

# PRODUCT MONOGRAPH

## FLUVIRAL<sup>®</sup> (2011-2012)

**Influenza Virus Vaccine  
Trivalent, Inactivated  
Split Virion  
Prepared in Eggs**

ATC Code J07BB02

For active immunization against influenza strains:

A/California/7/2009 (H1N1)-like strain: A/California/7/2009 NYMC X-181  
A/Perth/16/2009 (H3N2)-like strain: A/Victoria/210/2009 NYMC X-187  
B/Brisbane/60/2008-like strain: B/Brisbane/60/2008

Manufactured by:  
**ID Biomedical Corporation of Quebec**  
Ste-Foy, Quebec

Distributed by:  
**GlaxoSmithKline Inc.**  
7333 Mississauga Road N.  
Mississauga, Ontario

Control # 146413

Date of Approval: April 21, 2011

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**FLUVIRAL<sup>®</sup> (2011-2012)**

Influenza Virus Vaccine  
Trivalent, Inactivated Split-Virion  
Prepared in Eggs

**PART I: HEALTH PROFESSIONAL INFORMATION****SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
IM	Suspension for Injection  15 µg influenza virus Hemagglutinin/strain/ 0.5 mL dose	Thimerosal, trace amounts of egg proteins, formaldehyde, sodium deoxycholate and sucrose. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

**DESCRIPTION**

FLUVIRAL<sup>®</sup> is a trivalent, split-virion influenza vaccine prepared from virus grown in the allantoic cavity of embryonated hens' eggs. The virus is inactivated with ultraviolet light treatment followed by formaldehyde treatment, purified by centrifugation and disrupted with sodium deoxycholate. FLUVIRAL<sup>®</sup> is used for active immunization against influenza disease caused by the influenza subtypes A and type B contained in the vaccine.

FLUVIRAL<sup>®</sup> conforms to the current requirements of the World Health Organization (WHO). The influenza virus strains for the 2011-2012 season are A/California/7/2009 (H1N1)-like strain (A/California/7/2009 NYMC X-181), A/Perth/16/2009 (H3N2)-like strain (A/Victoria/210/2009 NYMC X-187) and B/Brisbane/60/2008-like strain (B/Brisbane/60/2008).

**INDICATIONS AND CLINICAL USE**

FLUVIRAL<sup>®</sup>, split-virion influenza vaccine, is indicated for the active immunization against influenza caused by the specific strains of influenza virus contained in the vaccine in adults and children 6 months of age or older.

The National Advisory Committee on Immunization (CCDR, August 2010) recommends administration of influenza vaccines to the following groups:

1. **People at high risk of influenza-related complications or those more likely to require hospitalization**
  - Adults (including pregnant women) and children with the following chronic health conditions:
    - cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis, and asthma)
    - diabetes mellitus and other metabolic diseases
    - cancer, immunodeficiency, immunosuppression (due to underlying disease and/or therapy)
    - renal disease
    - anemia or hemoglobinopathy
    - conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration
    - children and adolescents with conditions treated for long periods with acetylsalicylic acid.
  - People of any age who are residents of nursing homes and other chronic care facilities.
  - People  $\geq 65$  years of age.
  - Healthy children aged 6 to 23 months of age.
  - Healthy pregnant women (the risk of influenza-related hospitalization increases with length of gestation; e.g. it is higher in the third than the second trimester).
2. **People capable of transmitting influenza to those at high risk**
  - Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications.
  - Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):
    - Household contacts of individuals at high risk, as listed in the section above
    - Household contacts of infants  $< 6$  months of age who are at high risk of complications from influenza but for whom influenza vaccine is not authorized, and
    - Members of a household expecting a newborn during the influenza season.
  - Those providing regular child care to children  $< 24$  months of age, whether in or out of the home.
  - Those who provide services within closed or relatively closed settings to persons at high risk (e.g. crew on ships).
3. **Others**
  - People who provide essential community services.
  - People in direct contact during culling operations with poultry infected with avian influenza.

