PRODUCT MONOGRAPH

AREPANRIX™ H5N1

AS03-adjuvanted Quebec H5N1 Influenza Vaccine

Emulsion for Injection

ATC Code J07BB02

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

Date of Preparation:
31 January 2017
Date of Approval:

Submission Control No: - 190247

TABLE OF CONTENTS

PAGE

PART I: HEALTH PROFESSIONAL INFORMATION 3
- SUMMARY PRODUCT INFORMATION 3
- DESCRIPTION 3
- INDICATIONS AND CLINICAL USE 3
- CONTRAINDICATIONS 4
- WARNINGS AND PRECAUTIONS 4
- ADVERSE REACTIONS 5
- DRUG INTERACTIONS 10
- DOSAGE AND ADMINISTRATION 10
- OVERDOSAGE 13
- ACTION AND CLINICAL PHARMACOLOGY 13
- STORAGE AND STABILITY 13
- DOSAGE FORMS, COMPOSITION AND PACKAGING 13

PART II: SCIENTIFIC INFORMATION 15
- PHARMACEUTICAL INFORMATION 15
- CLINICAL TRIALS 15
- DETAILED PHARMACOLOGY 20
- TOXICOLOGY 21

PART III: CONSUMER INFORMATION 22

AREPANRIX™ H5N1

AS03-adjuvanted Quebec H5N1 Influenza Vaccine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
IM injection	Each 0.5 mL vaccine dose contains 3.75 micrograms of A/Indonesia/5/2005 (H5N1) and is adjuvanted with AS03	Thimerosal, trace amounts of egg proteins including ovalbumin, formaldehyde, sodium deoxycholate and sucrose. *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

AREPANRIX™ H5N1 influenza vaccine is a two-component vaccine consisting of an H5N1 immunizing antigen (as a suspension), and an AS03 adjuvant system (as an oil-in-water emulsion).

The H5N1 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 homogeneous milky emulsion composed of DL-α-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Immediately prior to use, the full contents of the AS03 vial is withdrawn and added to the antigen vial (mix ratio 1:1).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.

INDICATIONS AND CLINICAL USE

AREPANRIX™ H5N1 is indicated for active immunization of adults and children from 6 months of age against influenza caused by the H5N1 subtype virus contained in the vaccine. This indication is based on immunological data as the vaccine has not been evaluated in efficacy trials against influenza disease (see *Part II, Clinical Trials*).

AREPANRIX™ H5N1 should be used according to official guidance.

CONTRAINDICATIONS

History of an anaphylactic reaction (i.e., life-threatening) to any of the constituents or trace residues of this vaccine, including egg protein. See *Dosage Forms, Composition and Packaging*.

WARNINGS AND PRECAUTIONS

General
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 an anaphylactic event following the administration of the vaccine.

Immunization shall be postponed in patients with severe febrile illness or acute infection, unless the benefits outweigh the potential risks of administering the vaccine to those patients.

AREPANRIX™ H5N1 should under no circumstances be administered intravascularly or intradermally.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

There are no data on co-administration of AREPANRIX™ H5N1 with other vaccines. Therefore, co-administration is not recommended. However, if administration of AREPANRIX™ H5N1 with another vaccine is deemed necessary following benefit/risk assessment, immunization should be carried out on separate limbs. In such case, it should be noted that the adverse reactions may be intensified.

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

A protective immune response may not be elicited in all vaccinees.

Neurologic
If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give AREPANRIX™ H5N1 should be based on the careful consideration of the potential benefits and risks.

Immunization should be delayed in a patient with an active neurologic disorder, but should be considered when the disease process has been stabilized.

Special Populations

Pregnant Women: No data have been generated in pregnant women with AREPANRIX™ H5N1 and with the AS03 adjuvant system contained in the vaccine. Data from vaccinations with seasonal trivalent influenza vaccines in pregnant women do not indicate that adverse fetal and maternal outcomes were attributable to the vaccine.

Healthcare providers need to assess the benefits and potential risks of administering the vaccine to pregnant women.

Nursing Women: No data have been generated in breast-feeding women.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Symptoms reported after vaccination with AREPANRIX™ H5N1 were predominantly local and general reactogenicity and mostly mild to moderate. Symptoms resolved mostly within a few days. The most frequently reported reactogenic symptoms were: injection site pain and swelling, muscle aches, headache, fatigue, joint pain, shivering and sweating. In children 6 months to <6 years of age, the following additional side effects have been frequently observed: irritability, drowsiness and loss of appetite.

