PRODUCT MONOGRAPH

FLUVIRAL®
2015-2016

Trivalent Influenza Vaccine (Split Virion, Inactivated)

Suspension for Injection

ATC Code J07BB02

Manufactured by:
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Quebec, Quebec

Distributed by:
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FLUVIRAL®
(2015-2016)

Trivalent Influenza Vaccine (Split virion, Inactivated)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
IM	Suspension for Injection 15 µg influenza virus Hemagglutinin/strain/ 0.5 mL dose	Egg proteins, sodium deoxycholate, ethanol, formaldehyde, sucrose, α-tocopheryl hydrogen succinate, polysorbate 80, thimerosal* *For a complete listing see Dosage Forms, Composition and Packaging section.*

* multidose presentation

DESCRIPTION

FLUVIRAL® 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® is used for active immunization against influenza disease caused by the influenza subtypes A and type B contained in the vaccine.

This vaccine complies with the World Health Organization (WHO) recommendation (Northern Hemisphere) for the 2015-2016 season.

Each 0.5 mL dose of vaccine contains 15 micrograms haemagglutinin of each of the following three influenza virus strains:

15µg HA - A/California/7/2009 (H1N1)pdm09-like virus;
15µg HA - A/Switzerland/9715293/2013 (H3N2)-like virus
15µg HA - B/Phuket/3073/2013-like virus

INDICATIONS AND CLINICAL USE

FLUVIRAL® is indicated for active immunization of adults and children from 6 months of age against influenza disease caused by influenza virus types A and B contained in the vaccine.

The National Advisory Committee on Immunization (NACI) provides additional guidance on the use of the influenza vaccine in Canada. Please refer to published *Statement on Seasonal Influenza Vaccine* for the current season. (1)

CONTRAINDICATIONS

FLUVIRAL® should not be administered to subjects with known hypersensitivity to egg proteins or after previous administration of any influenza vaccine produced in eggs or to any component of the vaccine.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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.

FLUVIRAL® should under no circumstances be administered intravascularly.

General

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and the possible occurrence of undesirable events) and a clinical examination.

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.

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

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

Febrile or acute disease

As with other vaccines, vaccination with FLUVIRAL® should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Hematologic

As with other vaccines administered intramuscularly, FLUVIRAL® should be given with caution in individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Immune

It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immune response may not be elicited.

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® 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 the most current NACI recommendations regarding revaccination of subjects who experienced more severe oculo-respiratory syndrome.

Special Populations

Pregnant Women: The safety of FLUVIRAL when administered to pregnant women has not been evaluated. Animal studies with FLUVIRAL® do not indicate direct or indirect harmful effects with respect to reproductive and developmental toxicity. FLUVIRAL® should be used during pregnancy only when clearly needed and the possible advantages outweigh the potential risks for the foetus.

Nursing Women: The safety of FLUVIRAL® when administered to breast-feeding women has not been evaluated. It is unknown whether FLUVIRAL® is excreted in human breast milk. FLUVIRAL® should only be used during breast-feeding when the possible advantages outweigh the potential risks.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most commonly reported adverse drug reactions with FLUVIRAL® are pain and redness at the injection site, fatigue, headache and myalgia. The most commonly reported adverse drug reactions in children included appetite loss, drowsiness and irritability. Reactions are generally mild and of limited duration.

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.

In six adult clinical studies conducted in the United States and Canada, FLULAVAL was administered to more than 2,200 subjects at least 18 years of age and in one paediatric clinical study conducted in the United States, FLULAVAL was administered to more than 1,000 children 3 to 17 years of age.

Local and general symptoms were solicited by a diary aid used by the subjects for at least the day of vaccination and 3 days post-vaccination. Subjects were also requested to report any clinical events occurring during the 21 day (for adults) and 28 day (for children) study period.