Note: Healthy persons aged 2 to 64 years without contraindication are also encouraged to receive influenza vaccine even if they are not in one of the aforementioned priority groups.

**Pediatrics:** Healthy children aged 6 to 23 months are at increased risk of influenza-associated hospitalization compared with healthy older children and young adults. Children and adolescents (aged 6 months to 18 years) treated for long periods with ASA may be at increased risk of Reye Syndrome after influenza infection.

**Geriatrics (≥ 65 years of age):** The risk of severe morbidity and mortality related to influenza is moderately increased in healthy persons over 65 years of age but is not nearly as great as in persons with chronic underlying disease.

**HIV-Infected Persons:** Limited information exists regarding the frequency and severity of influenza illness among HIV-infected persons, but reports suggest that symptoms may be prolonged and the risk for complications increased for some HIV-infected persons. Because influenza can result in serious illness and complications, vaccination is a prudent precaution and will result in protective antibody levels in many recipients. However, the antibody response to vaccine may be low in persons with advanced HIV-related illnesses; giving a second dose of vaccine 4 or more weeks after the first does not improve the immune response for these persons. Further studies are also required to determine whether influenza immunization can adversely affect patients infected with HIV. To date, some studies indicate that influenza immunization can be associated with transient increases in plasma HIV concentration, but no study has demonstrated an adverse effect of this temporary change on HIV disease progression.

**Pregnant women:** Vaccination is recommended for pregnant women in high-risk groups (see above section). Vaccine is considered safe for pregnant women - regardless of their stage of pregnancy. Although excess morbidity and mortality were observed among pregnant women during the pandemic outbreaks in 1918-19 and 1957-58, further studies are needed to determine whether pregnancy per se is a risk factor that warrants routine influenza immunization. Pregnant women should be immunized in their third trimester if they are expected to deliver during influenza season, as they will become household contacts of their newborn (children < 6 months of age are at increased risk of complications from influenza).

**Breast-feeding mothers:** Influenza immunization does not adversely affect the health of breast-feeding mothers or their infants. Breast-feeding is not a contraindication for influenza immunization.

People at high risk of influenza complications embarking on foreign travel to destinations where influenza is likely to be circulating should be vaccinated with the most current available vaccine. In the tropics, influenza can occur throughout the year. In the southern hemisphere, peak activity occurs from April through September. In the northern hemisphere, peak activity occurs from November through March.

Employers and their employees should consider yearly influenza immunization for healthy working adults as this has been shown to decrease work absenteeism because of respiratory and other illnesses.

Concern has been raised regarding the possibility that a pandemic influenza strain may emerge through human-avian gene reassortment within workers directly involved in poultry culling

operations, who may become simultaneously infected with a human influenza virus strain and an avian influenza virus strain. This is a theoretical concern, given that this gene reassortment has not been documented to date. FLUVIRAL<sup>®</sup> protects against human but not avian influenza strains. Immunization is recommended for those directly involved in the destruction (culling) of avian influenza-infected poultry before the culling operation. Direct involvement may be defined as sufficient contact with infected poultry to allow transmission of avian virus to the exposed person. The relevant individuals include those performing the cull as well as others (such as supervising veterinarians and inspectors) who may be directly exposed to the avian virus. Those persons who would be expected by reason of their employment to come into direct contact with infected poultry during culling operations in the event of potential avian influenza outbreaks should be immunized with trivalent influenza vaccine on a yearly basis prior to the human influenza season (CCDR, October 2009).

## CONTRAINDICATIONS

- Known or suspected hypersensitivity to FLUVIRAL<sup>®</sup>, to thimerosal, or to any other ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Vaccination is not recommended for subjects who develop anaphylactic type reactions when they eat eggs (urticaria (hives), oedema of the mouth and throat, difficulty in breathing, hypotension and shock). Allergic reactions are extremely rare and usually attributable to extreme sensitivity to certain components of the vaccine, probably to trace amounts of residual egg protein. Subjects whose allergy to eggs is not of the anaphylactic type, as well as those who are allergic to chicken and to feathers may be vaccinated.
- Subjects with an acute respiratory infection or with any other active infection or serious febrile illness. On the other hand, a minor indisposition such as a mild infection of the upper respiratory tract is not necessarily a contraindication to vaccination.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

- Sterile epinephrine hydrochloride solution 1:1000 should always be readily available in case of an acute anaphylactic reaction following administration of the vaccine.