Clinical Trial Adverse Drug Reaction
Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adults
In a randomized, placebo-controlled, observer-blind, multi-centre study, conducted in the US and Canada, subjects 18 years of age and older were vaccinated with Influenza Virus Vaccine containing A/Indonesia/5/2005 (AREPANRIX™ H5N1; N = 3,422) or placebo (N = 1,139) as a 2-dose vaccination series (Total Vaccinated Cohort) with 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 reported frequencies of solicited local and general adverse reactions after each dose are presented below:

Table 1: Percentage of Subjects Reporting Solicited Local or General Adverse Reactions Within 7 Days Following Each Vaccination (Total Vaccinated Cohort[a]) – Study Q-PAN-H5N1-002

Adverse Reaction	AREPANRIX™ H5N1		Placebo	
	Post dose 1	Post dose 2	Post dose 1	Post dose 2
Local	**N= 3372 subjects (%)**	**N=3275 subjects (%)**	**N= 1118 subjects (%)**	**N= 1091 subjects (%)**
Pain	76.2	69.8	13.9	10.2
Swelling	7.1	6.4	0.4	0.3
Redness	5.3	5.0	0.4	0.4
General	**N= 3367 subjects (%)**	**N= 3272 subjects (%)**	**N= 1118 subjects (%)**	**N= 1092 subjects (%)**
Muscle Aches	32.8	30.0	12.2	8.2
Headache	22.2	19.6	17.1	11.2
Fatigue	21.4	21.4	15.1	9.1
Joint Pain	14.8	15.7	7.0	4.9
Shivering	7.4	10.7	5.5	3.7
Sweating	5.4	6.0	3.8	2.8
Fever ≥38.0ºC	1.2	2.7	1.2	0.9

[a] 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 % of AREPANRIX™ H5N1 doses and 3.6% of placebo doses. The most common severe solicited adverse event was local injection site pain; severe general solicited adverse events occurred after <2% of doses.

The incidence of unsolicited adverse reactions has been evaluated from clinical studies in approximately 3,800 subjects aged 18 years and older who received a 0.5 mL dose of AREPANRIX™ H5N1 containing A/Indonesia/5/2005 (H5N1) strain.

Unsolicited adverse reactions reported are listed per dose according to the following frequencies:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

Blood and lymphatic system disorders
Uncommon: lymphadenopathy

Psychiatric disorders
Uncommon: insomnia

Nervous system disorders
Uncommon: dizziness, paresthesia

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
Uncommon: pruritus, rash

Musculoskeletal and connective tissue disorders
Uncommon: back pain, musculoskeletal stiffness, neck pain, muscle spasms, pain in extremity
General disorders and administration site conditions
Uncommon: injection site reactions (such as bruising, induration, pruritus, warmth), asthenia, chest pain, malaise

During the entire Q-PAN-002 study, one subject who received AREPANRIX™ H5N1 developed facial palsy which was an adverse event considered not causally associated to the vaccine.

Children
In a randomized, placebo-controlled, observer-blind, multi-centre study, conducted in the United States, Canada and Thailand, 838 subjects aged 6 months through 17 years received Influenza Virus Vaccine containing A/Indonesia/5/2005 (AREPANRIX™

H5N1; N = 607) or placebo (N = 231) as a 2-dose vaccination series of 0.25 mL (half the adult dose).

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 reported frequencies of solicited local and general adverse reactions after each dose are presented below:

Table 2: Incidence of Solicited Local or General Adverse Reactions within 7 Days Following Each Vaccination[b] in Children Aged 6 Months through 17 Years

Adverse Reaction	AREPANRIX™ H5N1		Placebo	
	Post Dose 1	Post Dose 2	Post Dose 1	Post Dose 2
Aged 6 Months through 17 Years				
Local	**n = 602 subjects (%)**	**n = 592 subjects (%)**	**n = 229 subjects (%)**	**n = 223 subjects (%)**
Injection site pain	58.1	51.0	23.6	19.3
Injection site swelling	5.0	3.9	0.0	0.4
Injection site erythema	4.2	1.4	0.0	0.0
Aged 6 Months through 5 Years				
General	**n = 293 subjects (%)**	**n = 287 subjects (%)**	**n = 122 subjects (%)**	**n = 118 subjects (%)**
Irritability/ Fussiness	30.0	28.9	26.2	19.5
Drowsiness	22.5	20.6	15.6	16.1
Loss of appetite	18.4	15.7	17.2	14.4
Fever ≥38.0ºC	10.6	11.5	10.7	7.6
Aged 6 Years through 17 Years				
General	**n = 306 subjects (%)**	**n = 305 subjects (%)**	**n = 107 subjects (%)**	**n = 104 subjects (%)**
Myalgia	30.7	23.9	10.3	10.6
Headache	24.5	18.4	10.3	11.5
Fatigue	21.6	17.0	8.4	13.5
Joint pain	11.8	8.5	2.8	6.7
Gastrointestinal[a]	8.8	6.9	12.1	6.7
Shivering	3.9	5.2	2.8	4.8
Sweating	6.5	2.0	1.9	1.9
Fever ≥38.0ºC	3.6	3.3	0.9	1.9

[a] Nausea, vomiting, diarrhea, and/or abdominal pain.
[b] Total vaccinated cohort – Year 1
n = number of subjects with documented doses

Post-Market Adverse Drug Reactions

No post-marketing surveillance data are available following administration of AREPANRIX™ H5N1. The safety experience with other pandemic influenza vaccines, as well as seasonal vaccines is provided below.