Adverse reactions reported are listed according to the following frequency:
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 disorders
Uncommon: lymphadenopathy
Eye disorders
Common: red eyes[2]
Gastrointestinal disorders
Uncommon: nausea
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[2]
Uncommon: Influenza-like illness, injection site pruritus, injection site hematoma, injection site warmth, injection site hemorrhage
Infections and infestations
Uncommon: upper respiratory tract infection
Metabolism and nutrition disorders
Very common: appetite loss[1]
Musculoskeletal and connective tissue disorders
Very common: myalgia
Common: arthralgia
Nervous system disorders
Very common: headache, drowsiness[1]
Uncommon: dizziness
Psychiatric disorders
Very common: irritability[1]

Respiratory, thoracic and mediastinal disorders
Common: sore throat[2], cough[2]
Skin and subcutaneous tissue disorders
Uncommon: swelling of the face[2]

[1]solicited in subjects < 5 years of age
[2]These symptoms can be associated to the oculorespiratory 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.

The clinical trial data with FLUVIRAL® are supported by 2 studies conducted with FLULAVAL® TETRA, a vaccine manufactured by the same process containing three influenza virus strains shared with FLUVIRAL® plus a second influenza B virus strain. Therefore, adverse reactions attributed to FLULAVAL® TETRA (60 µg hemagglutinin per 0.5 mL) are likely to predict those expected with FLUVIRAL® (45 µg hemagglutinin per 0.5 mL).
Safety data in FLULAVAL® TETRA studies were collected by the same method used in FLUVIAL® studies, except that solicited local and general symptoms were collected over a 7-day rather than a 4-day period.

In more than 1200 adults, FLULAVAL® TETRA had a similar safety profile to that observed for FLUVIRAL® in adults. Additional adverse reactions were gastrointestinal symptoms (including nausea, vomiting, diarrhoea and /or abdominal pain) reported as common and injection site reactions (such as haemorrhage, haematoma, warmth), lymphadenopathy, pruritus and rash reported as uncommon.

In 299 children 6 to 35 months of age, FLULAVAL® TETRA had a similar safety profile to that observed for FLUVIRAL® in children 3 to 4 years of age. Additional adverse reactions were diarrhoea and vomiting reported as uncommon.

Adults: ***Study Q-QIV-007 (Immunogenicity Non-Inferiority):*** A randomized, double-blind, active-controlled study evaluated 1,703 adults 18 years of age and older who received FLULAVAL® TETRA, a quadrivalent seasonal vaccine, with two A strains and two B strains, one of Victoria lineage and one of Yamagata lineage (N = 1,272), or FLUVIRAL® manufactured for the 2010-2011 season with a B strain of Victoria lineage (N = 213), or a TIV with the same two A strains as FLUVIRAL® but with a B strain of Yamagata lineage (N = 218). The mean age of subjects was 50 years. Solicited local adverse reactions and systemic adverse events were collected using diary cards for 7 days (day of vaccination and the next 6 days).

Table 1: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 7 Days[a] of Vaccination in Adults[b] (Total Vaccinated Cohort)

	FLULAVAL Tetra[c] N = 1,260 %	**FLUVIRAL (B Victoria)[d] N = 208 %**	**TIV (B Yamagata)[e] N = 216 %**
Local			
Pain	60	45	41
Swelling	3	1	4
Redness	2	3	1
Systemic			
Myalgia	26	25	19
Headache	22	20	23
Fatigue	22	22	17
Arthralgia	15	17	15
Gastrointestinal symptoms[f]	9	10	7
Shivering	9	8	6
Fever ≥100.4°F (38.0°C)	2	1	1

TIV = trivalent influenza vaccine.

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Study 1: NCT01196975.

[c] Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata lineage.

[d] Contained two A strains and a B strain of Victoria lineage.

[e] Contained the same two A strains as FLUVIRAL® and a B strain of Yamagata lineage.

[f] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

Unsolicited adverse events: Unsolicited events that occurred within 21 days of vaccination (day 0-20) were recorded based on spontaneous reports or in response to queries about changes in health status. The incidence of unsolicited adverse events reported during the 21-day post-vaccination period for subjects who received FLULAVAL® TETRA (N = 1,272), FLUVIRAL® (N = 213), or TIV (B Yamagata) (N = 218) was 19%, 23%, and 23%, respectively. Unsolicited events reported for FLULAVAL® TETRA considered as possibly related to vaccination and occurring in ≥0.1% of subjects included dizziness, injection site hematoma, injection site hemorrhage, injection site warmth, lymphadenopathy, pruritus, rash, and upper respiratory tract infection.