### General

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.

Influenza vaccine can inhibit the clearance of warfarin and theophylline. However, clinical studies have not shown any adverse effects attributable to these drugs in people receiving influenza vaccine.

**Hematologic**

As with other vaccines administered intramuscularly, FLUVIRAL<sup>®</sup> should be given with caution in individuals with bleeding disorders such as hemophilia or on anticoagulant therapy to avoid the risk of hematoma following the injection.

**Immune**

It is possible that the protective immune response following influenza vaccination may not develop in subjects undergoing immunosuppressive therapy.

Corticosteroid therapy can result in immunosuppression although the exact dose and duration of therapy required to suppress the immune system is not well defined. Persons treated with high doses of systemic steroids, e.g.,  $\geq 2$  mg/kg/day of prednisone orally for more than 2 weeks, or  $\geq 60$  mg prednisone/day in an adult, should be considered to have a compromised immune system.

FLUVIRAL<sup>®</sup> is not effective against all possible strains of influenza virus. FLUVIRAL<sup>®</sup> is intended to provide protection against those strains of virus from which the vaccine is prepared and to closely related strains.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

**Local Skin Reactions at Vaccination Sites**

Soreness and redness at the injection site may occur and may last for up to two days. Prophylactic acetaminophen may decrease the frequency of pain at the injection site.

**Neurologic**

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUVIRAL<sup>®</sup> 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.

**Respiratory**

Revaccination of individuals who have previously experienced oculo-respiratory symptoms is safe. Previously affected individuals should be encouraged to be revaccinated. The risk of recurrence of oculo-respiratory symptoms after revaccination is minimal compared to the serious threat posed by influenza. Please refer to most current NACI recommendations regarding revaccination of subjects who experienced more severe oculo-respiratory syndrome.

**Special Populations**

**Pregnant Women:** The National Advisory Committee on Immunization considers influenza vaccine safe in pregnancy.

Limited data from vaccinations in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. This vaccine may be given from the second

trimester of pregnancy in healthy women. For pregnant women with medical conditions that increase their risk of complications from influenza, administration of the vaccine is recommended, irrespective of the stage of pregnancy.

**Pediatrics:** In infants < 6 months of age, influenza vaccine is less immunogenic than in infants and children aged 6 to 18 months. Therefore, immunization with currently available influenza vaccine is not recommended for infants < 6 months.

Since the likelihood of febrile convulsions is greater in children aged 6 to 35 months, special care should be taken in weighing relative risks and benefits in this group.

### **Laboratory Tests**

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).

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The most commonly reported adverse drug reactions with FLUVIRAL<sup>®</sup> are pain and redness at the injection site, fatigue, headache and myalgia. Common reactions are red eyes, sore throat, cough, arthralgia, swelling at the injection site, fever, chills, malaise and chest tightness. Reactions are generally mild and of limited duration. Prophylactic acetaminophen may decrease the frequency of some side effects in adults.

Immediate, allergic-type responses, such as hives, angioedema, allergic asthma, or systemic anaphylaxis occur extremely rarely. These reactions probably result from sensitivity to some vaccine component - most likely residual egg proteins (see **CONTRAINDICATIONS**).

### **Clinical Trial Adverse Drug Reactions**

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.

FLUVIRAL<sup>®</sup> was administered to 2,220 adult and elderly subjects in six clinical trials. General symptoms were solicited by a diary aid used by the subjects for 3 days post-vaccination.

Adverse reactions considered possibly related to vaccination have been categorised by frequency as follows.