Other pandemic influenza vaccines

The safety experience with other pandemic influenza vaccines, AREPANRIX™ H1N1 influenza vaccine (A/California/7/2009 H1N1, manufactured in Quebec, Canada) and Pandemrix™ (H1N1) influenza vaccine (A/California/7/2009 H1N1, manufactured in Dresden, Germany), may be relevant to AREPANRIX™ H5N1 because these vaccines are AS03-adjuvanted. These vaccines were widely used during the 2009 Influenza A (H1N1) pandemic.

During post approval use of these influenza vaccines containing AS03 adjuvant, the following adverse events were identified. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their incidence or to establish a causal relationship to the vaccine. Adverse events described here are included because: a) they represent reactions which are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

Immune system disorders
Anaphylaxis, allergic reactions

Nervous system disorders
Febrile convulsions, Guillain Barré syndrome, somnolence, paresthesia

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

General Disorders and Administration Site Conditions
Injection site reactions (such as inflammation, mass, necrosis, ulcer)

Epidemiological studies in several countries have reported an association between another pandemic influenza vaccine (Pandemrix™ H1N1 manufactured in Dresden, Germany) and narcolepsy with or without cataplexy. These studies have described an absolute risk increase of narcolepsy of approximately 1.4 to 8 additional cases per 100,000 vaccinated children/adolescents and approximately 1 additional case per 100,000 vaccinated adults compared to background rates of 0.12 to 0.79 per 100,000 children/adolescents per year and 0.67 to 1.10 per 100,000 adults per year. However, there are several limitations with the retrospective observational studies that need to be considered when interpreting the results. Further research is needed to investigate the observed association between Pandemrix™ and narcolepsy.

Seasonal vaccines

The following post-market adverse drug reactions have been reported with seasonal trivalent vaccines without AS03 adjuvant:

Blood and lymphatic system disorders
Rare: Transient thrombocytopenia.

Immune system disorders
Rare: Allergic reactions, including anaphylactic and anaphylactoid reactions, in rare cases leading to shock.

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.

Skin and subcutaneous tissue disorders
Rare: Angioedema, generalized skin reactions including urticarial

DRUG INTERACTIONS

There are no data on co-administration of AREPANRIX™ H5N1 with other vaccines. Therefore, co-administration is not recommended. However, if administration of AREPANRIX™ H5N1 with another vaccine is deemed necessary following benefit/risk assessment, immunization should be carried out on separate limbs. In such case, it should be noted that the adverse reactions may be intensified.

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

Drug-Laboratory Interactions
False positive ELISA serologic tests for HIV-1, Hepatitis C, and especially HTLV-1 may occur following influenza vaccination. 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).

DOSAGE AND ADMINISTRATION

Recommended Dose

Adults (≥ 18 years of age)

Adults 18 years of age and above should receive two doses (each 0.5 mL) of AREPANRIX™ H5N1 containing the Indonesia (H5N1) variant, the first administered at an elected date, the second at least three weeks after the first dose for maximum efficacy.

Pediatrics (6 months to 17 years of age):

Children and adolescents aged 6 months to 17 years should receive two doses (each 0.25 mL) of AREPANRIX™ H5N1 containing the Indonesia (H5N1) variant, the first administered at an elected date, the second at least three weeks after the first dose.

Children aged less than 6 months

Use of the vaccine is not recommended in this age group.