Children: *Study Q-TIV TF-008 (Immunogenicity Non-Inferiority)*: An observer-blind, active-controlled study evaluated subjects 3 through 17 years of age who received FLUVIRAL® (N = 1,055) or FLUZONE® (N = 1,061), a licensed trivalent, inactivated influenza virus vaccine, manufactured by Sanofi Pasteur SA. In the overall population, 53% were male. The mean age of subjects was 8 years. Children 3 through 8 years of age with no

history of influenza vaccination received 2 doses approximately 28 days apart. Children 3 through 8 years of age with a history of influenza vaccination and children 9 years of age and older received one dose. Solicited local adverse reactions and systemic adverse events were collected using diary cards for 4 days (day of vaccination and the next 3 days) (Table 2).

Table 2: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events Within 4 Days[a] of First Vaccination in Children 3 to 17 Years of Age[b] (Total Vaccinated Cohort)

	FLUVIRAL %	**Comparator[c] %**
	Age Group: 3 to 17 Years	
Local	**N = 1,042**	**N = 1,026**
Pain	56	53
Redness	4	5
Swelling	4	5
	Age Group: 3 to 4 Years	
Systemic	**N = 293**	**N = 279**
Irritability	25	27
Drowsiness	19	19
Loss of appetite	16	13
Fever ≥100.4°F (38.0°C)	5	3
	Age Group: 5 to 17 Years	
Systemic	**N = 749**	**N = 747**
Muscle aches	24	23
Headache	17	15
Fatigue	17	17
Arthralgia	8	10
Shivering	6	5
Fever ≥100.4°F (38.0°C)	5	4

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.

[a] 4 days included day of vaccination and the subsequent 3 days.

[b] Study 4: NCT00980005.

[c] licensed trivalent, inactivated influenza virus vaccine (manufactured by Sanofi Pasteur SA).

In children who received a second dose of FLUVIRAL® or the comparator vaccine, the incidences of adverse events following the second dose were generally lower than those observed after the first dose.

Unsolicited adverse events that occurred within 28 days (day 0-27) of any vaccination were recorded based on spontaneous reports or in response to queries about changes in health status. The incidence of unsolicited adverse events reported in subjects who received FLUVIRAL® (N = 1,055) or FLUZONE® (N = 1,061) was 40% and 37%, respectively.

Unsolicited events reported for FLUVIRAL® considered as possibly related to vaccination and occurring in ≥0.1% of subjects included diarrhea, influenza-like illness, injection site hematoma, injection site rash, injection site warmth, rash, upper abdominal pain, and vomiting. The rates of SAEs were comparable between groups (0.9% and 0.6% for FLUVIRAL® and the comparator, respectively); none of the SAEs were considered related to vaccination.

Children 6-35 months: Study Q-QIV-013 (Immunogenicity and Safety): A randomized, double-blind, active controlled study in which subjects received one or two 0.5 mL doses of FLULAVAL® TETRA (n = 299) or a comparator trivalent influenza vaccine (FLUARIX® n = 302) containing one B strain from the B/Yamagata lineage. Children with no history of prior influenza vaccination received 2 doses approximately 28 days apart (92.6% and 93.0 % for FLULAVAL® TETRA and FLUARIX®, respectively). Children with a history of prior influenza vaccination received one dose of vaccine (7.4% and 7.0%, respectively). Solicited local adverse reactions and systemic adverse events were collected using diary cards for seven days.

Table 3: Incidence of Solicited Local and Systemic Adverse Events Within 7 Days[a] of First Vaccination in Children 6 to 35 Months of Age[b] (Total Vaccinated Cohort)

Children 6-35 months	**FLULAVAL TETRA[c] %**	**FLUARIX[d]**
Local	**N = 564 doses**	**N = 573**
Pain	23.0	21.5
Swelling	1.1	1.2
Redness	1.2	1.0
Systemic	**N = 561 doses**	**N = 572 doses**
Irritability	29.1	29.5
Drowsiness	21.6	18.9
Loss of appetite	22.5	22.0
Fever ≥38.0°C	13.4	12.1

[a] 7 days included day of vaccination and the subsequent 6 days.
[b] Study Q-QIV-013: NCT01711736
[c] Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata lineage.
[d] Contained two A strains and one B strain from the Yamagata lineage

Unsolicited adverse events
During the 28-day post-vaccination period, overall, unsolicited AEs were experienced after 33.5% of FLULAVAL® TETRA doses and 35.8% of FLUARIX® doses. The most frequently reported unsolicited AEs were nasopharyngitis (16.1% and 17.7% respectively) followed by diarrhoea (7.5% and 7.2% respectively).