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 ( $< 1/10,000$ )

**Infections and infestations**

Uncommon: upper respiratory tract infection

**Nervous system disorders**

Very common: headache; Uncommon: dizziness

**Eye disorders**

Common: red eyes\*

**Respiratory, thoracic and mediastinal disorders**

Common: sore throat\*, cough\*

**Gastrointestinal disorders**

Uncommon: nausea

**Skin and subcutaneous tissue disorders**

Uncommon: swelling of the face\*

**Musculoskeletal and connective tissue disorders**

Very common: myalgia; Common: arthralgia

**General disorders and administration site conditions**

Very common: pain and redness at the injection site, fatigue; Common: swelling at the injection site, fever, chills, malaise, chest tightness\*

\*These symptoms can be associated to the oculo-respiratory syndrome (ORS). ORS consists of the following signs and symptoms: bilateral red eyes and/or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness or sore throat) and/or facial swelling. Although not explicitly identified as ORS during the clinical trials, these symptoms were solicited to detect possible cases of that syndrome.

A study was conducted in 130 children aged 3-12 years. The data in the table below show the percentage of reported symptoms to FLUVIRAL<sup>®</sup> split-virion vaccine versus a competitor subvirion vaccine. The most frequently reported local reaction was soreness at the injection site and usually resolved in 1-2 days. The most common systemic reactions were headache, loss of appetite and muscle aches. There were no significant differences between the two groups.

**Table 1: Percentage of subjects reporting symptoms**

<b>Subjects aged 3-12 years</b>	<b>Fluviral (n=65)</b>	<b>Competitor (n=65)</b>
<b>Local reactions (%)</b>		
Soreness	57	58
Redness	12	14
Swelling	15	22
Limitation of movement	12	14
<b>Systemic reactions (%)</b>		
Headache	15	17

Loss of appetite	12	8
Muscle aches	14	11
Chills	3	6
Nausea	3	3
Vomiting	1	0
Diarrhea	6	6
Redness/rash	3	3

### **Post-Market Adverse Drug Reactions**

#### **Immune system disorders**

Rare: Allergic reactions including anaphylactic and anaphylactoid reactions

#### **Nervous system disorders**

Rare: Guillain-Barré syndrome\*

\*Spontaneous reports of Guillain-Barré syndrome have been received following vaccination with FLUVIRAL. However, a causal association between vaccination and the Guillain-Barré syndrome has not been established.

#### **Skin and subcutaneous tissue disorders**

Rare: Angioedema, urticaria

Oculo-respiratory Syndrome (ORS) has been reported in Canada, US and Europe following administration of influenza vaccines. The symptoms associated with the ORS are red eyes, respiratory symptoms and facial oedema. Most cases are mild in severity and resolve spontaneously regardless of the influenza vaccine administered.

Revaccination of subjects with history of ocular or respiratory symptoms is considered to be safe regardless of the influenza vaccine used for the initial vaccination or the revaccination. Since the 2000-2001 influenza season when the symptom was first identified, the incidence of ORS has slowly declined and reporting rates are returning to background levels reported prior to 2000.

There have been reports of other neurological illnesses, including facial paralysis, encephalitis, encephalopathy, demyelinating disease and labyrinthitis, associated with other influenza vaccines. Any relationship, other than temporal, to the vaccine has not been established.

Unlike the 1976-77 swine influenza vaccine, subsequent vaccines prepared from other virus strains have not been clearly associated with an increased frequency of Guillain-Barré syndrome. Influenza vaccine is not known to predispose to Reye's syndrome.

#### **Notification of reactions**

It is desirable that all unusual reactions, arising from any vaccination whatsoever, or following shortly thereafter, be reported to the manufacturer of the product and to the provincial epidemiologist.

**DRUG INTERACTIONS****Drug-Drug Interactions**

There are no data to assess the concomitant administration of FLUVIRAL with other vaccines. If FLUVIRAL is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites. FLUVIRAL should not be mixed with any other vaccine in the same syringe or vial.