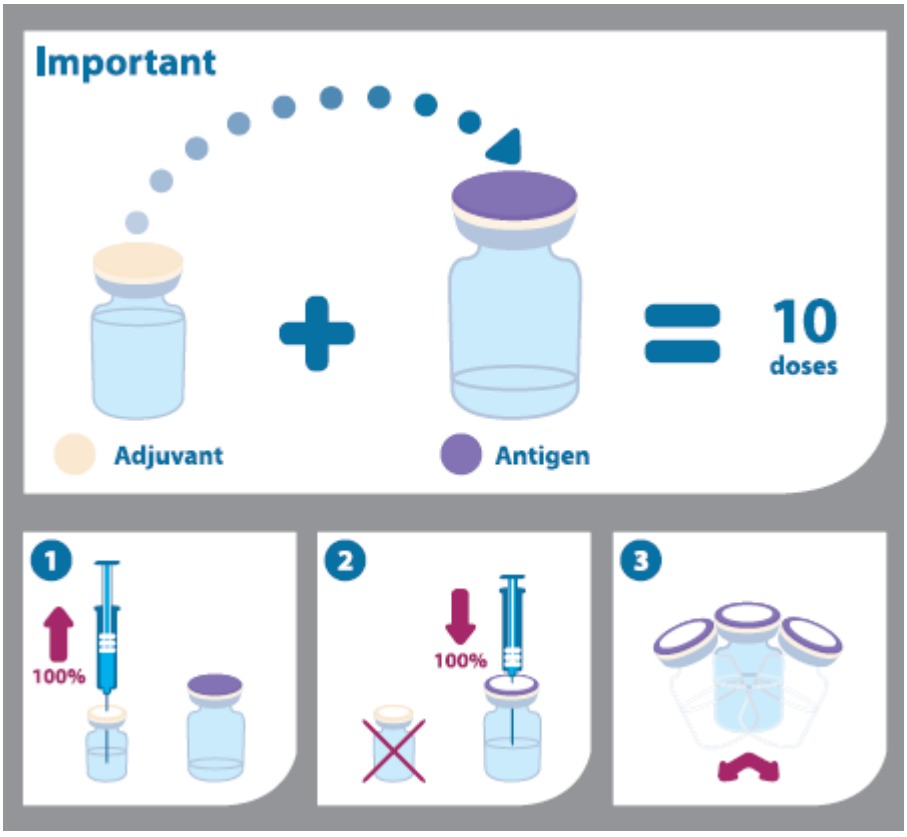
Administration

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

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

AREPANRIX™ H5N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant system (emulsion). The antigen suspension is a translucent to whitish opalescent suspension that may sediment slightly. The emulsion is a whitish to yellowish homogeneous milky liquid.

Prior to administration, the two components should be mixed.



Instructions for mixing and administration of the vaccine:

1. Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should be allowed to reach room temperature (allow a minimum of 15 minutes). Whitish sediments may be observed in the suspension vial; these sediments are part of the normal physical appearance of the suspension. The emulsion presents as a whitish to yellowish homogeneous milky liquid appearance.

2. Each vial should be mixed by inversion 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), do not mix the vaccine and do not administer.

3. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a 5 mL syringe and by adding it to the vial containing the antigen. It is recommended to equip the syringe with a 23-G needle. However, in the case this needle size would not be available, a 21-G needle might be used. The vial containing the adjuvant should be maintained in upside down position to facilitate the withdrawal of the full content.

4. After the addition of the adjuvant to the antigen, the vaccine should be mixed thoroughly by inversion. The mixed vaccine is a whitish to yellowish homogeneous milky liquid emulsion. In the event of other variation being observed, do not administer.

5. The volume of AREPANRIX™ H5N1 vial after mixing is at least 5 mL. The vaccine should be administered in accordance with the recommended posology (*see Dosage and Administration).*

6. The vial should be thoroughly mixed by inversion 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), do not administer.

7. Each vaccine dose of 0.5 mL (adults >18) or 0.25 mL (children 6 months – 17 years) is withdrawn into a 1 mL syringe for injection and administered intramuscularly. It is recommended to equip the syringe with a needle gauge not larger than 23-G.

8. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2°C - 8°C) or at room temperature (up to 30°C). If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature (allow a minimum of 15 minutes) before each withdrawal.

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

OVERDOSAGE
Insufficient data are available.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
The mechanism of action of type A (H5N1) influenza virus vaccines are based on their ability to induce antibodies against viral haemagglutinin (HA), a key viral protein for cell entry, thereby blocking viral attachment to human respiratory epithelial cells. Specific levels of haemagglutination-inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines, including H5N1 influenza virus vaccines, have not been correlated directly with protection from influenza illness but the antibody titers have been used as a measure of vaccine activity. In some human challenge studies with other influenza viruses, HI antibody titers of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.

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

The shelf-life is 1.5 years, based on the antigen component.

After mixing, the vaccine should be used within 24 hours (see *Instructions for mixing and administration of the vaccine*).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms
AREPANRIX™ H5N1 is a two-component vaccine containing a suspension and an emulsion that are mixed to prepare an emulsion for injection.

Composition
After combining and mixing the 2 components, each 0.5 mL vaccine dose contains 3.75 micrograms[1] of A/Indonesia/5/2005 (H5N1)[2] and is adjuvanted with AS03.
[1]haemagglutinin
[2]propagated in eggs

The GlaxoSmithKline proprietary AS03 adjuvant system is composed of squalene (10.69 milligrams per 0.5mL dose), DL-α-tocopherol (11.86 milligrams per 0.5 mL dose) and polysorbate 80 (4.86 milligrams per 0.5mL dose)

Preservative content is 5 micrograms thimerosal USP per 0.5 mL dose or 2.5 micrograms organic mercury (Hg) per 0.5 mL dose.

Additional Excipients
Thimerosal, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride and water for injection.

Residues
Egg residues including ovalbumin (≤ 0.083 μg per dose), formaldehyde, sucrose and sodium deoxycholate.

Packaging
2.5 mL of the antigen suspension is contained in a 10mL vial (type I glass) for 10 doses with a stopper (butyl rubber without latex). Pack size of 50.