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

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.

DRUG INTERACTIONS

Drug-Drug Interactions
No interaction studies have been performed. If FLUVIRAL® is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

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).

Drug-Lifestyle Interactions
The vaccine is unlikely to produce an effect on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

FLUVIRAL® should be administered as a single 0.5 mL injection.

Children 6 months to less than 9 years of age who have not previously been vaccinated against influenza should receive a second dose of 0.5 mL after an interval of at least 4 weeks.

Administration

FLUVIRAL® vaccine must not be administered intravenously.

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

FLUVIRAL® is an opalescent translucent to off-white suspension that may sediment slightly.

The vial should be shaken prior to each administration and inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

Each vaccine dose of 0.5 mL is withdrawn into a 1CC syringe for injection and administered intramuscularly. It is recommended to equip the syringe with a needle gauge not larger than 23-G.

Between uses, the multidose vial should be stored in a refrigerator (2°C - 8°C).

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

Any unused product or waste material should be disposed of in accordance with local requirements. Since FLUVIRAL® is a split-virion, inactivated vaccine, it presents no risk of contaminating the work area during manipulation.

OVERDOSAGE

Insufficient data are available.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

FLUVIRAL® provides active immunization against the three influenza virus strains (two A subtypes and one B type) contained in the vaccine. Although multiple mechanisms, including cellular immunity, may contribute to vaccine-induced protection against influenza, the humoral components of the immune response, in particular antibodies against virus hemagglutinin (HA) and neuraminidase (NA) antigens is best understood. Specific levels of vaccine-induced haemagglutination-inhibiting HI antibodies that protect against naturally occurring influenza disease have not been established in randomized, controlled trials.

In human challenge studies, HI antibody titers of ≥ 1:40 have been associated with reductions in influenza illness. In addition, HI antibody responses are used as a measure of vaccine activity. The effectiveness of inactivated influenza vaccines is influenced by the age and immunocompetence of the vaccine recipient and the degree of similarity between the virus strains used to prepare the vaccines and those circulating in the population.

Pharmacodynamics/Pharmacokinetics

No pharmacokinetic studies have been conducted with FLUVIRAL® in accordance with its status as a vaccine. For pharmacodynamic information see *Clinical Trials.*

Duration of Effect

Annual revaccination is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus might change from year to year.

STORAGE AND STABILITY

FLUVIRAL® must be stored between 2°C and 8°C. Do not freeze**.**
Discard if the vaccine has been frozen.

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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

This vaccine complies with the World Health Organization (WHO) recommendation (Northern Hemisphere) for the 2015-2016 season.

Each dose of 0.5 mL of FLUVIRAL® contains:

15µg HA - A/California/7/2009 (H1N1)pdm09-like virus (A/California/7/2009 NYMC X-179A),
15µg HA - A/Switzerland/9715293/2013 (H3N2)-like virus (A/Switzerland/9715293/2013 NIB-88),
15µg HA - B/Phuket/3073/2013-like virus (B/Phuket/3073/2013) from the B/Yamagata/16/88 lineage.

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. Each 0.5-mL dose contains, α-tocopheryl hydrogen succinate (200 µg), and polysorbate 80 (512 µg). Each 0.5-mL dose may also contain

residual amounts of egg proteins (ovalbumin ≤0.3 μg), sodium deoxycholate, ethanol, formaldehyde and sucrose from the manufacturing process.

Thimerosal, a mercury derivative, is added as a preservative. Each 0.5-mL dose contains 50 μg thimerosal (<25 μg mercury).

Antibiotics are not used in the manufacture of this vaccine.

FLUVIRAL® packaging does not contain latex.

