PRODUCT MONOGRAPH

FLULAVAL® TETRA
(2016-2017)

Quadrivalent Influenza Vaccine (Split Virion, Inactivated)

Suspension for Injection

ATC Code: J07BB02

Manufactured by:
ID Biomedical Corporation of Quebec
Quebec, Quebec, Canada

Distributed by:

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
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Quadrivalent influenza vaccine (split virion, inactivated)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular	Suspension for Injection Each 0.5 mL dose contains 15 µg of influenza virus haemagglutinin/strain for each strain listed below (see Description)	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

FLULAVAL® TETRA is a quadrivalent split-virion, inactivated 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.

This vaccine complies with the World Health Organization (WHO) recommendation (Northern Hemisphere) for the 2016-2017 season.

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

15µg HA - A/California/7/2009 (H1N1)pdm09-like virus
15µg HA - A/Hong Kong/4801/2014 (H3N2) -like virus
15µg HA - B/Phuket/3073/2013-like virus from B/Yamagata lineage
15µg HA - B/Brisbane/60/2008-like virus from B/Victoria lineage

INDICATIONS AND CLINICAL USE

FLULAVAL® TETRA is a quadrivalent vaccine indicated for active immunization of adults and children from 6 months of age for the prevention of 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.

CONTRAINDICATIONS

FLULAVAL® TETRA 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.

FLULAVAL® TETRA 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.

FLULAVAL® TETRA is not effective against all possible strains of influenza virus. FLULAVAL® TETRA 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 FLULAVAL® TETRA 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, FLULAVAL® TETRA should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Immune
An adequate immune response may not be elicited in patients receiving immunosuppressive treatment or patients with immunodeficiency.

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 FLULAVAL® TETRA 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 FLULAVAL® TETRA when administered to pregnant women has not been evaluated. Animal studies with FLULAVAL® TETRA do not indicate direct or indirect harmful effects with respect to reproductive and developmental toxicity. FLULAVAL® TETRA 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 FLULAVAL® TETRA when administered to breast-feeding women has not been evaluated. It is unknown whether FLULAVAL® TETRA is excreted in human breast milk. FLULAVAL® TETRA should only be used during breast-feeding when the possible advantages outweigh the potential risks.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical trials, FLULAVAL® TETRA was administered to more than 1,960 children between 6 – 35 months of age, more than 3,500 children between 3 – 17 years of age and more than 1,200 adults.

In adults, the most common (≥10%) solicited local reaction was pain (60%); the most common solicited systemic adverse events were myalgia (26%), headache (22%), fatigue (22%), and arthralgia (15%).

In children 3 to 17 years of age, the most common (≥10%) solicited local reaction was pain (65%). In children 3 to 4 years of age, the most common (≥10%) solicited systemic adverse events were irritability (26%), drowsiness (21%), and loss of appetite (17%). In children 5 to 17 years of age, the most common (≥10%) systemic adverse events were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), and gastrointestinal symptoms (10%).

In children 6 to 35 months of age, injection site pain was the most common (≥10%) solicited local reaction (40%). The most common solicited systemic adverse events were irritability (49%), drowsiness (37%), and loss of appetite (29%).

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 clinical trials, FLULAVAL® TETRA was administered to more than 6,660 subjects.

Adverse reactions reported for FLULAVAL® TETRA are listed per dose according to the following frequency categories:

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

The following adverse reactions have been reported in all age categories:

System Organ Class	Adverse Reactions	Frequency
General disorder and administration site condition	Injection site pain	Very common
	Injection site redness and fever	Common
Infections and infestations	Upper respiratory tract infection	Uncommon

The following adverse reactions have also been reported depending of the age category:

Children (5-17) and Adults:

System Organ Class	Adverse Reactions	Frequency
Nervous system disorders	Headache	Very common
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia	Very common
General disorder and administration site condition	Fatigue	Very common
	Shivering and injection site swelling	Common
Gastrointestinal disorders	Gastrointestinal symptoms (including nausea, vomiting, diarrhea, abdominal pain)	Common

