PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

AFLURIA® TETRA

Quadrivalent Inactivated Influenza Vaccine (Split Virion)

20XX/20XX Strains:
A/Official strain (H1N1)-like virus
A/Official strain (H3N2)-like virus
B/Official strain-like virus
B/Official strain-like virus

Suspension for Injection

Active Immunizing Agent for the Prevention of Influenza

ATC Code: J07B B

Sponsor:
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Submission Control No: 203436 Date of Approval: February 22, 2018

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AFLURIA® TETRA is indicated for the active immunization of adults and children aged 5 years or older 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 the published Statement on Seasonal Influenza Vaccine for the current season.

1.1 Pediatrics

Pediatrics (5 to <18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of AFLURIA® TETRA in pediatric patients has been established in children 5 years of age and older; therefore, Health Canada has authorized an indication for pediatric use. (See *Sections 7.1.3 Pediatrics, 8.3 Clinical Trial Adverse Reactions (Pediatrics) and 13.2 Study Results*).

Clinical data have not been evaluated for use of AFLURIA® TETRA in children under 5 years of age.

2 CONTRAINDICATIONS

AFLURIA® TETRA is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, or to a previous dose of any influenza vaccine. For a complete listing, see Section 5 *Dosage Forms, Strengths, Composition and Packaging*.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose

The recommended dosage schedule for AFLURIA® TETRA is presented in Table 1.

Table 1: AFLURIA® TETRA Recommended Dosage, by Age Group

Age Group	Dose	Number of Doses
5 to < 9 years	0.5 mL	1 or 2[a]
≥ 9 years	0.5 mL	1

[a] Previously unvaccinated children 5 to < 9 years of age should be given 2 doses at least 4 weeks apart.

3.2 Administration

Vaccination should be carried out by intramuscular injection, preferably into the deltoid muscle of the upper arm.

The vaccine is a clear to slightly opaque liquid with some sediment that resuspends upon shaking.

Immediately before use, shake the syringe or vial thoroughly and inspect visually. Do not use if particles remain or if the vaccine is discoloured.

When using the multi-dose vial, the vial should be thoroughly shaken and inspected prior to withdrawing each dose. It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss.

Please refer to the Canadian Immunization Guide, Public Health Agency of Canada, for general information regarding vaccine administration practices.

4 OVERDOSAGE

No specific information is available for overdose with AFLURIA® TETRA.

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

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
IM	Suspension for IM injection Each 0.5 mL dose contains 15 µg HA of each influenza virus strain listed below	-Calcium chloride -Dibasic sodium phosphate (anhydrous) -Monobasic potassium phosphate -Monobasic sodium phosphate -Potassium chloride -Sodium chloride -Thimerosal* -Water for injection Each dose may also contain sodium taurodeoxycholate, ovalbumin (egg proteins) and trace amounts of beta-propiolactone, neomycin sulfate, polymyxin B sulfate and sucrose.

* Multi-dose vials only.

For the 20XX/20XX Northern Hemisphere Influenza Season, AFLURIA® TETRA contains the following strains:

- A/Official strain (H1N1)-like virus (A/actual strain (H1N1)
- A/Official strain (H3N2)-like virus (A/actual strain (H3N2)
- B/Official strain-like virus (B/actual strain)
- B/Official strain-like virus (B/actual strain)

Packaging

Needle-Free Syringe
Single-dose pre-filled type 1 glass syringe.

The syringe barrel is designed with a Luer-Lok™ adaptor to allow the attachment of a commercially available needle prior to administration. The syringe and stopper components are latex-free. AFLURIA® TETRA is considered safe for use in persons with latex allergies.

The pre-filled syringes are packed in molded plastic trays with peel-off cover; the trays are packed in water resistant cartons.

Each carton contains 10 single dose syringes in two trays, and one package insert.

Multi-dose Vial
Multi-dose type 1 glass vial.

The multi-dose vial is closed with a stopper and sealed with an aluminium crimp and plastic

tear-away cap. Once removed, the cap cannot be re-affixed to the vial. The vial stopper does not contain latex. AFLURIA® TETRA is considered safe for use in persons with latex allergies.

One vial is packed into a water resistant carton, with the approved package insert.

6 DESCRIPTION

AFLURIA® TETRA is a sterile, clear to slightly opaque liquid with some sediment that resuspends upon shaking to form a homogeneous suspension.

AFLURIA® TETRA is an inactivated influenza vaccine prepared from virus grown in the allantoic cavity of embryonated chicken eggs, purified by zonal centrifugation, inactivated by beta-propiolactone and disrupted by sodium taurodeoxycholate.

This vaccine complies with the recommendations of the World Health Organization (WHO) and the National Advisory Committee on Immunization (NACI) for the Northern Hemisphere 20XX - 20XX season.

7 WARNINGS AND PRECAUTIONS

General

AFLURIA® TETRA should under no circumstances be administered intravascularly.

The pre-filled syringes are single use only.

Prior to administration of any dose of AFLURIA® TETRA, the vaccine recipient should be asked about their personal history, family history and recent health status, including immunization history, current health status, main allergies and any adverse event associated with previous immunizations.

Before the injection of any biological, the person responsible for administration should take all precautions known for the prevention of allergic or any other reactions. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine.

Immunization with AFLURIA® TETRA should be postponed in patients with febrile illness or acute infections.

As with any vaccine, immunization with AFLURIA® TETRA may not protect 100% of individuals against influenza disease.

Hematologic
As with other intramuscular injections, administration of AFLURIA® TETRA requires careful consideration in patients with clinically significant bleeding disorders.

Immune
In immunocompromised patients the antibody response may be lower.

Neurologic
If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give AFLURIA® TETRA should be based on careful consideration of the potential benefits and risks.

Sexual Health
Fertility
AFLURIA® TETRA has not been evaluated for possible effect on fertility.

A reproductive study of female rats vaccinated with a similar trivalent influenza vaccine manufactured by Seqirus revealed no impairment of fertility.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data for AFLURIA® TETRA administered to pregnant women to inform vaccine-associated risks in pregnancy. Available data on a similar trivalent influenza vaccine manufactured by Seqirus administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

An animal reproductive toxicity study has been conducted with a similar trivalent influenza vaccine manufactured by Seqirus. This study did not demonstrate any maternal or fetal developmental toxicity (see Section 14: *Non-clinical Toxicology*).

NACI considers influenza vaccination safe during pregnancy. NACI recommends influenza vaccination in pregnant women with high-risk conditions at any stage during pregnancy.

7.1.2 Breast-feeding

The safety and effectiveness of AFLURIA® TETRA has not been established in nursing mothers.

7.1.3 Pediatrics

Pediatrics (< 5 years)*:* No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in children less than 5 years of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of AFLURIA® TETRA has been studied in two Phase 3 clinical studies; one study in adults aged 18 years and above (N = 1721) and one in children aged 5 to < 18 years (N = 1621).

In adults 18 to <65 years, the most commonly reported injection-site adverse reaction observed in clinical studies with AFLURIA® TETRA was pain (≥ 40%). The most common systemic

adverse events observed were myalgia and headache (≥ 20%). In adults ≥ 65 years of age, the most commonly reported injection-site adverse reaction observed in clinical studies with AFLURIA® TETRA was pain (≥ 20%). The most common systemic adverse event observed was myalgia (≥10%).

In children 5 to < 18 years of age, the most commonly reported injection-site adverse reactions observed in clinical studies with AFLURIA® TETRA were pain (51.4%), redness (17.1%), and swelling (13.8%). The most common systemic adverse events were headache (15.5%) and myalgia (13.1%).

8.2 Clinical Trial Adverse Reactions (Adults)

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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical safety data for AFLURIA® TETRA in adults have been collected in one clinical trial, **Study CSLCT-QIV-13-01**, a randomized, double-blind, active-controlled trial conducted in the US in 3449 subjects aged 18 years and older. Subjects in the safety population received one dose of either AFLURIA® TETRA (N=1721) or one of two formulations of comparator trivalent influenza vaccine (TIV-1 N=864 or TIV-2 N=864) each containing an influenza type B virus that corresponded to one of the two B viruses in AFLURIA® TETRA (a type B virus of the Yamagata lineage or a type B virus of the Victoria lineage), respectively. The mean age of the population was 58 years, 57% were female, and racial groups consisted of 82% White, 16% Black, and 2% other; 5% of subjects were Hispanic/Latino. The age sub-groups were 18 to < 65 years and 65 years and older with mean ages of 43 years and 73 years, respectively. (see Section 13: *Clinical Trials*).

Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Table 3). Injection site cellulitis, cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump), and Grade 3 swelling/lump were monitored for 28 days post-vaccination. Unsolicited adverse events were collected for 28 days post-vaccination. Serious adverse events (SAEs), including deaths, were collected for 180 days post-vaccination.

Table 3: ***Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse Reaction or Systemic Adverse Events within 7 days after Administration of AFLURIA® TETRA or TIV (Study CSLCT-QIV-13-01)***

	Percentage (%)[a] of Subjects in each Age Cohort Reporting an Event											
	Subjects 18 to < 65 years						Subjects ≥ 65 years					
	AFLURIA® TETRA N= 854 [b]		TIV-1 N= 428 [b]		TIV-2 N= 430 [b]		AFLURIA® TETRA N= 867 [b]		TIV-1 N= 436 [b]		TIV-2 N= 434 [b]	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions [c]												
Pain	47.9	0.7	43.7	1.4	50.7	1.2	24.6	0.1	22.7	0	21.0	0.2
Swelling/Lump	3.7	0.1	2.3	0	3.5	0.2	3.2	0.5	1.8	0	1.6	0
Redness	2.9	0	2.8	0	2.8	0	4.2	0.3	2.1	0	2.5	0.2
Systemic Adverse Events [d]												
Myalgia (muscle ache)	25.5	1.9	23.4	1.4	24.2	1.2	12.7	0.3	14.0	0.7	12.2	0.5
Headache	21.7	1.7	15.2	0.9	19.1	1.2	8.4	0	7.1	0.2	7.8	0.7
Malaise	8.9	0.7	9.1	0	9.3	0.7	4.4	0.5	5.0	0.2	5.1	0.2
Nausea	6.9	0.6	7.7	0.5	6.3	1.2	1.6	0	1.8	0	2.1	0.2
Chills	4.8	0.6	4.4	0.2	4.7	0.5	2.0	0	2.1	0.5	1.4	0.2
Vomiting	1.5	0.4	0.9	0	2.3	0.7	0.5	0.1	0	0	0.7	0.2
Fever	1.1	0.4	0.9	0	0.5	0	0.2	0	0.9	0	0.5	0.2

Abbreviations: Gr 3, Grade 3; TIV-1, US licensed 2014-2015 Afluria® TIV; TIV-2, TIV with the alternate B strain

[a] Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by study vaccine group based on the number of subjects contributing any follow up safety information for at least one data value of an individual sign/symptom.

[b] N = number of subjects in the Safety Population for each study vaccine group.

[c] Local adverse reactions: Grade 3 pain is that which prevents daily activity; Swelling/Lump and redness: any = ≥ 20mm diameter, Grade 3 = ≥ 100mm diameter.

[d] Systemic adverse events: Fever: any = ≥ 38.0°C, Grade 3 = ≥ 39.0°C; Grade 3 for all other adverse events is that which prevents daily activity.

No subject experienced a cellulitis-like reaction or cellulitis at the injection site in any of the three vaccine groups during the study.

In CSLCT-QIV-13-01, headache (3.8 %) was the most commonly reported unsolicited adverse event in subjects ≥ 18 years of age administered AFLURIA® TETRA. Other commonly reported unsolicited adverse events (reported by ≥ 1% of subjects) were oropharyngeal pain (1.8%), back pain (1.5%), diarrhoea (1.3%) and rhinorrhoea (1.0%).

For subjects 18 to < 65 years receiving AFLURIA® TETRA, commonly reported unsolicited adverse events were headache (5.3%), oropharyngeal pain (2.5%), back pain (1.9%), diarrhoea (1.6%), cough (1.3%) and nausea (1.1%).

For subjects > 65 years, commonly reported unsolicited adverse events were headache (2.3%), rhinorrhoea (1.3%), oropharyngeal pain (1.2%), and back pain (1.2%).

In the 180 days following vaccination, 2.3%, 1.6%, and 1.5% of all subjects who received AFLURIA® TETRA, TIV-1, and TIV-2, respectively, experienced SAEs, including six deaths, five in the AFLURIA® TETRA group and one in the TIV-2 group. The majority of SAEs occurred after Study Day 28 and in subjects ≥65 years of age who had co-morbid illnesses. No SAEs or deaths appeared related to the study vaccines.

8.3 Clinical Trial Adverse Reactions (Pediatrics)

Clinical safety data for AFLURIA® TETRA in children and adolescents have been collected in one clinical trial, **Study CSLCT-QIV-13-02**, a randomized, double-blind, comparator-controlled trial conducted in the US in 2278 subjects aged 5 to less than 18 years. Subjects in the safety population (N=2252) received either AFLURIA® TETRA (N=1692) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=560). Study subjects were scheduled to receive either a single vaccination or two vaccinations 28 days apart based on their previous vaccination history. Subjects were stratified into one of two age cohorts of 5 to less than 9 years or 9 to less than 18 years (51.2% and 48.8% of the study population, respectively). The mean age of the population was 9.5 years, 52.1% were male, and racial groups consisted of 73.3% White, 20.7% Black, 0.8% Asian, 0.3% American Indian/Native American, and 0.7% Native Hawaiian/Pacific Islander; 23.8% of subjects were Hispanic/Latino(see Section 13: *Clinical Trials*).

Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Table 4). Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects were instructed to report and return to the clinic within 24 hours in the event of a cellulitis-like reaction. Unsolicited adverse events were collected for 28 days post-vaccination. SAEs, including deaths, were collected for 180 days post-vaccination.

Table 4: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA® TETRA or Comparator QIV, Irrespective of Causality (Study CSLCT-QIV-13-02)

	Percentage (%) [a] of Subjects in each Age Cohort Reporting an Event							
	Subjects 5 to < 9 years				Subjects 9 to < 18 years			
	AFLURIA® TETRA N= 829 [b]		Comparator QIV N= 274 [b]		AFLURIA® TETRA N= 792 [b]		Comparator QIV N= 261 [b]	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions [c]								
Pain	51.3	0.8	49.6	0.7	51.5	0.3	45.2	0.4
Redness	19.4	3.5	18.6	1.8	14.8	1.9	16.1	1.9
Swelling/Lump	15.3	3.4	12.4	2.2	12.2	2.0	10.7	1.9
Systemic Adverse Events [d]								
Headache	12.3	0.1	10.6	0.4	18.8	0.4	14.6	0.4
Myalgia	9.8	0.1	11.3	0.4	16.7	0.3	11.1	0.4
Malaise and Fatigue	8.8	0.4	5.8	0	10.0	0.4	7.7	0
Nausea	7.1	0.1	8.4	0	7.7	0	8.0	0
Diarrhea	5.2	0	3.6	0	5.4	0	4.2	0
Fever	4.5	1.2	3.6	0.7	2.1	0.5	0.8	0
Vomiting	2.4	0.2	4.4	0	1.8	0	2.3	0

Abbreviations: Gr 3, Grade 3; Comparator, Comparator quadrivalent influenza vaccine (Fluarix® Quadrivalent [GlaxoSmithKline Biologicals])

[a] Percent (%) is derived from the number of subjects that reported the event divided by the Solicited Safety Population in each vaccine group and age cohort.

[b] N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data) for each study vaccine group. Solicited Safety Population was the same for each event.

[c] Local adverse reactions: Grade 3 pain is that which prevents daily activity; Swelling/Lump and redness: any = ≥ 0mm diameter, Grade 3 = ≥ 30mm diameter.

[d] Systemic adverse events: Fever: any = ≥ 38.0°C, Grade 3 = ≥ 39.0°C; Grade 3 for all other adverse events is that which prevents daily activity.

One subject experienced a cellulitis-like reaction (defined as concurrent severe pain, redness and swelling) at the injection site after vaccination with AFLURIA® TETRA.

In CSLCT-QIV-13-02, cough (2.1%) was the most commonly reported unsolicited adverse event in subjects 5 to <18 years of age administered AFLURIA® TETRA. Other commonly reported unsolicited adverse events (reported by ≥ 1% of subjects) were oropharyngeal pain (1.3%), pyrexia (1.3%) and upper respiratory tract infection (1.1%).

The most commonly reported unsolicited adverse events among subjects who received AFLURIA® TETRA in ages 5 to < 9 years following the first or second dose included cough (2.8%), pyrexia (2.1%), headache (1.2%), rhinorrhea (1.2%), upper respiratory tract infection (1.2%), influenza-like illness (1.0%), and oropharyngeal pain (1.0%).

For subjects ages 9 to < 18 years who received AFLURIA® TETRA, the most common unsolicited adverse events included oropharyngeal pain (1.6%), cough (1.3%), and upper respiratory tract infection (1.0%).

No deaths were reported in pediatric study CSLCT-QIV-13-02. In the 180 days following vaccinations, AFLURIA® TETRA and comparator vaccine recipients experienced similar rates of SAEs. None of the SAEs appeared related to the study vaccines except for one case of influenza B infection (considered a vaccine failure) in an AFLURIA® TETRA recipient.

8.4 Post-Market Adverse Reactions

Administration of Seqirus' 2010 Southern Hemisphere trivalent influenza vaccine (AFLURIA® TIV, manufactured by CSL, now Seqirus Pty Ltd) was associated with increased rates of fever and febrile convulsions, predominantly in children below the age of 5 years as compared to previous years. Febrile events were also observed in children 5 to < 9 years of age.

Following a comprehensive investigation into the 2010 Southern Hemisphere adverse events, Seqirus has modified the manufacturing conditions. A clinical program has subsequently been conducted with AFLURIA® TETRA in adults and children. Fever rates in children 5 to < 9 years of age for AFLURIA® TETRA in Study CSLCT-QIV-13-02 were lower than those observed in several clinical studies for Afluria TIV conducted prior to 2010 (see Sections 8.2 and 8.3). The results indicate that the safety profile of AFLURIA® TETRA in children 5 years of age and older is similar to a U.S.-licensed comparator vaccine.

There are limited post-marketing data available for AFLURIA® TETRA. The AFLURIA® TETRA formulation is based on Seqirus' trivalent influenza vaccine (AFLURIA® TIV), with the exception of an additional B influenza strain. The adverse events spontaneously reported during post approval use of AFLURIA®TIV are presented below.

Blood and Lymphatic System Disorders
Thrombocytopenia

Immune System Disorders
Allergic or immediate hypersensitivity reactions including anaphylactic shock

Nervous System Disorders
Neuralgia, paresthesia and convulsions, encephalomyelitis, neuritis or neuropathy and Guillain-Barré syndrome

Vascular Disorders
Vasculitis which may be associated with transient renal involvement

Skin and Subcutaneous tissue disorders
Pruritus, urticaria and rash

General Disorders and Administration Site Conditions
Cellulitis and large injection site swelling. Influenza-like illness

9 DRUG INTERACTIONS

9.1 Overview

No interaction studies have been performed on interaction between influenza vaccines in general and other vaccines or medications.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977 antigenic variants of influenza A (H1N1 and H3N2) and influenza B viruses have been in global circulation. Since 2001, two distinct lineages of influenza B (Victoria and Yamagata lineages) have co-circulated worldwide. Specific levels of hemagglutination inhibition (HI) antibody titers post-vaccination with inactivated influenza vaccine have not been correlated with protection from influenza virus. In some human studies, antibody titers of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects.

Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual change to one or more new strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the HA of four strains (i.e., typically two type A and two type B) representing the influenza viruses likely to be circulating during the upcoming winter.

10.2 Pharmacodynamics

Seroprotection is generally obtained within 2 to 3 weeks.

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

11 STORAGE, STABILITY AND DISPOSAL

Temperature:
Store *refrigerated* at 2-8°C.
DO NOT FREEZE. If frozen, do not use.

***Light*:**
Store in original package to protect from light.

Other:
The shelf-life of the vaccine is 12 months.

Do not use AFLURIA® TETRA beyond the expiration date printed on the label.

Any remaining contents in the single-use syringe should be discarded.

Between uses, return the multi-dose vial to the recommended storage conditions.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Inactivated Influenza Vaccine (Split Virion)

Physicochemical properties: The vaccine is standardized according to the World Health Organization (WHO) and NACI requirements for the [YEAR - YEAR] influenza season and is formulated to contain 60 µg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 µg HA for each of the four influenza strains recommended for the [YEAR – YEAR] Northern Hemisphere influenza season.

Product Characteristics

AFLURIA® TETRA is a sterile, clear to slightly opaque liquid with some sediment that resuspends upon shaking to form a homogeneous suspension.

AFLURIA® TETRA is prepared from virus grown in the allantoic cavity of embryonated chicken eggs, purified by zonal centrifugation, inactivated by beta-propiolactone and disrupted by sodium taurodeoxycholate.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

The immunogenicity and safety of AFLURIA® TETRA has been studied in two Phase 3 clinical studies; one study in adults aged 18 years and above (Study CSLCT-QIV-13-01) and one in children aged 5 to < 18 years (Study CSLCT-QIV-13-02).

Table 5 - Summary of patient demographics for clinical trials with AFLURIA® TETRA

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
CSLCT-QIV-13-01	Phase 3, Randomised, Double-Blinded, Multicenter, Comparator Controlled study to demonstrate Immunogenicity, Non-Inferiority, Safety and Tolerability.	0.5 mL dose, IM	N = 3484	58 years (18 – 102 years)	M = 43% F = 57%
CSLCT-QIV-13-02	Phase 3, Randomised, Observer-Blinded, Comparator Controlled study to demonstrate Immunogenicity, Non-Inferiority, Safety and Tolerability	0.5 mL dose, IM (unprimed subjects 2 x 0.5 mL dose, IM injection, 28 days apart).	N = 2278	9.5 years (5 – 17 years)	M = 52% F = 48%

CSLCT-QIV-13-01 was a randomised, double-blind, active comparator-controlled trial conducted in the US in adults aged 18 years and older. Subjects received one dose of either QIV (N=1691) or one of two formulations of comparator trivalent influenza vaccine (TIV-1 N=854 or TIV-2 N=850), each containing an influenza type B virus that corresponded to one of the two B viruses in QIV (a type B virus of the Yamagata lineage (TIV-1) or a type B virus of the Victoria lineage (TIV-2)), respectively and the same influenza A subtype viruses. The comparator TIV was licensed in the US and manufactured by Seqirus using a similar process to AFLURIA® TETRA. The treatment randomization ratio was 2:1:1 (QIV:TIV-1:TIV-2). The age sub-groups were 18 to < 65 years and ≥ 65 years with mean ages of 43 years and 73 years, respectively. Post-vaccination immunogenicity was evaluated on sera obtained 21 days after administration of a single dose of QIV or TIV.

The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers) and the difference in seroconversion rates for each vaccine strain, 21 days after vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (TIV/QIV) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (TIV minus QIV) did not exceed 10% for each strain.

CSLCT-QIV-13-02 was a randomised, observer-blinded, comparator-controlled trial conducted in the US in children 5 to < 18 years of age. Subjects received either one or two doses of either QIV (N=1605) or a US-licensed comparator QIV (N=528, manufactured by another company) in a 3:1 randomisation treatment schedule. Subjects 5 to < 9 years of age were eligible to receive a second dose at least 28 days after the first dose depending on their influenza vaccination history. Approximately 25% of subjects in each treatment group in the 5 to < 9 years of age sub-group received two vaccine doses. Post-vaccination immunogenicity was evaluated by HI assay on sera obtained 28 days after the last vaccination dose. Baseline serology prior to vaccination was also collected for HI assessment.

The co-primary endpoints were HI Geometric Mean Titers (GMT) (adjusted for baseline HI titers and other covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (Comparator QIV/QIV) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator QIV minus QIV) did not exceed 10% for each strain.

13.2 Study Results

Adults:

Serum HI antibody responses to QIV were non-inferior to both TIVs for all influenza strains, for subjects 18 years of age and older. Additionally, non-inferiority was demonstrated for both endpoints in both age sub-groups, adults aged 18 to < 65 years and ≥ 65 years (Table 6), for all strains. Antibody responses were lower in adults aged ≥ 65 years. Superiority of the immune response to each of the influenza B strains contained in QIV was shown relative to the antibody response after vaccination with TIV formulations not containing that B lineage strain for subjects 18 years of age and older. Superiority against the alternate B strain was also demonstrated for each of the influenza B strains in both age sub-groups; 18 to < 65 years and ≥ 65 years. Post-hoc analyses of immunogenicity by gender did not demonstrate significant differences between males and females. The study population was not sufficiently diverse to assess differences between races or ethnicities.

Table 6: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA® TETRA Relative to Trivalent Influenza Vaccine (TIV) by Age Cohort (Study CSLCT-QIV-13-01) (Per Protocol Population)

	Post-vaccination GMT[a]		GMT Ratio	Seroconversion % [b]		Difference	Met both pre-defined non-inferiority criteria? [c]
Strain	AFLURIA® TETRA	Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)	Pooled TIV or TIV-1 or TIV-2 over AFLURIA® TETRA (95% CI)	AFLURIA® TETRA N=1691	Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)	Pooled TIV or TIV-1 or TIV-2 minus AFLURIA® TETRA (95% CI)	
18 to < 64 years	**AFLURIA® TETRA N=835, Pooled TIV N=845, TIV-1 N=424, TIV-2 N=421**						
A/H1N1	432.7	402.8	0.93 [d] (0.85, 1.02)	51.3	49.1	-2.1 [g] (-6.9, 2.7)	Yes
A/H3N2	569.1	515.1	0.91 [d] (0.83, 0.99)	56.3	51.7	-4.6 [g] (-9.4, 0.2)	Yes
B/Yamagata	92.3	79.3	0.86 [e] (0.76, 0.97)	45.7	41.3	-4.5 [h] (-10.3, 1.4)	Yes
B/Victoria	110.7	95.2	0.86 [f] (0.76, 0.98)	57.6	53.0	-4.6 [i] (-10.5, 1.2)	Yes
≥ 65 years	**AFLURIA® TETRA N=856, Pooled TIV N=859, TIV-1 N=430, TIV-2 N=429**						
A/H1N1	211.4	199.8	0.95 [d] (0.88, 1.02)	26.6	26.4	-0.2 [g] (-5.0, 4.5)	Yes
A/H3N2	419.5	400.0	0.95 [d] (0.89, 1.02)	25.9	27.0	1.1 [g] (-3.7, 5.8)	Yes
B/Yamagata	43.3	39.1	0.90 [c] (0.84, 0.97)	16.6	14.4	-2.2 [h] (-8.0, 3.6)	Yes
B/Victoria	66.1	68.4	1.03 [f] (0.94, 1.14)	23.5	24.7	1.2 [i] (-4.6, 7.0)	Yes

Abbreviations: CI, confidence interval; GMT, geometric mean titer;;TIV-1, US licensed 2014-2015 Afluria® TIV; TIV-2, TIV with the alternate B strain

[a] GMT ratio was computed after fitting a multi-variable model on the post-vaccination titers including sex, vaccination history, pre-vaccination HI titers and other factors.

[b] Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥ 1:10 or an increase in titer from < 1:10 to ≥ 1:40.

[c] The non-inferiority (NI) criteria for the GMT ratio: upper bound of 2-sided 95% CI on the ratio of Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)/AFLURIA® TETRA. GMT should not exceed 1.5. NI criteria for the SCR difference: upper bound of 2-sided 95% CI on the difference between SCR Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria) minus AFLURIA® TETRA should not exceed 10%.

[d] Pooled TIV/AFLURIA® TETRA

[e] TIV-1 (B Yamagata)/AFLURIA® TETRA

[f] TIV-2 (B Victoria)/AFLURIA® TETRA

[g] Pooled TIV - AFLURIA® TETRA

[h] TIV-1 (B Yamagata) - AFLURIA® TETRA

[i] TIV-2 (B Victoria) – AFLURIA® TETRA

Pediatrics (5 to <18 years):

Serum HI antibody responses to AFLURIA® TETRA were non-inferior for both GMT and seroconversion rates relative to the Comparator QIV for all influenza strains (Table 7). Analyses of immunogenicity endpoints by gender did not demonstrate meaningful differences between males and females. The study population was not sufficiently diverse to assess differences between races or ethnicities.

Table 7: ***Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of QIV Relative to Comparator QIV for each Strain 28 Days after Last Vaccination Among a Pediatric Population 5 to < 18 Years of Age (Per Protocol Population)***[f]

	Post-vaccination GMT		**GMT Ratio** [a]	**Seroconversion %** [b]		**SCR Difference** [c]	**Met both pre-defined non-inferiority criteria?** [d]
Strain	**AFLURIA® TETRA N=1605**	**Comparator N=528**	**Comparator over AFLURIA® TETRA (95% CI)**	**AFLURIA® TETRA N=1605 (95% CI)**	**Comparator N=528 (95% CI)**	**Comparator minus AFLURIA® TETRA (95% CI)**	
A/H1N1	952.6 (n=1604 [e])	958.8	1.01 (0.93, 1.09)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A/H3N2	886.4 (n=1604 [e])	930.6	1.05 (0.96, 1.15)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/Yamagata	60.9 (n=1604 [e])	54.3	0.89 (0.81, 0.98)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/Victoria	145.0 (n=1604 [e])	133.4	0.92 (0.83, 1.02)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

Abbreviations: CI: confidence interval; GMT (adjusted): geometric mean titer; SCR: seroconversion rate.
[a] GMT Ratio = Comparator QIV / QIV.
[b] Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.
[c] Seroconversion rate difference = Comparator QIV SCR percentage minus QIV SCR percentage.
[d] Noninferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the ratio of Comparator QIV/QIV. GMT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI on the difference between SCR Comparator QIV – QIV should not exceed 10%.
[e] Subject 8400394-0046 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio since the subject did not have information on all covariates (unknown prevaccination history).
[f] The Per-Protocol Population comprised all subjects in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.

14 NON-CLINICAL TOXICOLOGY

AFLURIA® TETRA has not been evaluated in non-clinical studies. A reproductive and developmental toxicity study has been conducted with a similar trivalent influenza vaccine manufactured by Seqirus. Female rats received 2 intramuscular injections (0.5 mL per occasion, divided) of trivalent vaccine 21 and 7 days before mating and 1 or 2 additional injections during

gestation on day 6, or days 6 and 20, respectively. On a body weight basis, each dose administered to rats was approximately 200 times the human AFLURIA QIV dose. There was no maternal toxicity and fertility was not affected. No vaccine-related foetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

AFLURIA® TETRA
Inactivated Quadrivalent Influenza Vaccine (Split Virion)

Read this carefully before you are given AFLURIA® 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 AFLURIA® TETRA.

What is AFLURIA® TETRA used for?

AFLURIA® TETRA is indicated for active immunization of persons aged 5 years and older against influenza disease caused by the influenza virus types A and B contained in the vaccine.

AFLURIA® TETRA vaccine helps prevent influenza, often called "the flu." Influenza is caused by infection with specific influenza viruses. New types of influenza viruses can appear each year. AFLURIA® TETRA vaccine contains fragments of four different types of influenza virus. Each year the World Health Organization decides which four types of viruses are most suitable to include in the vaccine.

For this season (20XX – 20XX) the viruses are A/[Official strain] (H1N1) – like strain, A/[Official Strain] (H3N2) – like strain, B/[Official Strain] – like strain and B/[Official strain]– like strain.

You cannot catch influenza from the vaccine, as the virus in the vaccine has been killed and split into small non-infectious particles.

The National Advisory Committee on Immunization (NACI) encourages annual influenza vaccination for all Canadians who are able to have the vaccine.

Vaccination against influenza is recommended every year, for anyone wanting to lower their chance of catching influenza.

How does AFLURIA® TETRA work?

AFLURIA® TETRA vaccine works by helping your body to protect itself against infection by the types of influenza viruses that are in the vaccine. The vaccine stimulates the body to make substances called antibodies. Antibodies fight the influenza virus. If you have been vaccinated, when you come into contact with the influenza viruses in the vaccine, your body is usually able quickly to destroy the virus, which may prevent you from getting influenza.

Your body takes a few weeks after vaccination to fully develop effective protection against the influenza virus.

Protection against influenza generally requires one dose of AFLURIA® TETRA vaccine. Some

people including children who have not received influenza vaccination before may require two doses.

Most people make satisfactory antibodies against the influenza virus. However, as with all vaccines, 100% protection cannot be guaranteed.

The chance of having a severe unwanted reaction after having AFLURIA® TETRA vaccine is very small. Whereas, the risks of not being vaccinated against influenza may be very serious.

What are the ingredients in AFLURIA® TETRA?
Medicinal ingredients:

Each 0.5 mL dose of the vaccine contains 15 µg of haemaglutinin (HA) from each influenza strain

- A/Official strain (H1N1)-like virus
- A/Official strain (H3N2)-like virus
- B/Official strain-like virus
- B/Official strain-like virus

Non-medicinal ingredients:

- Calcium chloride
- Dibasic sodium phosphate (anhydrous)
- Monobasic potassium phosphate
- Monobasic sodium phosphate
- Potassium chloride
- Sodium chloride
- Thimerosal*
- Water for injection

*Thimerosal is included in multi-dose vials only.

Each dose may also contain trace amounts of sodium taurodeoxycholate, ovalbumin (egg protein), beta-propiolactone, neomycin sulfate, polymyxin B sulfate and sucrose.

AFLURIA® TETRA vaccine does not contain lactose, gluten, tartrazine or any azo dyes. The syringe and vial components do not contain latex. AFLURIA® TETRA is considered safe for use in persons with latex allergies.

AFLURIA® TETRA comes in the following dosage forms:

AFLURIA® TETRA is supplied as a suspension for intramuscular injection in either a 0.5 mL, single dose, pre-filled syringe or a 5 mL multidose vial.

Do not use AFLURIA® TETRA if:

- Your child is under 5 years of age. AFLURIA® TETRA vaccine is only approved for use in children aged 5 years and over.

- You or your child have or previously have had an allergy to:
  - AFLURIA® TETRA or any of the ingredients listed in this leaflet
  - eggs

- the antibiotics neomycin sulfate or polymyxin B sulfate.

To help avoid side effects and ensure proper use, talk to your healthcare professional before being vaccinated with AFLURIA® TETRA. Talk about any health conditions or problems you may have, including if you or your child have or have had:

- **reaction to vaccination with any of the following**:
  - severe allergic reaction
  - difficulty breathing
  - swelling of the throat
  - fainting or collapse
  - fits or convulsions
  - high temperature (greater than 38.5°C)
  - severe skin reaction at the injection site, including severe bruising.

- **an infection or temperature higher than 38.5°C.**
  Your doctor may decide to delay vaccination until the illness has passed. A minor illness such as a cold is not usually a reason to delay vaccination.

- **low immunity due to ill health**, for example, some blood disorders, malaria, kidney disease requiring dialysis, HIV/AIDS or cancer

- **low immunity due to treatment with medicines** such as corticosteroids, cyclosporine or other medicines, used to treat cancer (including radiation therapy)

- **allergies or allergic reactions,** including; runny, blocked or itchy nose; itchy rash or hives; swelling of the face, lips, mouth or tongue

- **Guillain-Barré Syndrome (GBS)**, an illness which affects the nervous system and causes paralysis

- **allergies to other medicines or other substances**

- **if you are pregnant or breast feeding.** Your healthcare professional will be able to discuss the potential risks and benefits of having AFLURIA® TETRA while you are pregnant or breastfeeding.

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

How AFLURIA® TETRA is given

AFLURIA® TETRA is given as in injection into the muscle of your upper arm.

Usual dose:

AFLURIA® TETRA is given once every year as follows:

- Adults and children 5 years and over: one injection of 0.5mL

For children 5 to less than 9 years old who are receiving influenza vaccine for the first time, it is recommended that a follow-up (booster) dose of AFLURIA® TETRA is given 4 weeks after the first dose.

If the follow-up dose is missed, talk to your healthcare professional and arrange another visit as soon as possible.

Overdose:

If you think you have been given too many doses of AFLURIA® TETRA or have been given it by mistake, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using AFLURIA® TETRA?

These are not all the possible side effects you may feel when taking AFLURIA® TETRA. If you experience any side effects not listed here, contact your healthcare professional.

The following are the more common side effects of AFLURIA® TETRA. Mostly these are mild and short lived. Tell your doctor if you or your child notice any of these and they worry you:

- Reaction around the injection site such as tenderness, bruising, redness, warmth, pain, swelling or the formation of hard lumps
- Flu-like symptoms, such as headache, tiredness, fever, sore throat, runny nose, blocked nose, sneezing, cough, chills
- Vomiting, nausea, diarrhea
- Aching muscles

The following table lists more serious side effects that may need urgent medical attention or hospitalization. These side effects are rare.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Tingling or numbness		✓	
Allergic reaction Typical symptoms include rash, itching or hives on the skin, swelling of the face, lips tongue or other parts of the body		✓	
Shortness of breath, wheezing or trouble breathing		✓	

Fit, convulsions or seizure including convulsion associated with fever		✓	
Bleeding or bruising more easily than normal		✓	
Little or no urine		✓	
Severe stabbing or throbbing nerve pain		✓	
Neck stiffness, headache and high temperature associated with hallucinations, confusion, paralysis of part or all of the body, disturbances or behavior, speech and eye movements and sensitivity to light.		✓	
Guillain-Barré syndrome (GBS). GBS may make you feel weak; you may have difficulty moving around or you may experience numbness and tingling in your limbs.		✓	

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

Reporting Suspected Side Effects

For the general public: Should you experience a side effect following immunization, please report it to your doctor, nurse, or pharmacist.

Should you require information related to the management of the side effect, please contact your healthcare provider. The Public Health Agency of Canada, Health Canada and Seqirus 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:
Store in a refrigerator between 2°C and 8°C. Protect from light. Do not freeze. If frozen, do not use.

Keep out of reach and sight of children.

If you want more information about AFLURIA® 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; the manufacturer's website, www.seqirus.ca, or by calling 1-800-xxx-xxx.

This leaflet was prepared by Seqirus Pty Ltd, Parkville, VIC, 3052, AUSTRALIA

Last Revised: Jan-08-2017