2.5 mL of the adjuvant emulsion is contained in a 3mL vial (type I glass) for 10 doses with a stopper (butyl rubber without latex). Pack size of 25 X 2.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: AS03-adjuvanted Quebec H5N1 influenza vaccine

Physicochemical properties: Emulsion for injection

The H5N1 influenza virus HA antigen is prepared from virus propagated 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 antigen is suspended in a phosphate buffer solution. The virus antigen drug substance contains 15µg HA/mL A/Indonesia/5/2005 antigen, thimerosal (a mercury derivative) 20µg/mL as preservative and phosphate buffered saline composed of sodium chloride, potassium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate and water for injection. The drug substance contains trace residual amounts of egg proteins, formaldehyde, sodium deoxycholate and sucrose.

The AS03 adjuvant system is prepared separately and is a whitish to yellowish homogenous milky liquid emulsion. The oil phase contains two biodegradable oils, squalene and DL-α-tocopherol. The aqueous phase contains phosphate buffered saline and polysorbate 80.

Product Characteristics

The product is presented in two separate vials that must be mixed prior to administration. The final vaccine is prepared by withdrawing the AS03 adjuvant and adding it to the virus antigen. The mixed vaccine is a whitish to yellowish homogeneous milky liquid emulsion.

CLINICAL TRIALS

Study demographics and trial design

Five studies conducted with AREPANRIX™ H5N1 vaccine (Q-Pan-H5N1-001, Q-Pan-H5N1-002, Q-Pan-H5N1-005, Q-Pan-H5N1-009 and Q-Pan-H5N1-0021) are presented. An overview of the studies is given in the table below.

Table 3: Summary of Study Design and Patient Demographics for Clinical Trials in Specific Indication

Study Number	Trial Design	Dosage, Schedule, Route of administration	Number of Subjects Enrolled	Mean Age (Range)	Gender
Q-Pan-H5N1-001	Ph I/II, Observer blind, randomized, active-controlled. D- & Q-Equivalence	A/Indo Q-Pan H5N1 - 3.75 µg HA (No adjuvant) - 3.75 µg HA + AS03$_A$ - 3.75 µg HA + AS03$_B$ A/Indo D-Pan H5N1 - 3.75 µg HA + AS03$_A$ - 3.75 µg HA + AS03$_B$ Contingency arms: A/Indo Q-Pan H5N1 - 1.9 µg HA + AS03$_A$ - 1.9 µg HA + AS03$_B$ 2 doses (Days 0, 21) – IM injection	Q: 481 D: 299	38.6 yrs (18-64) (core group) 39.5% (18-64) Cont. arms	F: 57.8% M: 42.2% (core group) F: 56.0% M: 44.0% Cont. arms
Q-Pan-H5N1-002	Ph III, Observer blind, randomized, placebo controlled. Clinical consistency	A/Indo Q-Pan H5N1 - 3.75 µg HA (3 lots) + AS03$_A$ (3 lots) Placebo (control) 2 doses (Days 0, 21) – IM injection	Q: 3422 Pl: 1139	38.6 yrs (18-64) 71.9 yrs (65-91)	F: 57.0% M: 43.0% F: 54.9 M: 45.1
Q-Pan-H5N1-009	Ph II, Open, randomized. Dosing interval study	A/Indo Q-Pan H5N1 - 3.75 µg HA + AS03$_A$ 2 doses (Days 0.21; Days 0, 14; Days 0, 7 or Days 0, 0) – IM injection	312	40.3 yrs (18-65)	F: 53.2% M: 46.8%
Q-Pan-H5N1-005	Ph II, Observer-blind, randomized Heterologous prime-boost	<u>Priming (one dose):</u> A/Indo Q-Pan H5N1 - 7.5 µg HA + AS03$_B$ - 3.75 µg HA + AS03$_B$ - 7.5 µg HA + AS03$_A$ - 3.75 µg HA + AS03$_A$ <u>Booster (one dose):</u> A/Turkey Q-Pan H5N1 - 7.5 µg HA + AS03$_B$ - 3.75 µg HA + AS03$_B$ - 7.5 µg HA + AS03$_A$ - 3.75 µg HA + AS03$_A$ Placebo (one dose) 2 doses of active vaccine and 1 dose of placebo (Day 0, Months 6 and 18) – IM injection	841	50.0 yrs (18-87)	F: 60.0% M: 40.0%

Q PAN H5N1-021	Phase II/III, randomized, controlled, observer-blind	Q-Pan H5N1 vaccine (1.9 μg HA, A/Indonesia strain+ $AS03_B$)	607	85.7 mths (6-215)	F: 47.0% M: 53.0%
		Placebo (phosphate buffered saline)	231	82.8 mths (6-215)	F: 50.2% M: 49.8%
		2-doses (Day 0, 21) – IM injection			

D- and Q-, represent Dresden, Germany and Quebec, Canada for the production sources of antigen, respectively. Pl. represents placebo subjects. HA: haemagglutinin. A/Vietnam, strain H5N1 A/Vietnam/1194/2004. A/Indo, strain H5N1 A/Indonesia/05/2005. F and M represent female and male subjects, respectively. Cont. arms represent contingency arms within the clinical study. $AS03_A$ and $AS03_B$ represent 250 µL and 125 µL of AS03, respectively. IM represents intramuscular.