## DOSAGE AND ADMINISTRATION

### Recommended Dose and Dosage Adjustment

Influenza vaccine dosage, by age group

Age Group	Dosage	Route
6 - 35 months	1 x 0.25 mL or 2 x 0.25 mL*	IM
3 - 8 years	1 x 0.50 mL or 2 x 0.50 mL*	IM
9 years and older	1 x 0.50 mL	IM

\* Two doses administered at least one month apart are recommended for children younger than 9 years of age receiving influenza vaccine for the first time.

The recommended site of vaccination is the deltoid muscle for adults and older children. The preferred site for infants and young children is the anterolateral aspect of the thigh.

**Check the expiry date of the vaccine carefully.** Any vaccine beyond its expiry date should not be used.

### Administration

**FLUVIRAL<sup>®</sup> vaccine must not be administered intravenously.**

FLUVIRAL<sup>®</sup> is an opalescent translucent to off-white liquid suspension that may sediment slightly. Inspect FLUVIRAL<sup>®</sup> visually for particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.

Shake the multidose vial vigorously each time before withdrawing a dose of vaccine.

Proper aseptic technique should be used for withdrawal of each dose from the multidose vial. Once entered, return the multidose vial to the recommended storage conditions, between 2°C and 8°C. Once entered, the multidose vial should be discarded after 28 days.

A separate sterile 1-cc syringe and needle or a sterile disposable 1-cc unit should be used for each injection to prevent transmission of hepatitis B, HIV, or other infectious agents from one person to another.

Disinfect the skin at the site of injection with a suitable antiseptic and wipe dry with sterile cotton wool. The injection of FLUVIRAL<sup>®</sup> **should be given intramuscularly**, usually into the deltoid muscle. **Do not inject influenza vaccine intravenously.** No data are available on subcutaneous administration of FLUVIRAL<sup>®</sup>.

All vaccinees should be observed for about 15 minutes after vaccination. If an anaphylactic reaction develops, sterile epinephrine hydrochloride (1:1000) should be administered.

## OVERDOSAGE

In a study by Matzkin and Nili (1984), following administration of a dose of flu vaccine 10 times greater than the recommended dose of 0.5 mL, adverse events were not significantly different between study and control subjects.

There have been reports of patients who received higher than recommended doses of FLUVIRAL<sup>®</sup>. The adverse events noted in these patients were similar to those reported from patients who had received the recommended dose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

FLUVIRAL<sup>®</sup>, split-virion inactivated influenza vaccine, promotes an active immunization against influenza strains A (H1N1 and H3N2) and B. Within seven days after injection of the vaccine there is an increase in circulating antibody to the viral hemagglutinin, and peripheral blood lymphocytes are primed to respond to in vitro stimulation by vaccine antigens. As with other inactivated influenza vaccines, immunization is based on the humoral component of the specific immunological defense system, namely immunoglobulin G (IgG) antibodies against viral hemagglutinin (HA) and neuraminidase antigens. The effectiveness of inactivated influenza vaccines correlates with the age and immunocompetence of the vaccine recipient and the degree of similarity between the virus strains used in the preparation of the vaccines and those prevailing in the population.

Cytotoxic T lymphocyte response occurs after administrations of either killed or live virus vaccines and is detectable in the absence of demonstrable antibody response.

### Pharmacodynamics/Pharmacokinetics

No pharmacodynamics studies and no pharmacokinetics studies have been conducted with FLUVIRAL<sup>®</sup> in accordance with its status as a vaccine.

### Duration of Effect

Both humoral and cell-mediated responses are thought to play a role in immunity to influenza. Immunity declines over the year following vaccination. The production and persistence of antibody after vaccination depends on numerous factors, including age, prior and subsequent exposure to antigens, presence of immunodeficiency states, and polymorphisms in HLA class II molecules. Humoral antibody levels, which correlate with vaccine protection, are generally achieved by 2 weeks after immunization. It is postulated that immunity after administration of the inactivated vaccine lasts < 1 year. However, in the elderly, antibody levels may fall below protective levels within 4 months. Data are not available to support a recommendation for the administration of a second dose of influenza vaccine in elderly individuals in order to boost immunity.

## STORAGE AND STABILITY

FLUVIRAL<sup>®</sup> must be stored between 2°C and 8°C. **Do not freeze.** Freezing destroys activity. Do not use vaccine that has been frozen.

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

**Do not use vaccine after the expiration date.**

Once entered, the multidose vial should be discarded after 28 days.

## SPECIAL HANDLING INSTRUCTIONS

FLUVIRAL<sup>®</sup> and materials used during vaccination should be disposed of in the same way as other drugs administered by injection. Since split-virion influenza vaccine is an inactivated vaccine, it presents no risk of contaminating the work area during manipulation.

### Incompatibilities

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

## DOSAGE FORMS, COMPOSITION AND PACKAGING

The composition of FLUVIRAL<sup>®</sup> is established in agreement with the recommendations of the Canadian National Advisory Committee on Immunization (NACI) and the World Health Organization (WHO).

For the 2011-2012 season, each dose of 0.5 mL of FLUVIRAL<sup>®</sup> contains:

15 µg HA - A/California/7/2009 (H1N1)-like strain (A/California/7/2009 NYMC X-181),

15 µg HA - A/Perth/16/2009 (H3N2)-like strain (A/Victoria/210/2009 NYMC X-187)

15 µg HA - B/Brisbane/60/2008-like strain (B/Brisbane/60/2008)

The vaccine is formulated with phosphate buffered saline composed of: sodium chloride, potassium chloride, disodium hydrogen phosphate heptahydrate, potassium dihydrogen phosphate and water for injection. Thimerosal (100µg/mL) is added as a preservative. The vaccine also contains trace residual amounts of egg proteins, formaldehyde, sodium deoxycholate and sucrose. Antibiotics are not used in the manufacture of this vaccine.

FLUVIRAL<sup>®</sup> is supplied in 5 mL vials holding 10 x 0.5 mL doses.

FLUVIRAL<sup>®</sup> packaging does not contain latex.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Each of the three influenza virus strains is produced and purified separately. They are prepared from virus propagated in the allantoic cavity of embryonated hens' eggs.

#### Product Characteristics

FLUVIRAL<sup>®</sup> is a trivalent, split-virion, inactivated influenza vaccine prepared from virus grown in the allantoic cavity of embryonated hens' eggs. The virus is inactivated with UV light and formaldehyde, purified by centrifugation and disrupted with sodium deoxycholate. It is a homogenized and sterile, opalescent translucent to off-white liquid suspension in a phosphate-buffered saline solution and may sediment slightly.

### CLINICAL TRIALS

The immunogenicity of FLUVIRAL<sup>®</sup> was evaluated in six clinical trials. A total of 1,556 subjects aged 18-60 years and 609 subjects over 60 years of age received a single 0.5mL dose of FLUVIRAL<sup>®</sup>. Immunological response of vaccination is evaluated by measuring the anti-hemagglutinin antibody (HA) titer pre- and 21 days post-vaccination. The three measures evaluated are the anti-HA seroconversion rate (4-fold rise in reciprocal titer or change from undetectable [ $<10$ ] to a reciprocal titer of  $\geq 40$ ), the seroprotection rate (Day 21 reciprocal titer of  $\geq 40$ ) and geometric mean fold rise (GMFR) in titer.

**Table 2 Summary of Patient Demographics for Clinical Trials**

Study #	Trial design	Dosage, route of administration	Study subjects* (n)	Mean age** (Range)	Gender**
104	randomized, double-blind,	0.5 mL, IM	160	63 years (50-64 and $\geq 65$ years)	M = 65 F = 98
105	randomized, double-blind,	0.5 mL, IM	692	37.9 years (18-64 years)	M = 307 F = 414
107	open, annual	0.5 mL, IM	103	52 years (18-60 and $> 60$ years)	M = 33 F = 70
108	randomized, double-blind	0.5 mL, IM	592	66 years ( $\geq 50$ years)	M = 258 F = 334
109	randomized, double-blind	0.5 mL, IM	515	33 years (18-49 years)	M = 207 F = 308
110	open, annual	0.5 mL, IM	103	50.4 years (18-60 and $> 60$ years)	M = 42 F = 61

\*number of subjects evaluable for immunogenicity testing

\*\* According to Protocol data set

The six clinical studies were conducted over three influenza seasons and FLUVIRAL<sup>®</sup> was formulated with the influenza virus strains recommended by the WHO for each season.

