PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[D]INFLUVAC® TETRA

Quadrivalent influenza vaccine, surface antigen, inactivated

Suspension for Injection

Each 0.5 mL pre-filled syringe contains neuraminidase and 15 mcg haemagglutinin of each virus strain as recommended by the WHO and NACI

Intramuscular injection or deep subcutaneous injection

Active Immunizing Agent for the Prevention of Influenza
ATC Code: J07BB02

BGP Pharma ULC
85 Advance Road
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Date of Initial Approval:
March 1, 2019

Submission Control No: 200726

RECENT MAJOR LABEL CHANGES

Not Applicable – new Product Monograph.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

INFLUVAC® TETRA (quadrivalent influenza vaccine, surface antigen, inactivated) is indicated for the prevention of influenza infection caused by the specific strains contained in the vaccine, in adults of 18 years of age and older.

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 (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 61 years of age): Studies on healthy elderly showed that INFLUVAC® TETRA is well tolerated. For more details, see to **CLINCAL TRIALS**.

2 CONTRAINDICATIONS

INFLUVAC® TETRA is contraindicated in patients who are hypersensitive to the active substances, any ingredient in the formulation that may be present as traces such as eggs, chicken protein (such as ovalbumin), formaldehyde, cetyltrimethylammonium bromide, polysorbate 80, or gentamicin as well as any other non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

Immunization with INFLUVAC® TETRA should be deferred in the presence of febrile illness or acute infection.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Not applicable.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

See below.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of INFLUVAC® TETRA for adults above 18 years is 0.5 mL.

Health Canada has not authorized an indication for pediatric use.

4.3 Administration

INFLUVAC® TETRA should be administered by intramuscular or deep subcutaneous injection.

Do not administer intravascularly.

INFLUVAC® TETRA is a colourless clear liquid, in pre-filled single-dose syringes with / without a needle.

Parenteral biological products should be inspected visually for extraneous particulate matter and/or discolouration before administration. If these conditions exist, the product should not be administered.

INFLUVAC® TETRA should be allowed to reach room temperature before use.

For syringes without a needle, remove the cap and attach a needle, and bleed the syringe of air while holding the needle pointing vertically upward by pressing the plunger in slowly.

Shake the pre-filled syringe well to uniformly distribute the suspension before administration and remove the needle protection.

Needles should not be recapped, and the syringe should be disposed of properly.

This medicinal product must not be mixed with other medicinal products.

For information on vaccine administration, see the current Canadian Immunization Guide and the Health Canada Website.

The patient should be given a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization history in the permanent medical record of each patient. Thus the permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number.

4.4 Reconstitution

INFLUVAC® TETRA comes as 0.5 mL suspension ready for injection.

4.5 Missed Dose

Not applicable.

5 OVERDOSAGE

Overdosage is unlikely to have any untoward effect.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1. – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection or deep subcutaneous injection	0.5 ml suspension for injection in prefilled syringe with / without needle (glass, type I), containing neuraminidase and 15 mcg haemagglutinin per virus strain, pack of 1 or 10. *Not all pack sizes may be marketed.*	*Excipients* Calcium chloride dihydrate 0.067 mg Disodium phosphate dihydrate 0.67 mg Magnesium chloride hexahydrate 0.05 mg Potassium chloride 0.1 mg Potassium dihydrogen phosphate 0.1 mg Sodium chloride 4.0 mg Water for Injection To 0.5 mL *Manufacturing Process Residuals* May also contain trace amounts of cetyltrimethyl ammonium bromide, chicken protein, egg material, formaldehyde, gentamicin sulphate, hydrocortisone, neomycin sulphate*, polymyxin B sulphate*, polysorbate 80, sodium citrate, sucrose, tylosine tartrate. *Only used if gentamicin cannot be used. If not used, not present.

7 DESCRIPTION

INFLUVAC® TETRA is a quadrivalent subunit influenza vaccine. Each 0.5 mL dose contains neuraminidase and 15 mcg of haemagglutinin antigen for each virus strain present in the vaccine. The composition of INFLUVAC® TETRA is adapted annually to comply with the World Health Organization (WHO) and the National Advisory Committee on Immunization (NACI) recommendations (northern hemisphere).

INFLUVAC® TETRA is a colourless clear liquid. INFLUVAC is thimerosal-free, mercury-free, and contains no preservative.

