PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

FLULAVAL TETRA

(2023-2024)

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.
100 Milverton Drive
Mississauga, Ontario
L5R 4H1

Date of Initial Authorization:
Feb 06, 2014

Date of Revision:
Apr 26, 2024

Submission Control Number: 281970

RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.4 Administration	MM/YYYY

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

1.1 Pediatrics

Pediatrics (6 months - 17 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of FLULAVAL TETRA in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use.

2 CONTRAINDICATIONS

- FLULAVAL TETRA should not be administered to subjects with known history of hypersensitivity to any component of the vaccine or following a previous dose of any influenza vaccine produced in eggs. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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.

4 DOSAGE AND ADMINISTRATION

4.2 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.

4.4 Administration

For intramuscular use only. Do not inject intravascularly.

The preferred site for injection is the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in children and adults. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

Instructions for use:

FLULAVAL TETRA should not be mixed with other vaccines/medicinal products (see 9.4 Drug-Drug Interactions, Use with Other Vaccines).

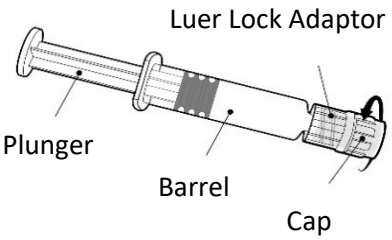
The vaccine presents as an opalescent translucent to off-white suspension, that may sediment slightly.

The vial/syringe 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.

For the multidose-vial presentation, each vaccine dose of 0.5 mL is withdrawn into a 1 mL syringe for injection and administered intramuscularly. It is recommended to equip the syringe with a needle gauge not larger than 23-G.

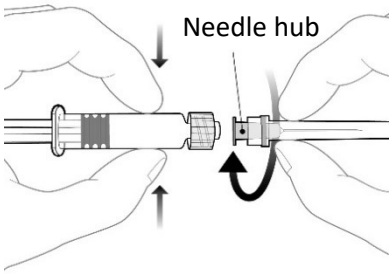
Between uses, the multidose vial should be stored in a refrigerator (2°C - 8°C).

Instructions for the pre-filled syringe



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

5 OVERDOSAGE

Insufficient data are available.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength /Composition	Non-medicinal Ingredients
Intramuscular	Suspension for Injection Each 0.5 mL dose contains 15 μg of influenza virus haemagglutinin/strain for each strain listed below. Available in multidose vial and single-dose pre-filled syringe*	Egg proteins, ethanol, formaldehyde, phosphate buffered saline, polysorbate 80, sodium deoxycholate, α-tocopheryl hydrogen succinate, sucrose. Thimerosal preservative in the multidose vial presentation only.

*The pre-filled syringe presentation is not available for the 2023-2024 season.

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 2023-2024 season. The quadrivalent vaccine contains 2 A strains and 2 B strains.

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

15 μg HA - A/Victoria/4897/2022 (H1N1)pdm09-like virus (A/Victoria/4897/2022 IVR-238)

15 μg HA - A/Darwin/9/2021 (H3N2)-like virus (A/Darwin/9/2021 IVR-228)

15 μg HA - B/Phuket/3073/2013-like virus (B/Phuket/3073/2013) from the B/Yamagata/16/88 lineage

15 μg HA - B/Austria/1359417/2021-like virus (B/Austria/1359417/2021 BVR-26) from the B/Victoria/2/87 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 (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.

The multidose vial presentation contains thimerosal, a mercury derivative, added as a preservative.
Each 0.5 mL dose contains 50 μg thimerosal (<25 μg mercury).

The single-dose pre-filled syringe presentation does not contain thimerosal or any other preservative.

Antibiotics are not used in the manufacture of this vaccine.

Multidose vial presentation:

6 mL vial (type I glass) containing 5 mL of vaccine (10 doses of 0.5 mL).

Pack size of 1 or 10 vials.

The vial stopper does not contain latex.

Single-dose pre-filled syringe presentation:

0.5 mL single-dose pre-filled syringe (type I glass) with Luer Lock.

Pack size of 1 or 10 syringes (packaged without needles).

The tip cap and plunger stopper of the pre-filled syringe do not contain latex.

This presentation is not currently available.

7 WARNINGS AND PRECAUTIONS

General

FLULAVAL TETRA should under no circumstances be administered intravascularly.

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.

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.

Skin

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.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of FLULAVAL TETRA when administered to pregnant women has not been evaluated in clinical trials. A systematic literature review on inactivated influenza vaccines do not indicate an increased risk of adverse pregnancy outcomes. Animal studies with FLULAVAL TETRA do not indicate direct or indirect harmful effects with respect to reproductive and developmental toxicity. The FLULAVAL TETRA vaccine may be administered to pregnant women following an assessment of the risks and benefits.

7.1.2 Breast-feeding

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.

8 ADVERSE REACTIONS

8.1 Adverse 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%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

Adults: 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 2 - 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.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

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 3).

Table 3 - 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 7 days (Table 4).

Table 4 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 5).