FLUVIRAL® is supplied in 5 mL vials holding 10 x 0.5 mL doses – pack size of 1vial.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

FLUVIRAL® contains three split-virion, inactivated influenza virus strains prepared from virus propagated in the allantoic cavity of embryonated hens' eggs. Each of the influenza virus strains is produced and purified separately. The virus is inactivated with ultraviolet light followed by formaldehyde treatment, purified by centrifugation and disrupted with sodium deoxycholate.

Product Characteristics

FLUVIRAL® is a sterile, opalescent translucent to off-white suspension in a phosphate-buffered saline solution and may sediment slightly. The vaccine has been formulated to contain 45 micrograms (µg) haemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 µg HA of each of the 3 influenza virus strains. Antibiotics are not used in the manufacture of this vaccine.

CLINICAL TRIALS

Study demographics and trial design

The immunogenicity of FLUVIRAL® has been evaluated as a trivalent or as a quadrivalent thimerosal-free formulation (FLULAVAL® TETRA) in controlled and open-label clinical trials involving adults 18 years and older, and children aged 3 to 17 years. Adults and children 9 years and older received a single 0.5 mL dose of FLUVIRAL® or a quadrivalent formulation of the vaccine (FLULAVAL® TETRA). Children 6 months through 8 years with a history of influenza vaccination received one 0.5 mL dose. Children 6 months through 8 years of age with no history of influenza vaccination received 2 doses approximately 28 days apart.

The humoral immune response was assessed in terms of a serum haemagglutinin-inhibiting (HI) antibody titer against each virus strain included in the vaccine. In adult studies the immune response was assessed 21 days following vaccination. In pediatric studies, the immune response was assessed 28 days following the last vaccination.

Table 4 Summary of Patient* Demographics for Clinical Trials

Study #	Trial design	Dosage, route of administration	Study subjects (n)	Mean age (Range)	Gender
Q-QIV-007	randomized, double-blind, immunogenicity and safety	0.5 mL, IM	1703 ≥18 years	50.0 years (18-97 years)	F = 1044 M = 659
Q-TIV-TF008	randomized, observer-blind, immunogenicity and safety.	0.5 mL, IM (unprimed: 2x0.5 mL IM, 28 days apart)	1055	7.8 years (3-17 years)	F = 500 M = 555

* Total Vaccinated Cohort

Adults 18 years of age and older

In clinical study Q-QIV-007, approximately 1,200 adults 18 years of age and older received a single dose of a quadrivalent formulation of FLUVIRAL® (FLULAVAL® TETRA) and approximately 200 subjects received a single dose of FLUVIRAL®.

The study assessed the non-inferiority of FLULAVAL® TETRA versus FLUVIRAL® for HI Geometric mean antibody titer (GMT) at Day 21 and HI seroconversion rate (4-fold rise in reciprocal titer or change from undetectable [< 10] to a reciprocal titer of ≥ 40) in adults 18 years of age and older.

Table 5: Non-inferiority of Q-QIV versus FLUVIRAL® for the common strains in terms of adjusted GMT ratios at Day 21

					Adjusted GMT ratio (Comparator / QIV)		
Strain	**Comparator**		**Q-QIV**			**95% CI**	
	N	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
TIV-VB+TIV-YB vs. QIV							
A/California/7/2009 (H1N1)	414	160.0	1238	205.1	0.78	0.68	0.90
A/Victoria/210/2009 (H3N2)	415	147.6	1237	124.2	1.19	1.05	1.35
TIV-VB vs. QIV							
B/Brisbane/60/2008 (Victoria)	203	133.0	1240	177.2	0.75	0.65	0.87
TIV-YB vs. QIV							
B/Florida/4/2006 (Yamagata)	211	311.7	1241	396.2	0.79	0.69	0.90

1. Q-QIV = Subjects received Q-QIV; TIV-VB = Subjects received TIV with B strain of Victoria lineage; TIV-YB = Subjects received TIV with B strain of Yamagata lineage; TIV-VB+TIV-YB = Pooled TIV-VB and TIV-YB groups;
2. Adjusted GMT = geometric mean antibody titer adjusted for baseline titer;
3. N = Number of subjects with both pre- and post-vaccination results available;
4. 95% CI = 95% confidence interval for the adjusted GMT ratio (ANCOVA model: adjustment for baseline titer - pooled variance); LL = lower limit, UL = upper limit