For the 2018/2019 season, each dose of INFLUVAC® TETRA contains neuraminidase and 15mcg of haemagglutinin of the following virus strains:

- A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181)
- A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012, X-223A)
- B/Massachusetts/2/2012-like strain (B/Massachusetts/2/2012, BX-51B)
- B/Brisbane/60/2008-like strain (B/Brisbane/60/2008, wild type)

8 WARNINGS AND PRECAUTIONS

General
As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

INFLUVAC® TETRA must not be administered intravascularly.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

Sterile epinephrine HCl solution (1:1000) and other appropriate agents should be made available for immediate use in case of an anaphylactic reaction or if acute hypersensitivity to the vaccine occurs. Health care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.

Before administration of any vaccine, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccine, determination of previous immunization history, and the presence of any contraindications to immunization, current health status, and a current knowledge of the literature concerning the use of the vaccine under consideration.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

INFLUVAC® TETRA should not be administered into the buttocks due to varying amounts of fatty tissue in this region, nor by the intradermal route, since these methods of administration may induce a weaker response.

Intramuscular injections should be given with care in persons suffering from coagulation disorders or on anticoagulant therapy because of risk of hemorrhage.

Influenza virus undergoes significant antigenic changes from time to time, so different vaccines are made every year. INFLUVAC® TETRA, as now constituted, is not effective against all possible strains of influenza virus. Protection is limited to those strains of virus from which the vaccine is prepared or against closely-related strains.

As with any vaccine, immunization with INFLUVAC® TETRA may not protect 100% of susceptible individuals.

Driving and Operating Machinery
INFLUVAC® TETRA has no or negligible influence on the ability to drive and use machines.

Hematologic
See **ADVERSE REACTIONS**.

Monitoring and Laboratory Tests
Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the results. The transient false positive reactions could be due to the IgM response to the vaccine.

Neurologic
See **ADVERSE REACTIONS**.

Sensitivity/Resistance
See **ADVERSE REACTIONS**.

Skin (Local) Reactions at Vaccination Sites
See **ADVERSE REACTIONS**.

8.1 Special Populations

8.1.1 Pregnant Women

Inactivated influenza vaccines, such as INFLUVAC® TETRA, can be used in all stages of pregnancy. Larger datasets on safety are available for the second and third trimester, compared with the first trimester; however, data from worldwide use of influenza vaccine do not indicate any adverse foetal and maternal outcomes attributable to the vaccine.

8.1.2 Breast-feeding

INFLUVAC® TETRA may be used during breast-feeding.

8.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

8.1.4 Geriatrics

Geriatrics (> 61 years of age): Studies on healthy elderly showed that INFLUVAC® TETRA is well tolerated. For more details, see **CLINCAL TRIALS**.

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

Safety data regarding the use of INFLUVAC® TETRA are based on a clinical study in healthy adults 18 years of age and older. Undesirable effects observed during the clinical trial were local and systemic adverse reactions, whereby these reactions usually disappeared within 1-2 days without treatment. The most frequently reported adverse reactions were vaccination site pain (16.3%) [for local reactions] as well as fatigue (11.2%) and headache (10.3%) [for systemic reactions]. See **Clinical Trial Adverse Reactions**.

There has been no post-marketing exposure to INFLUVAC® TETRA. However, all three of the influenza strains of trivalent influenza vaccine INFLUVAC® are included in INFLUVAC® TETRA. Thus, the adverse reactions reported from post marketing surveillance of trivalent influenza vaccine may also occur in vaccines receiving INFLUVAC® TETRA including allergic reactions in rare cases leading to anaphylactic shock requiring immediate medical help. See **Post-Market Adverse Reactions**.

9.2 Clinical Trial Adverse 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 vaccine. Adverse reaction information from clinical trials is useful for identifying vaccine-related adverse events and for approximating rates.

Safety data regarding the use of INFLUVAC® TETRA are based on a clinical study in healthy adults 18 years of age and older: The study was a randomized, double-blind, active-controlled study to assess the safety and immunogenicity of INFLUVAC® TETRA (QIV) and its noninferiority to INFLUVAC® (TIV). QIV was administered to 1,535 subjects, and 221 subjects each received the TIV formulation containing a B-strain of the Yamagata lineage and the TIV formulation containing a B-strain of the Victoria lineage. Solicited events for local and systemic reactogenicity were collected for 7 days (day of vaccination and the next 6 days) and unsolicited adverse events were collected up to 6 months (all adverse events up to Day 22, serious adverse events and new chronical illnesses (NCIs) between Day 22 and Day 183).

The most frequently reported solicited adverse reactions after vaccination observed in the clinical study for INFLUVAC® TETRA were vaccination site pain (16.3%) [for local reactions] (see **Table 2**) as well as fatigue (11.2%) and headache (10.3%) [for general reactions].

The incidence of solicited local and systemic reactions in adults, 18 years of age and older in the two study arms as well as the corresponding numbers derived from the INFLUVAC® safety database is presented in **Table 2**. This safety database consists of 16 clinical trials for the current thimerosal-free vaccine formulation INFLUVAC® (introduced in 2004; reactogenicity was evaluated in 3217 subjects, of whom 1473 were adults and 1744 subjects over 60 years of age.)

Table 2. - Incidence of solicited local and systemic reactions in Study INFQ3001 and the INFLUVAC® database in combined age groups (adults 18-60 years of age and elderly ≥61 years of age) within 7 days of vaccination[a] (Total vaccinated Cohort)

	Study INFQ3001				INFLUVAC® (TIV) Database[b]	
	INFLUVAC® TETRA		INFLUVAC® (TIV)			
	N=1531		N=441		N=3217	
	Any Grade	Grade 3[c]	Any Grade	Grade 3[c]	Any Grade	Grade 3[c]
Local						
Erythema	3.1%	-	2.5%	-	3.8%	0.1%
Swelling	5.0%	0.1%	4.8%	0.5%	4.2%	-
Induration	4.4%	0.1%	4.5%	0.2%	4.5%	0.1%
Vaccination Site Pain	16.3%	0.1%	12.7%	-	8.2%	0.1%
Ecchymosis	2.7%	-	1.4%	-	3.0%	-
Systemic						
Headache	10.3%	0.2%	8.8%	0.5%	9.5%	0.2%
Fatigue	11.2%	0.5%	12.3%	0.2%	11.4%	0.3%
Myalgia	7.4%	0.3%	6.8%	0.7%	5.8%	0.2%
Arthralgia	5.2%	0.3%	3.4%	0.2%	4.7%	0.1%
Malaise	6.1%	0.3%	7.7%	0.5%	5.8%	0.2%
Sweating	5.2%	0.1%	5.7%	-	3.9%	0.1%
Shivering	3.9%	0.2%	3.4%	-	2.2%	<0.1%
Fever	0.5%	0.2%	0.6%	0.2%	0.5%	0.1%

N: number of subjects in the safety sample

a.Local and systemic solicited events within 7 days; results shown are the maximum ratings from Day 1 to Day 7.

b.The safety database of trivalent INFLUVAC® consists of subjects from 16 clinical trials vaccinated with the thiomersal-free formulation comparable to the INFLUVAC® TETRA and the INFLUVAC® as used in study INFQ3001; there were 1,473 adults and 1,744 elderly subjects in the pooled safety sample; solicited events were coded in the same manner in the studies as well as study INFQ3001.

c. Grade 3 pain: Prevents normal daily activity.
Grade 3 redness, swelling: >10 cm.
Grade 3 swelling: > 10 cm or prevents normal daily activity.
Grade 3 muscle aches, headache, fatigue, myalgia, arthralgia, malaises, shivering: Prevents normal daily activity.
Grade 3 sweating: Prevents normal daily activity.
Grade 3 fever: Defined as >39°C.

These reactions usually disappear within 1-2 days without treatment.

In the clinical study for INFLUVAC® TETRA, all reporting rates in non-elderly adult subjects were lower than 10%, except for the local reaction of vaccination site pain (24.9% [QIV] versus 18.5% [TIV]), and the systemic reactions of headache (12.4% [QIV] versus 13.1% [TIV]) and fatigue/tiredness (11.9% [QIV] versus 12.6% [TIV]). The vast majority of the vaccination site pain reactions were reported within the first three days in both QIV and TIV groups and were mostly rated as mild (> 90%). Only one case was rated as severe (grade 3 toxicity grading) in the QIV group. In addition, for other local and systemic reactions, there were no relevant differences in reporting duration or severity grading; grade 3 (severe) reporting for each of the

reactions was low, both for systemic (≤ 0.3% in the QIV group and ≤0.9% in the TIV group) and local reactions (≤ 0.1% in the QIV group and 0 in the TIV group).