The demographic characteristics of subjects enrolled in Q-Pan adult studies are as follows: All subjects in adult Q-Pan studies were above 18 years of age. The majority of subjects (at least 85.0%) in studies Q-Pan-H5N1-001, -002,-005, and -009 were white Caucasians. The demographic profile for the different treatment groups and the age strata were comparable with respect to gender and racial distribution.

For study Q-Pan-H5N1-021, in the overall population, the mean age was 7 years (range: 6 months through 17 years); 52% were male; and the racial distribution was 45% white, 15% black, 35% Asian, and 5% other racial/ethnic groups.

Study results
Both homologous humoral immune responses (against the H5N1 strain contained in the vaccine) and cross-reactive humoral responses (against H5N1 strains not contained in the vaccine) following two doses of vaccine given 21 days apart are described. Persistence of immune response at 6 months after vaccination is also presented. In addition, limited data obtained using an alternative schedule (2 doses given 14 days apart), the immune response following boosting with a heterologous strain, are also described.

Humoral immune responses to the vaccine strain were measured through haemagglutination inhibition and by virus neutralization assays. The described humoral immune responses to a variant strain was measured through haemagglutination inhibition.

The haemagglutination inhibition responses are presented as the seroprotection rate (defined as the proportion of subjects with an antibody titre ≥ 1:40), the seroconversion rate (defined as the proportion of subjects who were either seronegative prior to vaccination and have a protective post-vaccination titre of ≥ 1:40 or who were seropositive prior to vaccination and have at least a 4-fold increase in titre post-vaccination) and the geometric mean fold rise (defined as the ratio of the post-vaccination geometric mean titre divided by the pre-vaccination geometric mean titre). The CHMP (CHMP/BWP/214/96) criteria applicable to these parameters are defined as follows:

- Seroprotection rate: >70% for subjects aged 18-60 years and >60% for subjects above 60 years

- Seroconversion rate: >40% for subjects aged 18-60 years and >30% for subjects above 60 years

- Geometric mean fold rise: >2.5 for subjects aged 18-60 years and >2.0 for subjects above 60 years.

Although CHMP criteria (based on point estimates) are not specifically defined for pediatrics, the same criteria as for adults 18-60 years have been used. Note that the CBER criteria (CBER, 2007) for acceptable immunogenicity for adults aged 18-60 years (which uses similar target values but based on meeting the lower 95% CI rather than point estimate), have been explicitly deemed relevant for children.

The virus neutralization responses are presented as the vaccine response rate (VRR), defined as the percentage of subjects having at least a 4-fold increase in serum neutralizing antibody titre (between the pre- and post-priming or pre- and post-booster vaccination time points).

Adults 18-60 and >60 years of age

Immune response against the vaccine strain

The immunogenicity of AREPANRIX™ H5N1 containing the A/Indonesia/5/2005 (H5N1) strain was evaluated in a clinical study (Q-Pan-H5N1-002) in which subjects 18-60 years of age (N=1,488) and >60 years of age (N=479) received two doses of vaccine 21 days apart. The haemagglutination-inhibition antibody response twenty-one days after the second dose and the persistence at 6 months following the first vaccination is presented in the following table:

Table 4: Haemagglutination-Inhibition Response Against the Vaccine Strain A/Indonesia/5/2005

Parameter	Against A/Indonesia/5/2005			
	21 days after 2nd dose		6 months after 1st dose	
	18-60 years	>60 years	18-60 years	>60 years
Number of Subjects	1488	479	353	104
Seroprotection Rate % (95% CI)	91.0 (89.4, 92,4)	76.8 (72.8, 80.5)	62.2 (56.8, 67.1)	63.5 (53.4, 72.7)
Seroconversion Rate % (95% CI)	91.0 (89.4, 92.4)	76.4 (72.3, 80.1)	62.2 (56.8, 67.1)	62.5 (52.5, 71.8)
Geometric Mean Fold Rise Value (95% CI)	51.4 (47.8, 55.3)	17.2 (14.9, 19.9)	7.4 (6.3, 8.7)	7.8 (5.9, 10.4)

According to Protocol Cohort
CI = Confidence interval

Twenty-one days after the second dose, the vaccine response rates (virus neutralization response) were 94.4% for subjects aged 18-60 years and 80.4% for subjects above 60 years.

In another clinical study (Q-Pan-H5N1-009), subjects 18-64 years of age received two doses of AREPANRIX™ H5N1 according to different schedules. Twenty-one days after the second dose, the seroprotection rate was 92.8% for subjects receiving two doses 14-days apart and 95.2% for subjects receiving two doses 21-days apart,

Cross-reactive immune response against a heterologous strain
The cross-reactive immune response against a heterologous strain A/Vietnam/1194/2004 (H5N1) was evaluated in a clinical study (Q-Pan-H5N1-001), in which subjects 18-64 years of age (N=144) received two doses of vaccine 21 days apart. Twenty-one days after the second dose, the seroprotection rate, seroconversion rate and geometric mean fold rise against A/Vietnam/1194/2004 (H5N1) were 63.9%, 61.8% and 7.6, respectively.

Immune response after heterologous boosting
In study Q-Pan-H5N1-005, subjects 18 years of age and above received a booster dose of vaccine containing A/turkey/Turkey/1/2005 18 months after a single dose of AREPANRIX™ H5N1 or 6 months after a placebo dose. Ten days following the booster dose, the seroprotection rate, seroconversion rate and geometric mean fold rise against A/turkey/Turkey/1/2005 were 95.2%, 85.5% and 32.0, respectively in the group who received a priming dose of AREPANRIX™ H5N1 and were 64.6%, 44.4% and 4.0, respectively in the unprimed group.

Children (6 months to 17 years of age)

The immunogenicity of AREPANRIX™ H5N1 containing the A/Indonesia/5/2005 (H5N1) strain was evaluated in a clinical study (Q-Pan-H5N1-021) in which children 6 months to <18 years of age (N=607) received two doses (each 0.25 mL) of vaccine 21 days apart. The persistence of the immune response was also evaluated in approximately 50% of subjects at 6 months (182 days) and approximately 50% of subjects at 1 year (385 days) following the first dose of AREPANRIX™ H5N1.

The haemagglutination-inhibition response against the vaccine strain A/Indonesia/05/2005 twenty-one days after the second dose (Day 42) and the persistence at 6 months following the first vaccination is presented in the following table:

Table 5: Haemagglutination-Inhibition Response Against the Vaccine Strain A/Indonesia/05/2005

Parameter	Against A/Indonesia/5/2005					
	21 days after 2nd dose			6 months after 1st dose		
	6 months - <36 months	3 years - <9 years	9 years - <18 years	6 months - <36 months	3 years - < 9 years	9 years - <18 years
Number of Subjects	175	185	203	84	89	87
Seroprotection Rate % [1] (D42: 98.3% CI) (D182: 95% CI)	100.0 (97.3, 100.0)	99.5 (96.4, 100.0)	99.0 (95.8, 99.9)	95.2 (88.3, 98.7)	84.3 (75.0, 91.1)	72.4 (61.8, 81.5)
Seroconversion Rate % (95% CI)	100.0 (97.9, 100.0)	99.5 (97.0, 100.0)	99.0 (96.5, 99.9)	95.2 (88.3, 98.7)	84.3 (75.0, 91.1)	70.1 (59.4;79.5)
Geometric Mean Titer Value (95% CI)	777.1 (705.6, 855.9)	543.8 (484.9, 609.8)	416.2 (371.5, 466.2)	90.6 (78.1, 105.0)	57.4 (50.8;64.9)	50.2 (43.3;58.2)

According to Protocol Cohort.

[1]The seroprotection rate at Day 42 (21 days after 2nd dose) was the primary endpoint, and 98.3% CIs are presented in order to account for multiple testing across the different age groups. All other analyses are descriptive and are not adjusted for multiple testing, and 95% CI are presented.

In addition to the results presented in Table 5, the persistence of the immune response continued to decline at Day 385 but remained above baseline with seroprotection rates of 85.7% for 6 months - <36 months, 55.3% for 3 years - <9 years and 28.4% for 9 years - <18 years.

Neutralizing antibody responses against homologous strain A/Indonesia/05/2005 and against the drift-variant virus A/Vietnam/1194/2004 strain, were also evaluated in approximately 40 subjects twenty-one days after the second dose in study Q-Pan H5N1-021. The homologous vaccine response rate was greater than 97.5% in all subjects. For the drift-variant virus, A/Vietnam/1194/2004 strain, the vaccine response rates were 40.0%, 72.2% and 88.2% in children aged 9-<18 years 3-<9 years and 6-<36 months, respectively.

DETAILED PHARMACOLOGY

Information from non-clinical studies

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

Challenge with a homologous H5N1 strain (A/Indonesia/5/2005)

In the homologous protection experiment, naïve ferrets (six ferrets/group) were immunized intramuscularly with vaccine candidate containing three different doses of H5N1 antigen derived from A/Indonesia/5/2005 (H5N1) (7.5, 3.8 and 1.9 µg of HA antigen) adjuvanted with the standard full dose ($AS03_A$) or half dose ($AS03_B$) of AS03.

Control groups included ferrets immunized with adjuvant alone and non-adjuvanted vaccine (7.5 micrograms HA). Ferrets were vaccinated on days 0 and 21 and then challenged by the intratracheal route on day 49 with homologous wild-type A/Indonesia/5/2005 virus. Only 50% of ferrets immunized with the non-adjuvanted influenza vaccine were protected from death, and showed slightly lower lung viral loads and degree of viral shedding in the upper respiratory track as those exhibited by ferrets immunized with adjuvant alone. Conversely the combination of a range of doses of H5N1 antigen with AS03 adjuvant was able to protect against mortality (100% protection) and to reduce lung virus loads and viral shedding after intratracheal challenge with a homologous H5N1 virus.