Adults:

System Organ Class	Adverse Reactions	Frequency
General disorder and administration site condition	Injection site swelling	Common
Blood and lymphatic disorders	Lymphadenopathy	Uncommon
Nervous system disorders	Dizziness	Uncommon

Children:

System Organ Class	Adverse Reactions	Frequency
6-35 months		
Metabolism and Nutrition disorders	Appetite Loss	Very Common
Psychiatric disorders	Irritability	Very Common
Nervous system disorders	Drowsiness	Very Common
Gastrointestinal disorders	Vomiting, diarrhoea	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon
Skin and subcutaneous tissue disorders	Rash	Uncommon
General disorders and administration site conditions	Injection site swelling	Uncommon
3-4 years		
Metabolism and Nutrition disorders	Appetite loss[1]	Very common
Psychiatric disorders	Irritability[1]	Very Common
Nervous system disorders	Drowsiness[1]	Very Common
3-17 years		
General disorders and administration site conditions	Influenza like illness, and injection site pruritus	Uncommon
	Injection site swelling	Common

[1]Reported as very common, with the same or lower percent frequency compared to 6-35 months

<u>Adults:</u> ***Study Q-QIV-007 (Immunogenicity Non-Inferiority and Superiority):***
A randomized, double-blind, active-controlled study evaluated 1,703 adults 18 years of age and older who received FLULAVAL® TETRA, with two A strains and two B strains, one of Victoria lineage and one of Yamagata lineage (N = 1,272), or a trivalent influenza vaccine (TIV): FLUVIRAL® (Influenza Virus Vaccine), 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 Q-QIV-007: 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-QIV-003 (Immunogenicity Non-Inferiority and Superiority):***
A randomized, double-blind, active-controlled study evaluated subjects 3 through 17 years of age who received FLULAVAL® TETRA, with two A strains and two B strains, one of Victoria lineage and one of Yamagata lineage (N = 932) or a trivalent influenza vaccine (TIV): FLUARIX® (Influenza Virus Vaccine), manufactured for the 2010-2011 season with a

B strain of Victoria lineage (N = 929), or a TIV with the same two A strains as FLUARIX® but with a B strain of Yamagata lineage (N = 932). Among recipients of FLULAVAL® TETRA, 53% were male. The mean age of subjects was 9 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 7 days (Table 2).

Table 2: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events Within 7 Days[a] of First Vaccination in Children 3 to 17 Years of Age[b] (Total Vaccinated Cohort)

	FLULAVAL® TETRA[c] %	**FLUARIX® (B Victoria)[d] %**	**TIV (B Yamagata)[e] %**
	Age Group: 3 to 17 Years		
Local	**N = 913**	**N = 911**	**N = 915**
Pain	65	55	56
Swelling	6	3	4
Redness	5	3	4
	Age Group: 3 to 4 Years		
Systemic	**N = 185**	**N = 187**	**N = 189**
Irritability	26	17	22
Drowsiness	21	20	23
Loss of appetite	17	16	13
Fever ≥100.4°F (38.0°C)	5	6	4
	Age Group: 5 to 17 Years		
Systemic	**N = 727**	**N = 724**	**N = 725**
Muscle aches	29	25	25
Fatigue	22	24	23
Headache	22	22	20
Arthralgia	13	12	11
Gastrointestinal symptoms[f]	10	10	9
Shivering	7	7	7
Fever ≥100.4°F (38.0°C)	2	4	3

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 Q-QIV-003: NCT01198756

[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 FLUARIX® and a B strain of Yamagata lineage.

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

In children who received a second dose of FLULAVAL® TETRA, FLUARIX®, or TIV (B Yamagata), the incidences of adverse events following the second dose were generally lower than those observed after the first dose.