In elderly subjects, the reporting rates of local and systemic reactions were generally slightly higher in the QIV group than in the TIV group. However, overall reporting rates of local reactions were low in both vaccination groups, i.e., all fell below 5%, except for vaccination site pain (7.6% [QIV] versus 5.9% [TIV]). For systemic reactions, fatigue/tiredness was reported by 10.6% and 6.8%; headache by 8.1% and 7.3%; arthralgia/joint pain by 5.8% and 2.3% of subjects in the QIV group and the TIV group, respectively. Grade 3 (severe) reporting for each of the reactions was low, both for systemic (≤ 0.7% in the QIV group and ≤ 0.5% in the TIV group) and local reactions (≤ 0.1% in the QIV group and ≤ 0.9% in the TIV group).

Although a slight increase in systemic reactions in elderly subjects due to a higher HA content cannot be excluded based on the above, this is not confirmed in adult subjects, where no flagging occurred. In addition, in terms of severity and duration of reactions, there were no marked differences between the QIV and TIV groups for any of the reactions in either adult or elderly subjects.

Overall, reporting rates of local reactions showed a tendency of being higher in adult subjects than in elderly subjects in both QIV and TIV groups, which is in line with historical data.

In general, reactions were reported within the first three days after vaccination. Only a few subjects reported systemic or local reactions beyond seven days (3 subjects for each [0.2%] in the QIV group versus 2 subjects each [0.5%] in the TIV group).

Unsolicited events reported for INFLUVAC® TETRA: Up to Day 22, 4.8% of adults (n=37) and 3.8% of elderly (n=29) reported at least one treatment-emergent adverse event (TEAE, adverse event that started or worsened in severity on or after the first study vaccination). 0.5% of adults and 0.8% of elderly had at least one TEAE that was considered to have a reasonable possibility for a causal relationship with the study vaccine as judged by the investigator. Events were asthenia (n=2), diarrhea and syncope (both n=1) reported in adults, and myalgia, musculoskeletal stiffness, vertigo, chills, nasopharyngitis and dizziness (all n=1) reported in elderly. No deaths were reported, and none of the subjects experienced TEAEs that led to study termination up to the Day 22 visit.

Between Day 22 and Day 183, 1.3% of adults (n=10) and 3.9% of elderly (n=30) reported at least one treatment-emergent serious adverse event (TESAE, including new chronical illnesses, NCIs). None of the TESAEs were considered to have a reasonable possibility for a causal relationship with the study vaccine by the investigator. Non-serious NCIs were reported in 1.3% of adults (n=10) and 4.0% of elderly (n=31). None of the NCIs were considered to have a reasonable possibility for a causal relationship with the study vaccine by the investigator.

9.3 Less Common Clinical Trial Adverse Reactions

See **Section 9.2 Clinical Trial Adverse Drug Reactions**.

9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Not applicable.

9.5 Clinical Trial Adverse Reactions (Pediatrics)

Not applicable.

9.6 Post-Market Adverse Reactions

There has been no post-marketing exposure to INFLUVAC® TETRA. However, as all three of the influenza strains of trivalent influenza vaccine are included in INFLUVAC® TETRA, the following adverse reactions reported from post marketing surveillance (in addition to reactions which have also been observed during clinical trials) of trivalent influenza vaccine (INFLUVAC®) may occur also in individuals receiving INFLUVAC® TETRA.

Blood and lymphatic system disorders:
Transient thrombocytopenia, transient lymphadenopathy

Immune system disorders:
Allergic reactions, in rare cases leading to shock, angioedema

Nervous system disorders:
Neuralgia, paraesthesia, febrile convulsions, neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome

Vascular disorders:
Vasculitis associated in very rare cases with transient renal involvement

Skin and subcutaneous tissue disorders:
Generalized skin reactions including pruritus, urticaria or non-specific rash

Guillain-Barré Syndrome (GBS) occurred in adults in association with the 1976 swine influenza vaccine, and evidence favours the existence of a causal relation between the vaccine and GBS during that season. In an extensive review of studies since 1976, the United States Institute of Medicine concluded that the evidence is inadequate to accept or reject a causal relation between GBS in adults and influenza vaccines administered after the swine influenza vaccine program in 1976.

In Canada the background incidence of GBS was estimated at just over 20 cases per million population in a study done in Ontario and Quebec. A variety of infectious agents, such as *Campylobacter jejuni*, have been associated with GBS. It is not known whether influenza virus infection itself is associated with GBS. Neither is it known whether influenza vaccination is causally associated with increased risk of recurrent GBS in persons with a previous history of GBS. Avoiding subsequent influenza vaccination of persons known to have developed GBS within 6 to 8 weeks of a previous influenza vaccination appears prudent at this time. The reporting rate of GBS associated with INFLUVAC is concluded to remain within the expected back-ground incidence.