TOXICOLOGY

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

PART III: CONSUMER INFORMATION

AREPANRIX™ H5N1
AS03-adjuvanted Quebec H5N1 Pandemic Vaccine

This leaflet is part III of a three-part "Product Monograph" published when AREPANRIX™ H5N1 was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AREPANRIX™ H5N1. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the vaccine is used for:
AREPANRIX™ H5N1 influenza vaccine is indicated for active immunization against influenza caused by the H5N1 subtype virus contained in the vaccine. This indication is based on immunological data as the vaccine has not been evaluated in efficacy trials against influenza disease. AREPANRIX™ H5N1 should be used according to official guidance.

What it does:
When a person is given the vaccine, the immune system (the body's natural defence system) will make antibodies against the H5N1 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™ H5N1 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 in 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:
H5N1 influenza antigen from A/Indonesia/5/2005 (H5N1) strain and AS03 adjuvant.

The AS03 adjuvant in AREPANRIX™ H5N1 vaccine enhances the vaccine-induced immune response and contains naturally occurring molecules (squalene and vitamin E) plus an emulsifier (polysorbate 80).

What the important nonmedicinal ingredients are:
Thimerosal, a mercury derivative is added as preservative. Each adult dose contains 2.5 micrograms of mercury (1.25 micrograms of mercury for pediatric dose). Other ingredients include: trace amounts of egg proteins, formaldehyde, sodium deoxycholate and sucrose.

What dosage forms it comes in:
AREPANRIX™ H5N1 is a two component vaccine consisting of a translucent to whitish opalescent suspension that may sediment slightly containing antigen and a whitish to yellowish homogeneous milky liquid emulsion containing the AS03 adjuvant. AREPANRIX™ H5N1 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 receive AREPANRIX™ H5N1, talk to your doctor or nurse if:
- you have had any allergic reaction other than a sudden life-threatening allergic reaction to any ingredient contained in the vaccine.
- you have a severe infection with a high temperature. In these cases, the vaccination may be postponed until recovery. A minor infection such as a cold should not be a problem, but talk to your doctor.
- you have a weakened immune system due to medication or disease such as HIV. In such cases you may not get full benefit from the vaccination.

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

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking or have recently taken any other medicines, including non-prescription or any other vaccine.

There is currently no information on the administration of AREPANRIX™ H5N1 with other vaccines. AREPANRIX™ H5N1 should not be given at the same time as other vaccines. However, if this cannot be avoided, the other vaccine will be injected into the other arm. Any side effects that occur may be more severe.

PROPER USE OF THIS MEDICATION

Each dose is injected into your upper arm muscle or thigh.

Adults 18 years of age and above should receive two doses (each 0.5 mL) of AREPANRIX™ H5N1 containing the Indonesia (H5N1) variant, the first administered at an elected date, the second at least three weeks after the first dose for maximum efficacy.

Children aged 6 months to 17 years should receive two doses (each 0.25 mL) of AREPANRIX™ H5N1 containing the Indonesia (H5N1) variant, the first administered at an elected date, the second at least three weeks after the first dose.

Use of the vaccine is not recommended in children aged less than 6 months.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, AREPANRIX™ H5N1 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
- Aching muscles, joint pain

Common (may occur up to 1 in 10 doses)
- Redness or swelling at the injection site
- Fever
- Shivering
- Sweating
- Feeling sick, diarrhea

Uncommon (may occur with up to 1 in 100 doses)
- Reactions at the injection site such as bruising, hard lump, itching, warmth
- Swollen glands in neck
- 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

In children 6 months to <6 years of age, the following additional side effects have been observed:
Very common (may occur with more than 1 in 10 doses):
- Loss of appetite
- Irritability
- Drowsiness

The following side effects were observed for other influenza vaccines containing AS03 adjuvant during the 2009 Influenza A (H1N1) pandemic.

- Allergic reaction 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
- Inflammation at injection site
- Swelling beneath the skin, giving rise to welts usually around the eyes and lips but also on hands and feet
- Numbness and tingling sensation
- Neurological disorders such as convulsions, sleepiness and a type of paralysis know as Guillain-Barré Syndrome

The following additional side effects were observed for other marketed seasonal vaccines.

- Severe stabbing of throbbing pain along one or more nerves
- Low blood platelet count which can result in bleeding or bruising
- 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) and neuritis (inflammation of nerves)

This is not a complete list of side effects. For any unexpected effects while taking AREPANRIX™ H5N1, contact your doctor or pharmacist.

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 case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada.

By toll-free telephone: 1-866-844-0018
By toll-free fax: 1-866-844-5931
Email: caefi@phac-aspc.gc.ca
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.
7333Mississauga Road
Mississauga, Ontario L5N 6L4
1-800-387-7374

This leaflet was prepared by GlaxoSmithKline Inc.

AREPANRIX™ H5N1

Last Revised: 31 January 2017