Table 5 - 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.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of FLULAVAL TETRA or FLULAVAL (trivalent influenza vaccine). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Blood and Lymphatic System Disorders
Lymphadenopathy.

Eye Disorders
Eye pain, photophobia.

Gastrointestinal Disorders
Dysphagia, vomiting.

General Disorders and Administration Site Conditions
Chest pain, injection site inflammation, asthenia, injection site rash, influenza-like symptoms, abnormal gait, injection site bruising, injection site sterile abscess.

Immune System Disorders
Allergic reactions including anaphylaxis, angioedema.

Infections and Infestations
Rhinitis, laryngitis, cellulitis.

Musculoskeletal and Connective Tissue Disorders
Muscle weakness, arthritis.

Nervous System Disorders
Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor, somnolence, syncope, Guillain-Barré syndrome, convulsions/seizures, facial or cranial nerve paralysis, encephalopathy, limb paralysis.

Psychiatric Disorders
Insomnia.

Respiratory, Thoracic, and Mediastinal Disorders
Dyspnea, dysphonia, bronchospasm, throat tightness.

Skin and Subcutaneous Tissue Disorders
Urticaria, localized or generalized rash, pruritus, sweating.

Vascular Disorders
Flushing, pallor.

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

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

9.4 Drug-Drug Interactions

Use with Other Vaccines

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.

9.7 Drug-Laboratory Test 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).

10 CLINICAL PHARMACOLOGY

10.1 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.

10.3 Pharmacokinetics

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.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2°C - 8°C).

Do not freeze.

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

The vaccine in multidose vials is stable for 13 months.

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

The vaccine in pre-filled syringes is stable for 12 months.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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 6 - Summary of patient demographics for clinical trials in specific indication

Study #	Study design	Dosage, route of administration and duration	Study subjects[1] (n)	Mean age[2] (Range)	Sex[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

14.2 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 7 for results.

Table 7 - 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)

	N	n	Attack Rates (n/N)[1] %	Vaccine Efficacy % (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

14.4 Immunogenicity

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 8 - 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)[3]	177.7 (167.8; 188.1)	135.9 (118.1; 156.5)
B (Yamagata)[4]	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 9 - 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)[3]	250.5 (230.8; 272.0)	245.4 (226.9; 265.4)
B (Yamagata)[4]	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 10 - 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]ATP: 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).

16 NON-CLINICAL TOXICOLOGY

General 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.

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

FLULAVAL TETRA (2023-2024)

Quadrivalent Influenza Vaccine Split Virion, Inactivated

Read this carefully before you receive **FLULAVAL TETRA**. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FLULAVAL TETRA.**

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.

What is FLULAVAL TETRA 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.

How does FLULAVAL TETRA work?

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.

What are the ingredients in FLULAVAL TETRA?

Medicinal ingredients:

This vaccine complies with the World Health Organization (WHO) recommendation (Northern Hemisphere) for the 2023-2024 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 four virus strains in this vaccine are:

- 15 µg HA - A/Victoria/4897/2022 (H1N1)pdm09-like virus
- 15 µg HA - A/Darwin/9/2021 (H3N2)-like virus
- 15 µg HA - B/Phuket/3073/2013-like virus
- 15 µg HA - B/Austria/1359417/2021-like virus.

Non-medicinal ingredients:

Phosphate buffered saline, polysorbate 80, α-tocopheryl hydrogen succinate. Trace amounts of egg proteins, ethanol, formaldehyde, sodium deoxycholate, and sucrose.

The multidose vial presentation contains thimerosal as a preservative.

The single-dose pre-filled syringe presentation does not contain thimerosal or any other preservative.

FLULAVAL TETRA comes in the following dosage forms:

- multidose vial of 5 mL (10 doses of 0.5 mL each)
- single-dose pre-filled syringe of 0.5 mL

Do not use FLULAVAL TETRA if:

- you had a severe allergic reaction (e.g., anaphylaxis) to any ingredient in the vaccine, including egg protein, or following a previous dose of any influenza vaccine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FLULAVAL TETRA. Talk about any health conditions or problems you may have, including 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.
- have a bleeding problem or bruise easily.
- have a weakened immune system due to HIV infection or due to medicines that suppress the immune system.
- have fainted before or after a previous injection.
- are taking any other medicines or you have recently received any other vaccine.
- have had Guillain-Barré syndrome (GBS) within 6 weeks of receiving a previous influenza vaccination.
- are pregnant or breast-feeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FLULAVAL TETRA:

- 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.

How to take FLULAVAL TETRA:

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:

If you think you, or a person you are caring for, have taken too much FLULAVAL TETRA contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using FLULAVAL TETRA?

These are not all the possible side effects you may have when taking FLULAVAL TETRA. If you experience any side effects not listed here, tell your healthcare professional.

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 healthcare professional 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.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and GlaxoSmithKline Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Keep out of reach and sight of children.

Store in a refrigerator between 2 and 8°C.

Do not freeze.

If you want more information about FLULAVAL TETRA

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.gsk.ca, or by calling 1-800-387-7374.

This leaflet was prepared by GlaxoSmithKline Inc.
Last Revised: