

PRODUCT INFORMATION LEAFLET

**AREPANRIX™ H1N1**

AS03-Adjuvanted H1N1 Pandemic Influenza Vaccine

Emulsion for Injection

ATC Code J07BB02

GlaxoSmithKline Inc.  
7333 Mississauga Road  
Mississauga, Ontario  
L5N 6L4

Date of Preparation:  
20 April 2010

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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 pandemic threat at the time of authorization 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 2009 pandemic H1N1 influenza strain.

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.

<http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/recommendation-recommandation-eng.php>

<http://www.phac-aspc.gc.ca/alert-alerte/h1n1/fs-fi-pregnancy-grossesse-eng.php>

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## 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, translucent to whitish 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 to yellowish 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 the 2009 pandemic H1N1 influenza strain.

(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 manufactured by GSK in Dresden, Germany (Pandemrix™ (H1N1)), also containing antigen derived from A/California/7/2009 (H1N1) (see section *Pharmacodynamics*) in healthy adults aged 18-60 years, in the elderly, in children and 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 Arepanrix™ H1N1, supplementary information regarding Pandemrix™ (H1N1), the disease characteristics of the current influenza pandemic and the recommendations of the Public Health Agency of Canada, which may change based on emerging additional data.

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 Pandemrix™ (H1N1) containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) at 0 and 21 days
- limited safety and immunogenicity data from several studies obtained three weeks after administration of one or two doses of Pandemrix™ (H1N1) containing either 3.75 µg or 1.9 µg HA derived from A/California/7/2009 (H1N1) . See section *Pharmacodynamics*. Current data concerning Arepanrix™ H1N1 are limited and preliminary in nature, however they tend to support conclusions based on the Pandemrix™ (H1N1) experience.
- very limited safety and immunogenicity data from several studies obtained three weeks after administration of one dose of Arepanrix™ H1N1. See section *Pharmacodynamics*.

#### Adults aged 18-60 years:

One dose of 0.5mL.

Immunogenicity data obtained at three weeks after administration of AS03-adjuvanted H1N1 vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1) (Pandemrix™ (H1N1) or Arepanrix™ H1N1) 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 administered, it should be given after an interval of at least three weeks.

Elderly (>60 years):

There are limited data available from clinical studies with Pandemrix™ (H1N1) and with Arepanrix™ H1N1 vaccine in adults aged over 60 years.

The recommended dosage for this age group is one dose of 0.5mL. Immunogenicity data obtained at 3 weeks after administration of Pandemrix (H1N1) or Arepanrix™ H1N1 in clinical studies in this age group suggest that a single dose may be sufficient.

If a second dose is administered, 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 Arepanrix™ H1N1 in this age group. There are limited data available from a clinical study with Pandemrix™ (H1N1) in this age group.

The recommended dosage for this age group is in accordance with recommendations for adults.

Children aged 6 months to 9 years:

One dose of 0.25mL (i.e. half of the adult dose) at an elected date.

Preliminary immunogenicity data obtained in a limited number of children aged 6-35 months who received two doses of 0.25 mL of Pandemrix™ (H1N1) containing 1.9 µg HA derived from A/California/7/2009 (H1N1) and a limited number of children aged 3-9 years who received one dose of 0.5 mL of Pandemrix™ (H1N1) show that a good immune response is elicited after the first dose, but there is a further immune response to a second dose of 0.25 mL administered to children aged 6-35 months after an interval of three weeks.

The benefit of administering a second dose of 0.25 mL should be weighed against the potential safety concern associated with a second dose (see section Adverse Reactions).

If a second dose is administered there should be an interval of at least three weeks between the first and the second dose.

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. Anaphylaxis and severe allergic reactions have been observed in persons receiving Arepanrix™ H1N1 as part of mass vaccination campaigns; the overall incidence rate for anaphylaxis appears to be generally similar to that observed with other parenteral vaccines.

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 Arepanrix™ H1N1 in children between 6 months and 9 years, and with Pandemrix™ (H1N1) in children between 6 and 35 months of age, and between 3 and 17 years of age. See sections *Dosage and Administration*, *Adverse Reactions* and *Pharmacodynamics*.

Very limited data in children aged 6 to 35 months (N=51) who received two doses of 0.25 mL of Pandemrix™ (H1N1) (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 *Adverse Reactions*). In particular, rates of fever (axillary temperature  $\geq 38^{\circ}\text{C}$ ) may increase after the second dose.

### 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.

Data obtained on co-administration of Pandemrix™ (H1N1) with a 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 Pandemrix™ (H1N1). The immune response to Fluarix was also satisfactory. Co-administration was not associated with higher rates of local or systemic reactions compared to administration of Pandemrix™ (H1N1) alone. Similarly, sequential administration of Fluarix followed by Pandemrix™ (H1N1) (3-week interval) did not suggest any significant interference in the immune response to Pandemrix™ (H1N1), although there is a trend toward a modestly lower immune response to Pandemrix™ (H1N1) in subjects vaccinated with Fluarix 21 days earlier.

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:

#### Adults 18-60 years

Preliminary reactogenicity data (solicited local and general adverse events reported within 7 days of each vaccination) are provided for a study which evaluated the safety of Pandemrix™ (H1N1) in healthy subjects aged 18-60 years. A concurrent 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 4.8%. Similar safety observations were recently made in another study (Q-PAN H1N1-001) using Arepanrix™ H1N1.

#### **D-Pan H1N1-007 (Day 0 to Day 6 solicited adverse events following each of 2 doses of 3.75 µg HA + AS03 vaccine [Pandemrix™ (H1N1)] versus each of 2 doses of 15 µg HA unadjuvanted H1N1 vaccine) - Adverse Events with a causal relationship**

Adverse reactions	Post-Dose 1		Post-Dose 2	
	H1N1/AS03 N=63	H1N1 N=65	H1N1/AS03 N=62	H1N1 N=66
<b>Pain at the injection site</b>	90.5%	35.4%	90.3%	30.3%
<b>Redness</b>	1.6%	0.0%	4.8%	0.0%
<b>Swelling</b>	7.9%	0.0%	14.5%	0.0%
<b>Fatigue</b>	33.3%	24.6%	43.5%	19.7%
<b>Headache</b>	23.8%	12.3%	32.3%	12.1%
<b>Arthralgia</b>	11.1%	4.6%	21.0%	6.1%
<b>Myalgia</b>	31.7%	6.2%	37.1%	9.1%
<b>Shivering</b>	9.5%	3.1%	17.7%	3.0%
<b>Sweating</b>	9.5%	7.7%	19.4%	9.1%
<b>Fever (&gt;38°C)</b>	0.0%	0.0%	4.6%	0.0%

Serious adverse events (SAEs) were reported infrequently and most of them were not related to vaccination.

#### Adults 18 years and above

A clinical study evaluated the reactogenicity of the first dose of Pandemrix™ (H1N1) 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).

**D-Pan H1N1-008 Day 0 to Day 6 solicited adverse events following a single dose of 3.75 µg HA + AS03 vaccine [Pandemrix™ (H1N1)] - Adverse Events with a causal relationship**

Adverse reactions	H1N1/AS03 18-60 years N=120	H1N1/AS03 >60 years N=120
Pain	87.5%	65.0%
Redness	0.8%	7.5%
Swelling	9.2%	10.0%
Fatigue	31.7%	20.0%
Headache	33.3%	17.5%
Arthralgia	12.5%	11.7%
Myalgia	19.2%	19.2%
Shivering	16.7%	5.8%
Sweating	12.5%	5.0%
Fever ( $\geq 38^{\circ}\text{C}$ )	0.8%	0.8%

No serious adverse event (SAE) has been reported with this H1N1 study.