Unsolicited Adverse Events: 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 FLULAVAL® TETRA (N = 932), FLUARIX® (N = 929), or TIV (B Yamagata) (N = 932) was 30%, 31%, and 30%, respectively. Unsolicited events reported for FLULAVAL® TETRA considered as possibly related to vaccination and occurring in ≥0.1% of subjects included influenza-like illness, injection site hematoma, injection site pruritus, rash, and upper respiratory tract infection.

Children 6-35 months: *Study Q-QIV-022 (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 = 1207) or a comparator quadrivalent influenza vaccine (FLUZONE® QUADRIVALENT N = 1217). Children with no history of prior influenza vaccination received 2 doses approximately 28 days apart (43.0% and 43.5 % for FLULAVAL® TETRA and FLUZONE® QUADRIVALENT, respectively). Children with a history of prior influenza vaccination received one dose of vaccine (57.0% and 56.5%, respectively). Solicited local adverse reactions and systemic adverse events were collected using diary cards for seven days (Table 3).

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] %**	**FLUZONE® QUADRIVALENT[c] %**
Local	**N = 1151**	**N = 1146**
Pain	40.3	37.4
Redness	1.3	1.3
Swelling	1.0	0.4
Systemic	**N = 1155**	**N = 1148**
Irritability	49.4	45.9
Drowsiness	36.7	36.9
Loss of appetite	28.9	28.6
Fever ≥100.4°F (38.0°C)	5.6	5.8

[a] 7 days included day of vaccination and the subsequent 6 days.
[b] Study Q-QIV-022: NCT02242643
[c] Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata lineage.

In children who received a second dose of FLULAVAL® TETRA or FLUZONE® QUADRIVALENT the incidences of adverse events following the second dose were generally lower than those observed after the first dose.

Unsolicited Adverse Events: 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 FLULAVAL® TETRA (N = 1207), FLUZONE® QUADRIVALENT (N = 1217) was 45.5% and 44.1%, respectively. Unsolicited events reported for FLULAVAL® TETRA considered as possibly related to vaccination and occurring in ≥0.1% of subjects included upper respiratory tract infection, cough, diarrhea, nasopharyngitis and otitis media.

Children 3-8 years: Study Q-QIV-006 (Efficacy):
Safety information was collected in an observer-blind, non-influenza vaccine-controlled study evaluating the efficacy of FLULAVAL® TETRA. The study included subjects 3 through 8 years of age who received FLULAVAL® TETRA (N = 2,584) or HAVRIX® (Hepatitis A Vaccine) (N = 2,584). Children with no history of influenza vaccination received 2 doses of FLULAVAL® TETRA or HAVRIX® approximately 28 days apart. Children with a history of influenza vaccination received one dose of FLULAVAL® TETRA or HAVRIX®. In the overall population, 52% were male. The mean age of subjects was 5 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 4).

Table 4: Incidence of Solicited Local and Systemic Adverse Events Within 7 Days[a] of First Vaccination in Children 3 to 8 Years of Age[b] (Total Vaccinated Cohort)

	FLULAVAL® TETRA %	**HAVRIX® %**
	Age Group: 3 to 8 Years	
Local	**N = 2,546**	**N = 2,551**
Pain	39	28
Swelling	1	0.3
Redness	0.4	0.2
	Age Group: 3 to 4 Years	
Systemic	**N = 898**	**N = 895**
Loss of appetite	9	8
Irritability	8	8
Drowsiness	8	7
Fever ≥100.4°F (38.0°C)	4	4
	Age Group: 5 to 8 Years	
Systemic	**N = 1,648**	**N = 1,654**
Muscle aches	12	10
Headache	11	11
Fatigue	8	7
Arthralgia	6	5
Gastrointestinal symptoms[c]	6	6
Shivering	3	3
Fever ≥100.4°F (38.0°C)	3	3

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 Q-QIV-006: NCT01218308.

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

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

Unsolicited Adverse Events: Unsolicited events that occurred within 28 days of any vaccination (day 0-27) were recorded based on spontaneous reports or in response to queries about changes in health status. The incidence of unsolicited adverse events reported was similar among the groups (33% for both FLULAVAL® TETRA and HAVRIX®). Unsolicited events reported for FLULAVAL® TETRA considered as possibly related to vaccination and occurring in ≥0.1% of subjects included injection site pruritus.

Post-Market Adverse Drug Reactions

Immune system disorders
Rare: allergic reactions

As all three of the influenza strains contained in FLUVIRAL® are included in FLULAVAL® TETRA, the following additional adverse events that have been observed for FLUVIRAL® during post-marketing surveillance may occur in patients receiving FLULAVAL® TETRA.

System Organ Class	Adverse Reactions	Frequency
Immune system disorders	anaphylactic reactions and anaphylactoid reactions	Rare
Nervous system disorders	Guillain-Barré syndrome	Rare
Skin and subcutaneous tissue disorders	urticaria, angioedema	Rare

DRUG INTERACTIONS

Drug-Drug Interactions
If FLULAVAL® TETRA 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

FLULAVAL® TETRA 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

FLULAVAL® TETRA 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).

The vaccine presents as 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 1mL 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 FLULAVAL® TETRA 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

FLULAVAL® TETRA provides active immunization against the four influenza virus strains (two A subtypes and two B types) contained in the vaccine.

FLULAVAL® TETRA induces humoral antibodies against the haemagglutinins. These antibodies neutralize influenza viruses.

Specific levels of haemagglutination-inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the HI antibody titers have been used as a measure of vaccine activity. In some human challenge studies, HI antibody titres of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.

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

Pharmacodynamics/Pharmacokinetics

No pharmacokinetic studies have been conducted with FLULAVAL® TETRA 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 change from year to year.

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 vaccine is stable for 12 months.

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

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

This vaccine complies with the World Health Organization (WHO) recommendation (Northern Hemisphere) for the 2016-2017 season. The quadrivalent vaccine contains 2 A strains and 2 B strains.

Each dose of 0.5 mL of FLULAVAL® TETRA contains:

15µg HA - A/California/7/2009 (H1N1)pdm09-like virus (A/California/7/2009 (H1N1) NYMC X-179A)
15µg HA - A/Hong Kong/4801/2014 (H3N2)–like virus (A/Hong Kong/4801/2014 (H3N2) NYMC X-263B)
15µg HA - B/Phuket/3073/2013-like virus (B/Phuket/3073/2013) from the B/Yamagata/16/88 lineage
15µg HA - B/Brisbane/60/2008-like virus (B/Brisbane/60/2008 NIBSC) from the B/Victoria/2/87 lineage

Multi-dose vial presentation

5 mL vial (type I glass) for 10 doses – pack size of 1 and 10.

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 (267 µg), and polysorbate 80 (683 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.

The vial stopper does not contain latex.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

FLULAVAL® TETRA contains four 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 by treatment with ultraviolet light followed by formaldehyde treatment, purified by centrifugation, and disrupted with sodium deoxycholate.

Product Characteristics

FLULAVAL® TETRA is a sterile, opalescent translucent to off-white suspension in a phosphate-buffered saline solution that may sediment slightly. The vaccine has been formulated to contain 60 micrograms (μg) haemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 μg HA of each of the 4 influenza virus strains. Antibiotics are not used in the manufacture of this vaccine.

CLINICAL TRIALS

Study demographics and trial design

The efficacy of the FLULAVAL® TETRA has been demonstrated in children aged 3 to 8 years of age. The immunogenicity and safety of FLULAVAL® TETRA quadrivalent influenza vaccine has been demonstrated in clinical trials involving adults 18 years and older and children aged 6 months to 17 years.