FLULAVAL® TETRA met the non-inferiority criteria based on GMT's (upper limit of 2-sided 95% CI for GMT ratio (comparator / FLUVIRAL® ≤1.5)

Table 6: Post-vaccination GMT and seroconversion rates in adults 18 years of age and older (ATP Cohort for Immunogenicity)

	FLULAVAL Tetra N=1246 (95% CI)	**FLUVIRAL[1] N=204 (95% CI)**
GMT		
A/H1N1	204.6 (190.4;219.9)	176.0 (149.1;207.7)
A/H3N2	125.4 (117.4;133.9)	147.5 (124.1;175.2)
B (Victoria)[2]	177.7 (167.8;188.1)	135.9 (118.1;156.5)
B (Yamagata)[3]	399.7 (378.1;422.6)	176.9 (153.8;203.5)
Seroconversion rate		
A/H1N1	74.5% (71.9;76.9)	66.7% (59.7;73.1)
A/H3N2	66.5% (63.8;69.2)	73.0% (66.4;79.0)
B (Victoria)[2]	55.2% (52.4;58.0)	48.8% (41.7;55.9)
B (Yamagata)[3]	54.8% (52.0;57.6)	33.3% (26.9;40.3)

ATP = according to protocol ATP cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one study vaccine antigen.
[1]containing A/H1N1, A/H3N2 and B (Victoria lineage)
[2]recommended strain by WHO during the season 2010-2011
[3]additional B strain contained in FLULAVAL® TETRA recommended in season 2008-2009

The respective post-vaccination seroprotection rates (Day 21 reciprocal titer of ≥ 40) for FLUVIRAL® and FLULAVAL® TETRA in adults 18 years of age and older were 92.6% and 93.7% against A/H1N1, 92.2% and 90.8% against A/H3N2,94.6% and 96.4% against B (Victoria) and 98.0% and 99.8% against B (Yamagata).

Children (Immunogenicity Non-Inferiority)

In study Q-TIV-TF-008, the immune response of FLUVIRAL® (N = 987) was compared to FLUZONE®, a licensed trivalent, inactivated influenza virus vaccine (N = 979), manufactured by Sanofi Pasteur SA, in an observer-blind, randomized study in children 3 through 17 years of age. The immune responses to each of the antigens contained in FLUVIRAL® formulated for the 2009-2010 season were evaluated in sera obtained after one or 2 doses of FLUVIRAL and were compared to those following the comparator influenza vaccine.

Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera 28 days following one or 2 doses. The non-inferiority endpoints were geometric mean antibody titers (GMTs) adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination, performed on the According-to-Protocol (ATP) cohort. FLUVIRAL® was non-inferior to the comparator influenza for all strains based on adjusted GMTs and seroconversion rates.

Table 7: Immune Responses to Each Antigen 28 Days After Last Vaccination in Children 3 to 17 Years of Age (ATP Cohort for Immunogenicity)

	FLUVIRAL	Comparator[b]	
GMTs Against	**N = 987 (95% CI)**	**N = 979 (95% CI)**	**GMT Ratio[c] (95% CI)**
A/H1N1	320.9 (298.3, 345.2)	329.4 (306.8, 353.7)	1.03 (0.94, 1.13)
A/H3N2	414.7 (386.5, 444.9)	451.9 (423.8, 481.8)	1.05 (0.96, 1.13)
B	213.7 (198.5, 230.1)	200.2 (186.1, 215.3)	0.93 (0.85, 1.02)
Seroconversion[d]	**N = 987 % (95% CI)**	**N = 978 % (95% CI)**	**Difference in Seroconversion Rates[e] (95% CI)**
A/H1N1	59.8 (56.6, 62.9)	58.2 (55.0, 61.3)	-1.6 (-5.9, 2.8)
A/H3N2	68.2 (65.2, 71.1)	66.2 (63.1, 69.1)	-2.0 (-6.1, 2.1)
B	81.1 (78.5, 83.5)	78.6 (75.9, 81.2)	-2.4 (-6.0, 1.1)

ATP = according to protocol; CI = Confidence Interval.

ATP cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one study vaccine antigen.

[a] Results obtained following vaccination with influenza vaccines formulated for the 2009-2010 season.

[b] licensed trivalent, inactivated influenza virus vaccine (Sanofi Pasteur SA).

[c] FLULAVAL met non-inferiority criteria based on GMTs (upper limit of 2-sided 95% CI for GMT ratio [comparator vaccine/FLULAVAL] ≤1.5).

[d] Seroconversion defined as at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

[e] FLULAVAL met non-inferiority criteria based on seroconversion rates (upper limit of 2-sided 95% CI for difference of the comparator vaccine minus FLULAVAL ≤10%).

Toxicology

Non-clinical data reveal no special hazards for humans based on conventional studies of acute toxicity, local tolerance, repeated dose toxicity and reproductive/developmental toxicity.

The potential for toxicity of the trivalent vaccine was evaluated with FLULAVAL® TETRA, a quadrivalent thimerosal-free (Q-QIV TF) vaccine that was manufactured by the same process as the trivalent FLUVIRAL®. The Q-QIV TF vaccine was used as a representative

formulation for the toxicology assessment of thimerosal-plus and thimerosal-free formulations. The vaccine has not been evaluated for carcinogenicity or mutagenic potential.

Table 8 Toxicity Studies with Q-QIV TF Vaccine

Study	Species or Substrate	Route	Dosing Regimen	Tested Material
Single dose and local tolerance	New Zealand White rabbits	IM	Single dose: FHD	Q-QIV TF [a] Phosphate buffer saline
Repeated dose	New Zealand White rabbits	IM	3 doses at 2 weeks interval; FHD	Q-QIV TF [a] Phosphate buffer saline
Repeated dose	New Zealand White rabbits	IM	3 doses at 2 weeks interval; FHD	Q-QIV TF Phosphate buffer saline
Reproduction and development	Sprague-Dawley rats (Crl:CD (SD) IGS BR)	IM	Day -28 and -14 before pairing, then Days 3, 8, 11, 15 after mating and Day 7 of lactation; 2/5th HD	Q-QIV TF D-QIV TF [b] Phosphate buffer saline)
Female fertility and embryo-fetal survival	Sprague-Dawley rats (Crl:CD (SD) IGS BR)	IM	Day -28 and -14 before pairing, and then Days 3, 8, 11, 15 after mating; 2/5th HD	Q-QIV TF Phosphate buffer saline)

a. B strains from both lineages were not available at the time of testing: a trivalent influenza virus candidate vaccine was tested: 2 "A" strains + 1 "B" strain, with double the amount of antigen, in order to mimic the total amount of antigen included in the quadrivalent vaccine.
b. D-QIV TF: Dresden (Germany) manufactured antigens.
FHD: Full Human Dose
HD: Human Dose

Single Dose Toxicity
In the single dose/local tolerance study, a full human dose of Q-QIV TF vaccine was administered to New Zealand White rabbits. There were no deaths, clinical signs, or changes in body weights that could be attributed to the administration of the vaccine. There was no associated toxicity after treatment with the vaccine. Minor inflammation was seen in both treated groups; however there were no clear differences between the Q-QIV TF vaccine and the saline control group.

Repeat Dose Toxicity
In the two repeated dose studies, a full human dose of the Q-QIV-TF vaccine was administered three times within a 2-week interval. The repeated intramuscular treatment of rabbits with the vaccine induced mild, transient local effects in the injected muscles. A few hematology and clinical chemistry parameters related to the local inflammation were

transiently affected. The inflammation diminished distinctly over time and a clear recovery process was observed at the end of the 28-day observation period.

Reproductive Toxicity
Vaccination of female rats with Q-QIV TF vaccine, at doses shown to be immunogenic in the rat, had no effect on F0 female clinical condition, food consumption, weight, mating performance, fertility, or ability to produce a live litter. There was no effect on pre- or post-natal development of F1 offspring.

REFERENCES

1. National Advisory Committee on Immunization (NACI): Statement on Seasonal Influenza Vaccine for the current year. http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php#rec

PART III: CONSUMER INFORMATION

FLUVIRAL® (2015-2016)

Trivalent Influenza Virus Vaccine
Split Virion, Inactivated

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

ABOUT THIS VACCINE

What the vaccine is used for:
FLUVIRAL® is a trivalent vaccine for use in adults and children greater than 6 months of age to provide active immunization against disease caused by influenza virus types A and B contained in the vaccine.