**Children aged 3-9 years**

Another clinical study evaluated the reactogenicity in children 3 to 5 and 6 to 9 years of age who received a full dose of Pandemrix™ (H1N1). An increased reactogenicity was observed after the second dose in both age groups, especially for axillary fever ( $\geq 38^{\circ}\text{C}$ ), shivering and sweating. The per-dose frequency of the following adverse reactions was as follows:

**D-Pan H1N1-010 Day 0 to Day 6 solicited adverse events following 2 doses of 3.75 µg HA + AS03 vaccine [Pandemrix™ (H1N1)] - Adverse Events with a causal relationship**

Adverse reactions	3-5 years		6-9 years	
	Post dose 1 N=53	Post dose 2 N=52	Post dose 1 N=57	Post dose 2 N=57
Pain	75.5%	84.6%	94.7%	96.5%
Redness	28.3%	34.6%	24.6%	33.3%
Swelling	34.0%	30.8%	28.1%	45.6%
Fever ( $>38^{\circ}\text{C}$ ) (axillary)	5.7%	28.8%	1.8%	10.5%
Fever ( $>39^{\circ}\text{C}$ ) (axillary)	0.0%	3.8%	0.0%	1.8%
Shivering	3.8%	9.6%	7.0%	22.8%
Sweating	1.9%	7.7%	1.8%	7.0%
Drowsiness	15.1%	28.8%	NA	NA
Irritability	18.9%	26.9%	NA	NA
Loss of appetite	15.1%	32.7%	NA	NA

NA=not available

**Children aged 6-35 months**

A clinical study evaluated the reactogenicity in children aged 6 to 35 months who received half the adult dose (i.e. 0.25 mL) of Pandemrix™ (H1N1) following a 0, 21 days schedule. After the second dose, an increase in injection site reactions and general symptoms was observed overall in the 6 to 35 months age group, particularly in rates of axillary fever ( $\geq 38^{\circ}\text{C}$ ), drowsiness and loss of appetite. The overall per-dose frequency of the following adverse reactions was as follows:

**D-Pan H1N1-009 Day 0 to Day 6 solicited adverse events following 2 doses of 1.9 µg HA + AS03 vaccine [half the adult dose of Pandemrix™ (H1N1)] - Adverse Events with a causal relationship**

Adverse reactions	Post-dose 1 N=51	Post-dose 2 N=51
Pain	31.4%	41.2%
Redness	19.6%	29.4%
Swelling	15.7%	23.5%
Fever ( $\geq 38^{\circ}\text{C}$ ) axillary	5.9%	43.1%
Fever ( $\geq 39^{\circ}\text{C}$ ) axillary	0.0%	3.9%
Drowsiness	7.8%	35.3%
Irritability	21.6%	37.3%
Loss of appetite	9.8%	39.2%

Similar post-dose 1 safety observations were recently made in another study (Q-PAN H1N1-003) using Arepanrix™ H1N1 vaccine. Post-dose 2 safety data are not yet available from this study.

**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 (ISS) 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.

*Serious Adverse Events (ISS):* 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.

*Adverse Events of Special Interest (AESI from ISS):* 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.

*Potential Immune-Mediated Disease (pIMD from ISS):* 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.

In conclusion, in AS03-adjuvanted H5N1 controlled studies, 11 pIMD cases and 7 AESI cases were reported in 7224 subjects who received AS03-adjuvanted H5N1 vaccine compared to one case in 2408 subjects who received a control (Fluarix or Placebo). An association between the occurrence of these rare events and the use of the vaccine can neither be ruled out, nor established.

#### **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)	4.0%	0%	11.3%	0%	2.0%	5.6%	17.3%	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**Pandemic vaccines

From Post-marketing surveillance with AS03-adjuvanted H1N1 vaccines (including Arepanrix™ H1N1 and Pandemrix™ (H1N1)), the following adverse events have been reported:

Immune system disorders

Rare: anaphylaxis, allergic reactions

Skin and subcutaneous tissue disorders

Rare: Angioedema, generalised skin reactions, urticaria

Seasonal trivalent vaccines

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

Blood and lymphatic system disorders

Rare: Transient thrombocytopenia.

Nervous system disorders

Rare: Neuralgia, convulsions.

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

Vascular disorders

Very rare: Vasculitis with transient renal involvement.

## Overdose

Insufficient data are available.

## 4.0 PHARMACOLOGICAL PROPERTIES

### Pharmacodynamics

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB02.

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.

Clinical studies with Arepanrix™ H1N1 currently provide:

- Limited safety and immunogenicity data obtained three weeks after administration of a single dose of Arepanrix™ H1N1 to healthy adults aged 18-60 years and greater than 60 years.

Clinical studies with Pandemrix (H1N1) currently provide:

- Limited safety and immunogenicity data obtained three weeks after administration of two doses of Pandemrix (H1N1) to healthy adults aged 18-60 years.
- Very limited safety and immunogenicity data obtained three weeks after administration of a single dose of Pandemrix (H1N1) to healthy adults aged over 60 years (60-80 years).
- Very limited safety and immunogenicity data obtained three weeks after a 2-dose administration of half the adult dose (i.e. 0.25 mL) of Pandemrix (H1N1) to healthy children aged 6-35 months.
- Very limited safety and immunogenicity data obtained three weeks after a single administration (0.5mL) of Pandemrix (H1N1) to healthy children aged 3-17 years of age.

The definitions used for each of the immunogenicity parameters are as follows:

- the seroprotection rate is the proportion of subjects with haemagglutination inhibition (HI) titre  $\geq 1:40$ ;

- the seroconversion rate is the 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;

- the seroconversion factor is ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

**Arepanrix™ H1N1 Studies:****Adults 18-60 years and > 60 years:**

Immune response to Arepanrix™ H1N1 containing 3.75 µg HA, from three clinical studies in adults:

Preliminary results for 2 studies that evaluated the immunogenicity of Arepanrix™ H1N1 containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like in healthy subjects in Europe and Japan aged 18-64 years are provided for the anti-HA antibody responses post-dose 1.

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like 21 days post-dose	
	(FLU-D-PAN H1N1-017) Arepanrix™ H1N1 18-60 years N=166	(FLU-Q-PAN H1N1-016) Arepanrix™ H1N1 20-64 years N=100
Sero-protection rate	97.6%	95%
Sero-conversion rate	94%	94%
Sero-conversion factor	32.2	26.3

Additional results are available from a third study (Q-Pan H1N1-001) that evaluated the immunogenicity post-dose 1 of Arepanrix™ H1N1 containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like in healthy North American (US and Canadian) subjects aged 18-60 years and greater than 60 years.

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like			
	18-60 years		>60 years	
	15µg Non-Adjuvanted H1N1 Vaccine N=81	3.75µg AS03-Adjuvanted H1N1 Vaccine N=165	15µg Non-Adjuvanted H1N1 Vaccine N=139	3.75µg AS03-Adjuvanted H1N1 Vaccine N=273
Sero-protection rate	87.7%	98.8%	75.5%	92.3%
Sero-conversion rate	70.4%	92.1%	54.7%	76.6%
Sero-conversion factor	10.3	31.0	6.0	10.4

**Other AS03-adjuvanted vaccine (Pandemrix™ (H1N1)) Studies:****Adults 18-60 years:**

Immune response to a 3.75µg HA dose of Pandemrix™ (H1N1) in adults aged 18-60 years (D-PAN H1N1-007)

In a clinical study (D-Pan H1N1-007) that evaluated the immunogenicity of a 3.75µg HA dose of Pandemrix™ (H1N1) in healthy subjects aged 18-60 years the anti-HA antibody responses post-dose 1 and post-dose 2 were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like			
	21 days after 1st dose		21 days after 2nd dose (day 42)	
	Non-Adjuvanted H1N1 Vaccine N=66	AS03-Adjuvanted H1N1 Vaccine N=60	Non-Adjuvanted H1N1 Vaccine N=66	AS03-Adjuvanted H1N1 Vaccine N=59
Sero-protection rate	93.9%	100%	100%	100%
Sero-conversion rate	84.8%	98.3%	92.4%	98.3%
Sero-conversion factor	28.7	38.1	31.5	72.9

### **Adults 18 and above**

Immune response to a 3.75µg HA dose of Pandemrix™ (H1N1) in adults aged 18 years and above (D-PAN H1N1-008)

In a clinical study (D-Pan H1N1-008) that evaluated the immunogenicity of one 3.75µg HA dose of Pandemrix™ (H1N1) in healthy subjects aged 18 years and above, the anti-HA antibody responses were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like 21 days after single dose	
	AS03-Adjuvanted H1N1 Vaccine 18-60 years N=120	AS03-Adjuvanted H1N1 Vaccine >60 years N=120
Sero-protection rate	97.5%	87.5%
Sero-conversion rate	95.0%	79.2%
Sero-conversion factor	42.15	13.66

### **Children aged 3-17 years**

In a clinical study (D-PAN H1N1-010) that evaluated the immunogenicity of one 3.75µg HA dose of Pandemrix™ (H1N1) in children aged 3 to 17 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 single dose		
	AS03-Adjuvanted H1N1 Vaccine 3-5 years N=50	AS03-Adjuvanted H1N1 Vaccine 6-9 years N=54	AS03-Adjuvanted H1N1 Vaccine 10-17 years N=97
Sero-protection rate	100%	100%	100%
Sero-conversion rate	100%	100%	96.9%
Sero-conversion factor	49.9	55.9	69.0

### Children aged 6-35 months

Another clinical study (D-PAN H1N1-009) evaluated the immunogenicity of a half adult dose (i.e. 0.25 mL) of one 3.75µg HA dose of Pandemrix™ (H1N1) per 0.5mL 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 dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like						
	6-11 months			12-23 months <sup>1</sup>		24-35 months <sup>1</sup>	
	Post dose 1	Post dose 2	Post dose 1	Post dose 1	Post dose 2	Post dose 1	Post dose 2
	Total enrolled subjects		Seronegative subjects prior to vaccination	Total enrolled subjects		Total enrolled subjects	
	N=17	N = 17	N=14	N=17	N= 16	N=16	N= 17
Seroprotection rate	100%	100%	100%	100%	100%	100%	100%
Seroconversion rate	94.1%	100%	100%	100%	100%	100%	100%
Seroconversion factor	44.4	221.9	70.67	76.9	378.0	53.8	409.1

<sup>1</sup>All subjects seronegative prior to vaccination

The clinical relevance of the haemagglutination inhibition (HI) titre  $\geq 1:40$  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).

### **Information from ferret challenge studies**

Preliminary results concerning protection against A/California/7/2009-like H1N1 have been generated in a challenge study in ferrets. Groups of immunologically-naive animals were immunised with one or two doses of AS03-adjuvanted formulations containing from 1.9 to 15 µg HA of antigen (A/California/7/09 strain) manufactured in Germany, two doses of 15µg HA (A/California/7/09 strain) in an unadjuvanted formulation, or phosphate buffered saline (PBS) as control. Following vaccination, the ferrets underwent intratracheal challenge with a high dose of the closely related H1N1v virus A/The Netherlands/602/09.

Initial results indicate that a single vaccination with the AS03-adjuvanted formulations provide better protection than two injections of unadjuvanted antigen or PBS control against macroscopic lung pathology, and resulted in a significant reduction in virus titers

in lung tissue. The proportion of lung tissue involved in pathology, and total lung weights, were lowest in animals that received adjuvanted vaccine. Animals receiving adjuvanted vaccine had the highest HI titers and neutralization assay titers compared to unadjuvanted vaccine which had baseline titers equivalent to the PBS control. Animals receiving 2 doses of adjuvanted vaccine experienced higher HI and neutralization titers than animals receiving 1 dose of adjuvanted vaccine.

These initial results need to be interpreted carefully and need to take into consideration the limitations of the ferret challenge model, which include the fact that ferrets are immunologically completely naïve to H1N1 viruses and are exposed to a dose and route of viral challenge that may not be representative of human experience.

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

The Pandemrix™ (H1N1) vaccine is an AS03-adjuvanted H1N1 vaccine containing 3.75 µg or 1.9 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™ (H1N1) vaccine.

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.

### **Non-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

Do not use the vaccine after the expiration date indicated on the box label.

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

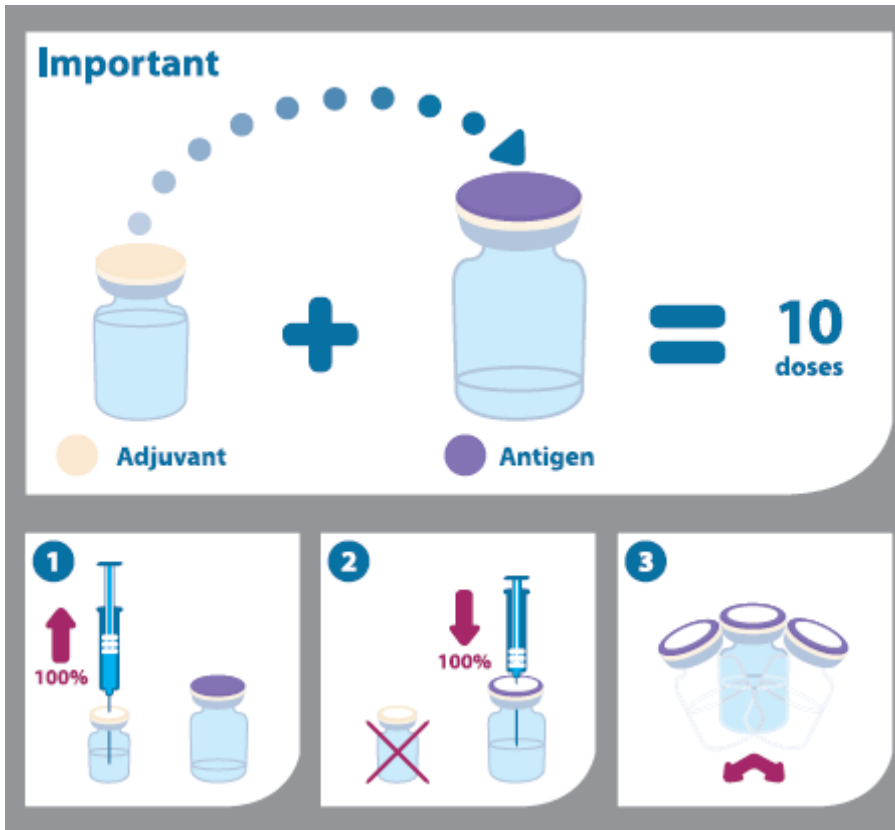
Arepanrix™ H1N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The antigen suspension is a translucent to whitish opalescent suspension that may sediment slightly. The emulsion is a whitish to yellowish 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 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 with a whitish to yellowish 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 emulsion by means of a 5mL syringe and by adding it to the vial containing the antigen suspension. It is recommended to equip the syringe with a 23-G needle. The vial containing the adjuvant should be maintained in upside down position to facilitate the withdrawal of the full contents.
4. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish to yellowish emulsion. In the event of other variations being observed, discard the vaccine.
5. The volume of Arepanrix™ H1N1 vial after mixing is at least 5 mL. The vaccine should be administered in accordance with the recommended dosage (see section 3 *Dosage and Administration*).
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 0.5mL (full dose) or 0.25mL (half dose) is withdrawn into a 1mL syringe for injection. It is recommended to equip the syringe with a needle gauge not larger than 23-G. The vaccine should be allowed to reach room temperature before use.
8. After mixing, use the vaccine within 24 hours (refer to *Shelf-life* section above).

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 pandemic threat at the time of authorization 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 2009 pandemic H1N1 influenza strain.

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 2009 pandemic 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.

The AS03 adjuvant in AREPANRIX™ H1N1 vaccine enhances the vaccine-induced immune response and contains naturally occurring molecules (squalene and vitamin E) plus an emulsifier (polysorbate 80). This adjuvant has been tested in approximately 45,000 people around the world. Health Canada has evaluated its safety in about 10,000 people who received the H5N1 vaccine combined with this adjuvant, in the pre-pandemic period. **No special safety concern has been raised, but rare adverse events can only be identified through careful post-marketing surveillance in large populations.**

#### 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

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
- Swelling beneath the skin, giving rise to welts usually around eyes and lips but also on hands and feet

**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  
Web: <http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php>**

**By regular mail:  
The Public Health Agency of Canada  
Vaccine Safety Section  
130 Colonnade Road  
Ottawa, ON K1A 0K9  
A/L 6502A**

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

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™AREPANRIX H1N1

Last Revised: 20 April 2010