The humoral immune response was assessed in terms of a serum haemagglutinin-inhibiting (HI) antibody titer against each virus strain included in the Q-QIV 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 5: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration	Study subjects[1] (n = number)	Mean age[2] (Range)	Gender[1]
Q-QIV-003	randomized, double-blind, immunogenicity non inferiority and safety	0.5mL, IM (unprimed: 2x0.5mL IM, 28 days apart)	n = 878	8.9 years (3-17 years)	F = 406 M = 472
Q-QIV-006	randomized, observer blind, efficacy and safety	0.5mL, IM (unprimed: 2x0.5mL, IM, 28 days apart)	n = 2376	5.4 years (3-8 years)	F = 1158 M = 1218
Q-QIV-007	randomized, double-blind, immunogenicity non inferiority and safety	0.5mL, IM	n = 1246 ≥18 years	50.0 years (18-97 years)	F = 766 M = 480
Q-QIV-013	randomized, double-blind, immunogenicity and safety	0.5 mL, IM (unprimed, 2x0.5mL IM, 28 days apart)	n = 284	18.2 months (6-35 months)	F = 149 M = 135
Q-QIV-021	randomized, observer-blind, immunogenicity and safety	0.5 mL, IM (unprimed, 2x0.5mL IM, 28 days apart)	n = 143	19.6 months (6-35 months)	F = 67 M = 76
Q-QIV-022	randomized, double-blind, immunogenicity non inferiority and safety	0.5 mL, IM (unprimed, 2x0.5mL IM, 28 days apart)	n = 1013	19.4 months (6-35 months)	F = 462 M = 551

[1] According to Protocol Cohort receiving FLULAVAL® TETRA
[2] Total Vaccinated Cohort receiving FLULAVAL® TETRA

Study results

Efficacy of FLULAVAL® TETRA

Clinical study Q-QIV-006, performed in approximately 2,500 children 3 to 8 years of age, evaluated the efficacy of FLULAVAL® TETRA to prevent laboratory confirmed influenza A and/or B disease presenting as influenza-like illness, compared to a non-influenza vaccine control. Influenza-like illness (ILI) was defined by the presence of an oral or axillary temperature ≥37.8°C in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose or nasal congestion. See table below for results.

Table 6: Attack rates and Vaccine Efficacy against Illness associated with evidence of influenza A and/or B Infection in children 3 to 8 years of age (According to Protocol cohort for efficacy)

			Attack Rates (n/N)[1]	Vaccine Efficacy
	N	n	%	% (CI[2])
Any RT-PCR[3] confirmed influenza cases				
FLULAVAL TETRA	2,379	58	2.4	55.4 (95% CI: 39.1;67.3)
Control	2,398	128	5.3	-
Moderate to severe influenza cases[4]				
FLULAVAL TETRA	2,379	14	0.6	73.1 (97.5% CI: 47.1; 86.3)
Control	2,398	52	2.2	-

[1] n/N: number of case/total number of subjects
[2] CI: Confidence Interval
[3] Reverse Transcriptase Polymerase Chain Reaction
[4] Moderate to severe influenza is defined by RT-PCR-confirmed ILI with fever >39 degree Celsius (39°C), and/or physician-verified shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, croup, or acute otitis media, and/or physician-diagnosed serious extra-pulmonary complication of influenza, including myositis, encephalitis, seizure, and/or myocarditis

Immunogenicity of FLULAVAL® TETRA versus FLUVIRAL®, FLUARIX®, FLUZONE® and FLUZONE® QUADRIVALENT.

Clinical study Q-QIV-007 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.

Clinical study Q-QIV-003 assessed the non-inferiority of FLULAVAL® TETRA versus FLUARIX® for HI GMT at Day 28 and HI seroconversion rate (4-fold rise in reciprocal titer or change from undetectable [< 10] to a reciprocal titer of ≥ 40) in children 3 to 17 years of age. In an open-label, independent arm of this study, the immunogenicity and safety of the vaccine was evaluated in children 6 to 35 months of age.

In both studies, the immune response elicited by FLULAVAL® TETRA against the three strains in common was non-inferior to FLUVIRAL® or FLUARIX®, providing evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine. FLULAVAL® TETRA elicited a superior immune response against the additional B strain included in FLULAVAL® TETRA compared to FLUVIRAL® or FLUARIX®.

Clinical study Q-QIV-022 assessed the non-inferiority of FLULAVAL® TETRA versus FLUZONE® QUADRIVALENT for HI GMT and HI seroconversion rate (4-fold rise in reciprocal titer or change from undetectable [< 10] to a reciprocal titer of ≥ 40) 28 days after the last dose in children 6 to 35 months of age. The immune response elicited by FLULAVAL® TETRA against the four strains was non-inferior to FLUZONE® QUADRIVALENT based on GMT and seroconversion rates. In addition, in two other studies (Q-QIV-013 and Q-QIV-021) in children 6-35 months of age, FLULAVAL® TETRA elicited a superior immune response against the additional B strain included in FLULAVAL® TETRA compared to FLUARIX® or FLUZONE®.

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 FLULAVAL® TETRA and approximately 200 subjects received a single dose of FLUVIRAL®.

Table 7: Post-vaccination GMTs and seroconversion rates from study Q-QIV-007 in adults 18 years of age and older (ATP[1] cohort for analysis of immunogenicity)

Adults 18 years of age and older	**FLULAVAL® TETRA N=1246**	**FLUVIRAL®[2] N=204**
GMT[5] (95% confidence interval)		
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 (95% confidence interval)		
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)[3]	55.2% (52.4;58.0)	48.8% (41.7;55.9)
B (Yamagata)[4]	54.8% (52.0;57.6)	33.3% (26.9;40.3)

[1]ATP: According-to-protocol
[2]Containing A/H1N1, A/H3N2 and B (Victoria lineage)
[3]Recommended strain by WHO during the season 2010-2011
[4]Additional B strain contained in FLULAVAL® TETRA recommended in season 2008-2009
[5]GMT is reported as the absolute value

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

Children 3-17 years of age

In clinical study Q-QIV-003, approximately 1,700 children 3-17 years of age were randomized to receive one or two doses based on prior vaccination status of FLULAVAL® TETRA or FLUARIX®.

Table 8: Post-vaccination GMTs and seroconversion rates from study Q-QIV-003 in children 3 to 17 years of age (ATP[1] cohort for analysis of immunogenicity)

Children 3-17 years of age	**FLULAVAL® TETRA N=878**	**FLUARIX[2] N=871**
GMT[5] (95% confidence interval)		
A/H1N1	362.7 (335.3;392.3)	429.1 (396.5;464.3)
A/H3N2	143.7 (134.2;153.9)	139.6 (130.5;149.3)
B (Victoria)[2]	250.5 (230.8;272.0)	245.4 (226.9;265.4)
B (Yamagata)[3]	512.5 (477.6;549.9)	197.0 (180.7;214.8)
Seroconversion rate (95% confidence interval)		
A/H1N1	84.4% (81.8;86.7)	86.8% (84.3;89.0)
A/H3N2	70.1% (66.9;73.1)	67.8% (64.6;70.9)
B (Victoria)[3]	74.5% (71.5;77.4)	71.5% (68.4;74.5)
B (Yamagata)[4]	75.2% (72.2;78.1)	41.3% (38.0;44.6)

[1]ATP: According-to-protocol
[2]Containing A/H1N1, A/H3N2 and B (Victoria lineage)
[3]Recommended strain by WHO during the season 2010-2011
[4]Additional B strain contained in FLULAVAL® TETRA recommended in season 2008-2009
[5]GMT is reported as the absolute value

Post-vaccination seroprotection rates for FLULAVAL® TETRA in children 3 to 17 years were 96.8% against A/H1N1, 92.9% against A/H3N2, 95.4% against B (Victoria) and 99.0% against B (Yamagata).

Immunogenicity of FLULAVAL® TETRA versus FLUZONE® QUADRIVALENT

Children 6-35 months of age

In clinical study Q-QIV-022, children 6 to 35 months of age who received either one (57.0% of subjects) or two doses (43.0% of subjects) of FLULAVAL® TETRA or FLUZONE® QUADRIVALENT were evaluated.

Table 9: Post-vaccination GMTs and seroconversion rates from study Q-QIV-022 in children 6 to 35 months of age (ATP[1] cohort for analysis of immunogenicity)

Children 6-35 months of age	**FLULAVAL® TETRA N= 1013**	**FLUZONE® QUADRIVALENT N= 1028**
GMT[2] (95% confidence interval)		
A/H1N1	98.8 (90.3;108.2)	84.4 (76.9;92.6)
A/H3N2	97.7 (90.3;105.7)	84.3 (77.6;91.6)
B (Victoria)	55.1 (50.8;59.8)	33.4 (30.6;36.4)
B (Yamagata)	257.5 (240.9;275.3)	164.2 (151.8;177.6)
Seroconversion rate (95% confidence interval)		
A/H1N1	73.7% (70.8;76.4)	67.3% (64.3;70.3)
A/H3N2	76.1% (73.3;78.8)	69.4% (66.4;72.3)
B (Victoria)	64.9% (61.8;67.9)	48.5% (45.3;51.6)
B (Yamagata)	85.5% (83.2-87.7)	73.8% (70.9;76.5)

[1]According-to protocol
[2]GMT is reported as the absolute value

Post-vaccination seroprotection rates for FLULAVAL® TETRA in children 6 to 35 months were 80.4% against A/H1N1, 82.2% against A/H3N2, 66.0% against B (Victoria) and 97.0% against B (Yamagata).

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.

FLULAVAL® TETRA has not been evaluated for carcinogenic or mutagenic potential.

REFERENCES

1. Langley JM, Carmona Martinez A, Chatterjee A, Halperin SA, McNeil S, Reisinger KS, Aggarwal N, Huang LM, Peng CT, Garcia-Sicilia J, Salamanca de la Cueva I, Cabañas F, Treviño-Garza C, Rodríguez-Weber MA, de la O M, Chandrasekaran V, Dewé W, Liu A, Innis BL, Jain VK. (2013). Immunogenicity and Safety of an Inactivated Quadrivalent Influenza Vaccine Candidate: A Phase III Randomized Controlled Trial in Children. The Journal of Infectious Diseases; 208(4):544-53.

PART III: CONSUMER INFORMATION

FLULAVAL® TETRA (2016-2017)
Quadrivalent Influenza Vaccine
Split Virion, Inactivated

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

ABOUT THIS VACCINE

What the vaccine is used for:
FLULAVAL® TETRA is a quadrivalent vaccine for use in adults and children greater than 6 months of age to prevent influenza 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:
FLULAVAL® TETRA 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, FLULAVAL® TETRA 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 2016-2017 season.
Each 0.5mL dose of the vaccine contains 15 micrograms of haemagglutinin, a type of protein that has been purified from killed and split influenza viruses. The four virus strains in this vaccine are:
15µg HA - A/California/7/2009 (H1N1)pdm09-like virus
15µg HA - A/Hong Kong/4801/2014 (H3N2)-like virus
15µg HA - B/Phuket/3073/2013-like virus
15µg HA - B/Brisbane/60/2008-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

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 FLULAVAL® TETRA 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 VACCINE

FLULAVAL® TETRA must not be mixed with any other vaccine in the same syringe. If FLULAVAL® TETRA 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 VACCINE

Usual dose:
One injection of 0.5mL 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, FLULAVAL® TETRA 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
- Joint pain.

Common (may occur with up to 1 in 10 doses)
- Redness and swelling at the injection site
- Shivering
- Fever
- Feeling sick, diarrhea, vomiting, stomach pain

In children, very common side effects are irritability and drowsiness. A common side effect was loss of appetite.

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 FLULAVAL® TETRA, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store in a refrigerator between 2 and 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: 1-866-844-0018
By toll-free fax: 1-866-844-5931
By email: caefi@phac-aspc.gc.ca
At the following website:
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, 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.
7333Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374

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