N1 (A/California) pandemic vaccine.

### **Pharmacokinetics**

Evaluation of pharmacokinetic properties is not required for vaccines.

### **Pre-clinical Safety Data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, female fertility, embryo-fetal and postnatal toxicity up to the end of the lactation period.

Two reproductive studies were conducted with AS03-adjuvanted H5N1 antigen and evaluated the effect on embryo-fetal and peri-and post-natal development in rats, following intramuscular administration. Although no definite conclusion could be reached, regarding a possible relation to treatment with the H5N1 vaccine and/or the adjuvant AS03, and other findings were considered normal, the following observations deserve to be mentioned: In the first study, there was an increased incidence of fetal malformations with markedly medially thickened/kinked ribs and bent scapula as well as an increased incidence of dilated ureter and delayed neurobehavioral maturation. In the second study, there was an increased incidence of post-implantation loss, and the fetal variation of dilated ureter. Not all findings were observed in both studies, and hence the toxicological significance is uncertain.

## 5.0 PHARMACEUTICAL PARTICULARS

### List of Excipients

Antigen suspension vial: Thimerosal, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, water for injections. The drug substance contains trace residual amounts of egg proteins, formaldehyde, sodium deoxycholate and sucrose.

Adjuvant emulsion vial: sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, water for injections.

### Incompatibilities

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

### Shelf Life

The antigen suspension is stable for 18 months.

The adjuvant emulsion is stable for 3 years.

After mixing, the vaccine should be used within 24 hours. Although it is recommended to maintain the mixed product between 2°C and 8°C, it may be kept at room temperature during this period if required. However, if the product is refrigerated, it must be brought to room temperature before withdrawal. The chemical and physical in-use stability has been demonstrated for 24 hours at 30°C.

### Special Precautions for Storage

Store at 2°C to 8°C (in a refrigerator).

Do not freeze.

Store in the original packaging in order to protect from light.

### Nature and Contents of Container

One pack contains:

- one pack of 50 vials (type I glass) of 2.5mL suspension (10 x 0.25mL doses) with a stopper (butyl rubber without latex)
- two packs of 25 vials (type I glass) of 2.5mL emulsion (10 x 0.25mL doses) with a stopper (butyl rubber without latex).

The volume after mixing 1 vial of suspension with 1 vial of emulsion allows the withdrawal of 10 doses of 0.5mL vaccine (5mL).

### **Instructions for Use/Handling**

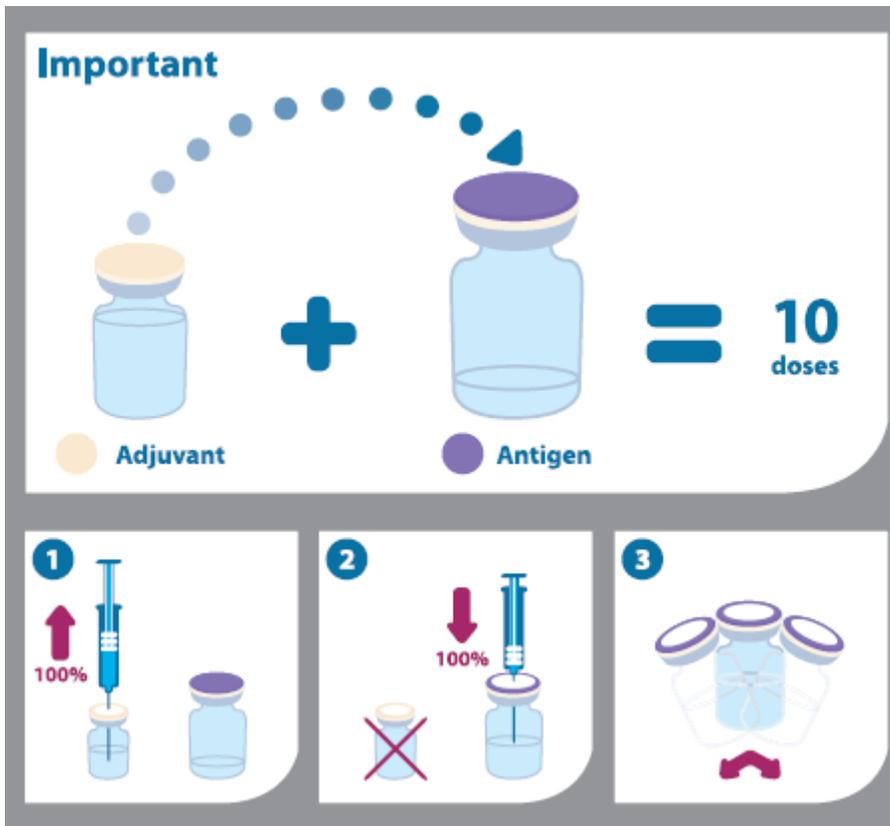
Arepanrix™ H1N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The antigen suspension is a translucent to whitish opalescent suspension that may sediment slightly. The emulsion is a whitish homogeneous liquid.

Prior to administration, the two components should be mixed. The entire contents of the adjuvant emulsion must be withdrawn and added to the antigen suspension and mixed.

Instructions for mixing and administration of the vaccine (as depicted in the pictogram below):

1. Before mixing the two components the vials should be brought to room temperature, and the emulsion and suspension should be shaken and inspected visually for any abnormal physical appearance.
2. The vaccine is mixed by withdrawing the entire contents of the vial containing the emulsion by means of a syringe and by adding it to the vial containing the antigen suspension.
3. After the addition of the emulsion to the suspension, the mixture should be well shaken. The mixed vaccine is a whitish emulsion. In the event of other variation being observed, discard the vaccine.
4. The volume of Arepanrix™ H1N1 (5mL) after mixing corresponds to 10 doses of vaccine.
5. The vial should be shaken prior to each administration.
6. Each vaccine dose of 0.5mL is withdrawn into a syringe for injection. The vaccine should be allowed to reach room temperature before use.
7. The needle used for withdrawal must be replaced by a needle suitable for intramuscular injection.

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



## CONSUMER INFORMATION

### AREPANRIX™ H1N1

AS03-Adjuvanted H1N1 Pandemic Influenza Vaccine

This leaflet is part of a "Package Insert" and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AREPANRIX™ H1N1. Contact your doctor or pharmacist if you have any questions about the vaccine.

Health Canada has authorized the sale of the Arepanrix™ H1N1 based on limited clinical testing in humans under the provision of an Interim Order (IO) issued on October 13, 2009. The authorization is based on the Health Canada review of the available data on quality, safety and immunogenicity, and given the current pandemic threat and its risk to human health, Health Canada considers that the benefit/risk profile of the Arepanrix™ H1N1 vaccine is favourable for active immunization against the H1N1 2009 influenza strain in an officially declared pandemic situation.

As part of the authorization for sale for Arepanrix™ H1N1, Health Canada has requested the sponsor agree to post-market commitments. Adherence to these commitments, as well as updates to information on quality, non-clinical, and clinical data will be continuously monitored by Health Canada and the Public Health Agency of Canada.

### ABOUT THIS VACCINE

What the vaccine is used for:

AREPANRIX™ H1N1 is a vaccine to prevent influenza (flu) caused by the H1N1 virus.

What it does:

When a person is given the vaccine, the immune system (the body's natural defense system) will make antibodies against the H1N1 virus. These antibodies are expected to protect against disease caused by flu. None of the ingredients in the vaccine can cause influenza. There is no live virus in this vaccine.

As with all vaccines, AREPANRIX™ H1N1 may not fully protect all people who are vaccinated.

When it should not be used:

Do not use this vaccine if you have previously experienced a life-threatening allergic reaction to:

- egg proteins (egg or egg products) or chicken proteins

- other influenza vaccination
- any ingredient of the vaccine

Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

What the medicinal ingredient is:

H1N1 influenza antigen from A/California/7/2009, NYMC X-179A (H1N1)v strain and AS03 adjuvant

What the important nonmedicinal ingredients are:

Thimerosal, a mercury derivative is added as preservative. Each dose contains 2.5 micrograms of mercury. Other ingredients include: squalene, vitamin E, polysorbate 80 and trace amounts of egg proteins, formaldehyde, sodium deoxycholate and sucrose.

For a full listing of nonmedicinal ingredients see the first part of the package insert (Section 5.0).

What dosage forms it comes in:

AREPANRIX™ H1N1 is a two component vaccine consisting of a translucent to whitish opalescent suspension that may sediment slightly containing antigen and a whitish emulsion containing the AS03 adjuvant. AREPANRIX™ H1N1 is an emulsion for injection.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

**Advise your doctor or nurse immediately if you experience these reactions shortly after receiving your injection:**

- **body rash**
- **tightness in the throat**
- **shortness of breath**

BEFORE you use AREPANRIX™ H1N1 talk to your doctor or nurse if:

- you have a severe infection with a high temperature
- you have a weakened immune system due to medication or disease such as HIV

## INTERACTIONS WITH THIS VACCINE

There is currently no information on the administration of AREPANRIX™ H1N1 with other vaccines.

## PROPER USE OF THIS VACCINE

### Usual dose:

One injection. A second dose of vaccine may be given. The second dose should be given at least 3 weeks after the first dose.

Children (>9 years) and adults: 0.5 mL/dose

Children 3-9 years: 0.25 mL/dose

Children 6-35 months: 0.25mL/dose (No clinical data are available for influenza vaccines with AS03 in this age group)

Information on this product will be updated regularly. Consult with Health Canada website for the most up-to date information on this product:

<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/legislation/interimorders-arretesurgence/index-eng.php>  
<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/legislation/interimorders-arretesurgence/index-fra.php>

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, AREPANRIX™ H1N1 can cause side effects. The very common and common side effects are usually mild and should only last a day or two.

**Very common** (may occur with more than 1 in 10 doses):

- Pain at the injection site
- Headache
- Fatigue
- Redness or swelling at the injection site
- Shivering
- Sweating
- Aching muscles, joint pain

**Common** (may occur with up to 1 in 10 doses):

- Reactions at the injection site such as bruising, itching and warmth
- Fever
- Swollen lymph nodes
- Feeling sick, diarrhea

**Uncommon** (may occur with up to 1 in 100 doses):

- Dizziness
- Generally feeling unwell
- Unusual weakness

- Vomiting, stomach pain, uncomfortable feeling in the stomach or belching after eating
- 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

**Rare** (may occur with up to 1 in 1000 doses):

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

**Very Rare** (may occur with up to 1 in 10,000 doses):

- 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 as 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.

## HOW TO STORE IT

Store in a refrigerator (2°C to 8°C) in the original package to protect from light. Do not freeze. Keep out of reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor vaccine safety, the Public Health Agency of Canada collects information on serious and unexpected adverse events following vaccination. If you suspect you have had a serious or unexpected event following receipt of a vaccine you may notify the Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018  
 By toll-free fax: 1-866-844-5931  
 By email: caefi@phac-aspc.gc.ca

By regular mail:  
 Vaccine Safety  
 Centre for Immunization & Respiratory  
 Infectious Diseases,  
 Public Health Agency of Canada  
 130 Colonnade Road  
 Address Locator: 6502A  
 Ottawa, Ontario K1A 0K9

**NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.**

**MORE INFORMATION**

This document plus the full package insert, prepared for health professionals can be found at:

<http://www.gsk.ca> or by contacting the sponsor:

GlaxoSmithKline Inc.  
 7333Mississauga Road  
 Mississauga, Ontario L5N 6L4  
 1-800-387-7374

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 ™AREPANRIX H1N1

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