Influenza is a disease of the upper airways and lungs caused by infection with a flu virus. The most commons symptoms are: high temperature (fever), sore throat, coughing, general aches and pains, headaches, weakness and tiredness.

What it does:
FLUVIRAL® causes the body's immune system to make antibodies to protect the person from being infected by certain types of influenza virus. This vaccine is only effective against infection by A and B virus types it is designed to prevent and closely related types of virus. None of the ingredients in the vaccine can cause influenza. As with all vaccines, FLUVIRAL® may not fully protect all people who are vaccinated.

When it should not be used:
If you had a severe allergic reaction (e.g., anaphylaxis) to egg proteins, a previous dose of any influenza vaccine produced in eggs or any ingredient in the vaccine.

What the medicinal ingredient is:
This vaccine complies with the World Health Organization (WHO) recommendation (Northern Hemisphere) for the 2015-2016 season.
Each 0.5 mL dose of the vaccine contains 15 micrograms of haemagglutinin, a type of protein that has been purified from killed and split influenza viruses. The three virus strains in this vaccine are:
- A/California/7/2009 (H1N1)pdm09-like virus;
- A/Switzerland/9715293/2013 (H3N2)-like virus;
- B/Phuket/3073/2013-like virus.

What the important nonmedicinal ingredients are:
Phosphate buffered saline, polysorbate 80, α-tocopheryl hydrogen succinate, thimerosal. Trace amounts of: egg proteins, ethanol, formaldehyde, sodium deoxycholate, and sucrose.

What dosage forms it comes in:
- multidose vial (type 1 glass) of 5 mL for 10 doses
The packaging does not contain latex.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
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.

BEFORE you receive FLUVIRAL® talk to your doctor or nurse if:

- You have a **severe infection** with a high temperature. In these cases, the vaccination will be postponed until you recover. A minor infection should not be a problem.
- You have a **bleeding problem** or **bruise easily**.
- You have a **weakened immune system** due to HIV infection or due to medicines that suppress the immune system.
- You have **fainted** before or after a previous injection.
- If you are **taking any other medicines** or you have recently received any other vaccine.
- If Guillain-Barré (GBS) has occurred within 6 weeks of receiving a previous influenza vaccination.
- If you are **pregnant or breast-feeding** seek advice from your doctor.

INTERACTIONS WITH THIS MEDICATION

FLUVIRAL® must not be mixed with any other vaccine in the same syringe. If FLUVIRAL® is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

PROPER USE OF THIS MEDICATION

Usual dose:
One injection of 0.5 mL into the shoulder muscle or the mid-thigh muscle.

Children 6 months to less than 9 years of age who have not been vaccinated against influenza in the past will receive a second injection at least one month after the first injection.

Overdose:

In case of 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 effect worries you, or you have any unusual symptoms, please contact your doctor, nurse or pharmacist.

Very common (may occur with more than 1 in 10 doses):
- Pain at the injection site
- Fatigue
- Headache
- Aching muscles
- Loss of appetite
- Drowsiness
- Irritability.

Common (may occur with up to 1 in 10 doses)
- Red eyes
- Feeling sick, vomiting, diarrhea, stomach pain
- Redness and swelling at the injection site, fever, chills, malaise, chest tightness
- Join pain
- Sore throat, cough

Contact your doctor, nurse or pharmacist urgently if you experience :
- allergic reaction (including anaphylactic and anaphylactoid reactions). These can be recognized by:
  - itchy rash of the hands and feet
  - swelling of the eyes and face
  - difficulty in breathing or swallowing
  - sudden drop in blood pressure and loss of consciousness.
- Temporary inflammation of the nerves causing pain, weakness and paralysis called Guillain-Barré syndrome

This is not a complete list of side effects. *For any unexpected effects while taking FLUVIRAL®, contact your doctor, nurse or pharmacist.*

HOW TO STORE IT

FLUVIRAL® should be stored in the refrigerator at +2° C to +8° C. Do not freeze.

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: 866-844-0018
By toll-free fax: 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:
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:

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