**Table 3 Overview of WHO-recommended strains by season**

Season	A/H1N1	A/H3N2	B	Studies
2004/2005	New Cal	Wyoming	Jiangsu	104, 105
2005/2006	New Cal	New York	Jiangsu	107, 108, 109
2006-2007	New Cal	Wisconsin	Malaysia	110

Strains used: A/New Caledonia/20/99, A/Wyoming/03/03, A/New York/55/2004, A/Wisconsin/67/2005, B/Jiangsu/10/03 and B/Malaysia/2506/2004

Criteria established by the European Committee for Proprietary Medicinal Products are used to evaluate the immunogenicity of the vaccine. For each virus stain and age group, at least one of the assessments must meet the stated criteria.

**Table 4: CPMP Criteria by Age Group**

Parameter	Subjects 18-60 years	Subjects >60 years
% Seroconversion rate or significant increase in titer*	> 40%	> 30%
Seroconversion factor (ratio Day 21 GMT / Day 0 GMT)	> 2.5	> 2
% Seroprotection (Titer $\geq$ 40)	> 70%	> 60%

\* Seroconversion defined as a 4-fold rise in reciprocal titer or change from undetectable (< 10) to a reciprocal titer of  $\geq$  40

**Table 5 Summary of Pooled Immunogenicity Results**

	Subjects 18-60 years N = 1556	Subjects > 60 years N = 609
<b>Seroprotection</b>		
A/H1N1	97%	91%
A/H3N2	97%	95%
B	71%	76%
<b>Seroconversion</b>		
A/H1N1	79%	32%
A/H3N2	84%	77%
B	64%	47%
<b>GMFR</b>		
A/H1N1	13.78	2.55
A/H3N2	16.94	10.95
B	6.81	3.77

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**PART III: CONSUMER INFORMATION****FLUVIRAL® (2011-2012)**

Influenza Virus Vaccine  
Trivalent, Inactivated Split-Virion  
Prepared in Eggs

This leaflet is part III of a three-part "Product Monograph" and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FLUVIRAL®. If you have any questions, or if you are not sure about anything, ask your doctor, nurse or pharmacist.

Please read this leaflet carefully before receiving FLUVIRAL® as it contains information about the vaccine. It may be useful to keep this leaflet in case you need to read it again after vaccination.

**ABOUT THIS MEDICATION**

FLUVIRAL® is a vaccine used to prevent influenza in adults and children.

**What is influenza?**

- Influenza is a contagious disease of the upper respiratory tract
- It is caused by a virus
- Influenza is spread by nasal droplets
- Symptoms can include sudden fever, headache, chills, muscle aches and cough
- Occurs in Canada every year during late fall and winter months
- Occurs worldwide (globally)

Vaccination is the principal means of influenza prevention and associated complications.

**What is FLUVIRAL® and what does it do?**

FLUVIRAL® is a vaccine against influenza. It is an inactivated (killed) influenza (flu) virus vaccine in suspension for injection, which has been prepared in hens' eggs. The vaccine is made from the strains of flu virus which are expected in the coming winter. It is normally given in the autumn to protect you in the winter.

Flu immunization gives good protection against flu, and lasts for about one year. In order to be protected against the flu, you need to be given yearly injections of the vaccine.

Flu immunization does not *cause* illness. It is a coincidence if you develop a cough or cold shortly after having a flu immunization.

Flu immunization does not prevent other virus infections that can cause coughs and colds. It protects only against the influenza virus that is expected in the coming winter.

**What Is In Your Medication?**

- Each 0.5 mL dose of the vaccine contains 15 micrograms of highly purified sub-units (hemagglutinin) of strains A/California/7/2009 (H1N1)-like strain (A/California/7/2009 NYMC X-181), A/Perth/16/2009 (H3N2)-like strain (A/Victoria/210/2009 NYMC X-187) and B/Brisbane/60/2008-like strain (B/Brisbane/60/2008). These are the flu viruses that are likely to cause flu this winter.
- FLUVIRAL® contains thimerosal as a preservative. The vaccine also contains very small amounts of egg proteins, formaldehyde, sodium deoxycholate and sucrose.

**What Dosage Forms Does Your Medication Come In?**

FLUVIRAL® is supplied in 5 mL vials holding 10x0.5mL doses. FLUVIRAL® vaccine packaging does not contain latex.

**WARNINGS AND PRECAUTIONS****Who should not receive the vaccine?**

- People who have had a life-threatening allergic reaction to the vaccine or any of its components (e.g. egg, thimerosal)
- People with moderate to severe illness may have to delay immunization
- People who take oral theophylline or oral anticoagulants should consult with their physician before immunization
- Children under the age of 6 months

Make sure your prescriber knows if you have any of the following:

- any kind of infection or a high temperature at the moment
- a weakened immune system due to illness
- you are taking medicines which weaken the immune system (e.g. steroids such as prednisone)

If you have previously experienced oculo-respiratory symptoms, such as red eyes, respiratory symptoms and facial swelling, after having received a flu vaccine, you can receive the vaccine again this year. The risk of having oculo-respiratory symptoms again after revaccination is minimal compared to the serious threat posed by the flu.

**INTERACTIONS WITH THIS MEDICATION**

The metabolism of oral theophylline or oral anticoagulants may be affected by vaccination with FLUVIRAL® (see *Who should not receive the vaccine*).

FLUVIRAL® may be given at the same time as other vaccines, such as the vaccine against pneumococcal disease and routine

pediatric vaccines. The vaccines should be injected at different sites to reduce the risk of side effects.

### PROPER USE OF THIS MEDICATION

#### Usual Dose

**Children 6-35 months:** one dose of 0.25 mL

**Children (>3 years) and adults:** one dose of 0.5 mL

**Note:** Children under 9 years of age require two doses, one month apart, the first time they have the vaccine

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, FLUVIRAL® may cause side effects in some persons. If any side effects worry you, or you have any unusual symptoms, please contact your doctor, nurse or pharmacist.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in cases of very rare but serious allergic reactions. This would normally happen immediately after the injection had been given - please tell the nurse if you get a rash, have tightness in the throat or shortness of breath.

If you notice any other side effects not mentioned below, please inform your doctor, nurse or pharmacist.

You may notice some pain, reddening or swelling at the site of the injection. In some cases you may feel unwell and experience fever or swelling of the lymph glands. More rarely headache, shivering, sweating, tiredness and aches in your muscles and joints may occur. In addition, red eyes, respiratory problems and facial swelling may occur. These reactions are usually mild and should only last a day or two.

You should tell your doctor if you get any of the following unwanted effects: nerve pain (neuralgia), numbness / pins and needles (possibly with fever), convulsions, unexplained or easy bruising, skin rash, urinary symptoms

### HOW TO STORE IT

FLUVIRAL® should be stored in the refrigerator at +2° C to +8° C (DO NOT FREEZE). Do not use vaccine that has been frozen. Do not use vaccine after the expiration date.

### 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: 866-844-0018**

**By toll-free fax: 866-844-5931**

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

**By regular mail:**

**Public Health Agency of Canada**

**Vaccine Safety Section**

**130 Colonnade Road**

**Ottawa, Ontario K1A 0K9**

**Address Locator: 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 product monograph, prepared for health professionals can be found at: <http://www.gsk.ca> or by contacting the sponsor:

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

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Last revised: April 21, 2011