



**Notice of Decision
for
AREPANRIX™ H1N1**

On October 13, 2009, an Interim Order was issued by the Minister of Health at the request of the Public Health Agency of Canada to allow the authorization for sale of a vaccine for the novel Influenza A H1N1 virus in response to the influenza A H1N1 pandemic. An Interim Order is issued by the Minister of Health under Section 30.1 of the *Food and Drugs Act* in rare situations where the Minister believes that immediate action is required to deal with a significant risk, direct or indirect, to human health, public safety, or the environment.

The Minister authorized the sale of the Arepanrix™ H1N1 vaccine (AS03-Adjuvanted H1N1 Pandemic Influenza Vaccine) on October 21, 2009 based on limited clinical testing in humans under the provision of the Interim Order.

Based on the Health Canada review of the available data on quality, safety and immunogenicity, and given the current pandemic threat and its risk to human health, Health Canada considers that the benefit/risk profile of the Arepanrix™ H1N1 vaccine is favourable for active immunization against the H1N1 2009 influenza strain in an officially declared pandemic situation.

As part of the authorization for sale for Arepanrix™ H1N1, Health Canada has requested the sponsor to 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.

A prototype or “mock” vaccine was developed in the pre-pandemic period using an H5N1 strain. During this period, Health Canada inspected the vaccine manufacturing facilities, evaluated data on the vaccine production process, and reviewed results from both animal and human studies conducted with the mock vaccine. In addition, the safety and effectiveness of the AS03 adjuvant to be used with the vaccine was assessed by Health Canada. All results were considered acceptable. Once the H1N1 virus emerged as the pandemic virus, the manufacturer initiated vaccine production using the strain recommended by the World Health Organization (WHO).

The following data were used to support the authorization for sale of the Arepanrix™ H1N1 vaccine:

- Quality (chemistry and manufacturing) data for the vaccine manufacturing process to support the strain change from H5N1 to H1N1;
- Clinical safety and immunogenicity data from studies in humans to indicate that the H1N1 vaccine has an acceptable safety profile and that the recommended dose is appropriate to produce an adequate immune response; and
- Safety and other data from the review of the prototype H5N1 vaccine.

Data from international clinical studies using similar or related pandemic vaccines that became available during the authorization process were also considered. Further clinical studies and post-market surveillance will be continually assessed post-authorization.

Arepanrix™ H1N1 vaccine is indicated for active immunization against the H1N1 2009 influenza strain in an officially declared pandemic situation. Please refer to the Product Information Leaflet for details on recommended dosage for specific age groups.

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 (an inactivated, split-virion, influenza A H1N1 virus antigen) is based on the strain derived from A/California/07/2009 (H1N1)v, the strain officially recommended by the WHO for the manufacture of vaccines during the current influenza pandemic. The AS03-adjuvant component is intended to increase the immunogenicity of the pandemic influenza virus HA antigen, thus allowing a dose-sparing mechanism that permits the administration of a smaller dose of antigen while providing comparable immunogenicity to a non-adjuvanted vaccine.

The Arepanrix™ H1N1 antigen component is manufactured in accordance with previously established procedures for the commercially available seasonal influenza vaccine Fluviral®, produced at ID Biomedical Corporation of Quebec, doing business as GlaxoSmithKline Biologicals North America's facilities in Ste. Foy, Québec. Fluviral® has been an approved seasonal flu vaccine in Canada since 1992.

Each 0.5mL dose of the Arepanrix™ H1N1 vaccine contains 3.75 µg haemagglutinin (HA) derived from A/California/07/2009 (H1N1)v. The AS03-adjuvant component is composed of an oil phase containing the natural, biodegradable oil, squalene (10.69 mg per dose) and DL- α -tocopherol (Vitamin E oil; 11.86 mg per dose), mixed with an aqueous phase composed of an isotonic phosphate buffered saline solution. Polysorbate 80 (Tween 80; 4.86 mg per dose) is used as an emulsifier to stabilize the oil/water interfaces. Each dose also contains 5 µg of the preservative thimerosal. Prior to administration, the contents of the adjuvant vial are withdrawn and mixed in a one-to-one ratio with the contents of the antigen vial.

The authorization for sale for the Arepanrix™ H1N1 vaccine was based on quality and available non-clinical and clinical information submitted for the Arepanrix™ H1N1 vaccine, the Pandemrix™ vaccine (a similar H1N1 pandemic influenza vaccine manufactured by GlaxoSmithKline in Dresden, Germany), and supporting quality and safety data from the prototype H5N1 vaccine.

A number of clinical studies are currently underway in Europe and North America to evaluate the safety and immunogenicity of a two-dose schedule of the Arepanrix™ H1N1 vaccine as well as the Pandemrix™ vaccine. Results from these studies will be assessed by Health Canada as soon as they become available. The preliminary results of two studies with Pandemrix™ have been submitted to Health Canada for review. The first study, D-Pan-H1N1-021, is a Phase II, multicentre, observer-blind, randomized study, while the second study, D-Pan-H1N1-007, is a Phase III, single-centre, observer-blind, randomized study.

Preliminary results from both studies indicate that at Day 21, following one dose of vaccine, both the adjuvanted and non-adjuvanted vaccines met the internationally accepted immunogenicity criteria. A strong immune response was observed, for both formulations, after one single vaccine dose. Given the short amount of time that has elapsed since the initiation of these studies, the persistence of this response cannot be determined at this time, nor is it possible to determine if a second dose or a booster dose will be required at a later date.

In Study D-Pan-H1N1-007, general systemic reactions were more common in the adjuvanted-vaccine group but were considered generally mild. The most common reactions were fatigue, headache, and pain at the injection site (in both the adjuvant and the non-adjuvant groups), and muscle ache (in the adjuvanted-vaccine group). A small percentage (~2%) of Grade 3 (severe) reactions was reported for headache and muscle ache in the adjuvanted-vaccine group and fatigue and shivering in the non-adjuvanted vaccine group. Fever was not reported in either vaccine group.

Clinical data for the use of the Arepanrix™ H1N1 vaccine or the AS03-adjuvant component in pregnant women are not available at the time of publication of this Notice of Decision. In addition, no data are available in breast-feeding women or in children under the age of 3 years.

The vaccine should be injected intramuscularly preferably in the deltoid muscle or anterolateral thigh. Instructions for mixing and administration of the vaccine are available in the Product Information Leaflet.

Arepanrix™ H1N1 is contraindicated for patients with a history of life-threatening anaphylactic reaction to any of the constituents or trace residues of this vaccine as listed in the Product Information Leaflet.

Arepanrix™ H1N1 should be administered under the conditions stated in the Product Information Leaflet taking into consideration the potential risks associated with the administration of this drug product. Detailed conditions for the use of Arepanrix™ H1N1 are described in the Product Information Leaflet.

Full consideration has been given to international activities and declarations and notices issued by the WHO.

AREPANRIX™ H1N1 is a trademark of the GlaxoSmithKline group of companies.

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