Physicians, nurses and pharmacists should report any immediate adverse reactions arising from any vaccination, or following shortly thereafter, in accordance with local requirements and to the manufacturer: Drug Safety, BGP Pharma ULC, 85 Advance Rd., Etobicoke, ON M8Z 2S6 Canada. Telephone: 1-844-596-9526.

10 DRUG INTERACTIONS

10.1 Serious Drug Interactions Box

Not applicable.

10.2 Overview

No interaction studies have been performed. For relevant interaction please see **Drug-Drug Interactions** section below.

10.3 Drug-Drug Interactions

No data are available to address the concomitant use of INFLUVAC® TETRA with other vaccines. When INFLUVAC® TETRA is given at the same time as other vaccines, immunization should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

10.4 Drug-Food Interactions

Not known.

10.5 Drug-Herb Interactions

Not known.

10.6 Drug-Laboratory Test Interactions

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the results. The transient false positive reactions could be due to the IgM response by the vaccine.

10.7 Drug-Lifestyle Interactions

See **WARNINGS AND PRECAUTIONS** - **Driving and Operating Machinery**.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

INFLUVAC® TETRA provides active immunisation against four influenza virus strains: an A/(H1N1) strain, an A/(H3N2) strain, a B/(Victoria) strain and a B/(Yamagata) strain. INFLUVAC® TETRA, manufactured according to the same process as the trivalent influenza vaccine (INFLUVAC®), induces humoral antibodies against the haemagglutinins. These antibodies neutralise influenza viruses.

Specific levels of hemagglutination-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.

Protective antibody levels (seroprotection) are generally obtained within 2 to 3 weeks after vaccination. The duration of postvaccinal immunity to homologous strains or to strains closely related to the vaccine strains varies but is usually 6-12 months.

Influenza A viruses are classified into subtypes on the basis of 2 surface antigens: hemagglutinin (H) and neuraminidase (N). Three subtypes of hemagglutinin (H1, H2, H3) and 2 subtypes of neuraminidase (N1, N2) are recognized among influenza A viruses that have caused widespread human disease. Immunity to these antigens, especially to the hemagglutinin, reduces the likelihood of infection and lessens the severity of disease if infection occurs. Infection with a virus of one subtype confers little or no protection against viruses of other subtypes. Antigenic variation over time within a subtype may be so marked that infection or vaccination with one strain may not induce immunity to distantly related strains of the same subtype. Influenza B viruses can be further classified into two lineages: B/Yamagata and B/Victoria. Although influenza B viruses have shown more antigenic stability than influenza A viruses, antigenic variation does occur. For these reasons, major epidemics of respiratory disease caused by variants of influenza still occur. The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the virus strains included in each year's vaccine.

11.2 Pharmacodynamics

See Section **15.2 Study Results**.

11.3 Pharmacokinetics

As a vaccine product, pharmacokinetic studies are not applicable.

12 STORAGE, STABILITY AND DISPOSAL

INFLUVAC® TETRA should be stored at 2 to 8°C (in a refrigerator). Do not freeze. Store in the original package in order to protect from light.

Do not use vaccine after expiration date as stated on the label.

13 SPECIAL HANDLING INSTRUCTIONS

INFLUVAC® TETRA should be allowed to reach room temperature before use. Shake well before use. Inspect visually prior to administration (See **Administration**).

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

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Quadrivalent influenza virus subunit vaccine (surface antigen, inactivated).

Chemical name: Monovalent Bulk containing inactivated hemagglutinin and neuraminidase surface antigens of WHO/NACI recommended strains of influenza virus.

Physicochemical properties: The Monovalent Bulk is a clear to slightly opalescent liquid. The pH of the Monovalent Bulk is in the range 6.9 to 7.5.

Product Characteristics

This vaccine complies with the WHO and NACI recommendations (northern hemisphere) for the 2018-2019 season. The active substances are:
Influenza virus surface antigens (haemagglutinin and neuraminidase) of the following strains:

- A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181)
- A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012, X-223A)
- B/Massachusetts/2/2012-like strain (B/Massachusetts/2/2012, BX-51B)
- B/Brisbane/60/2008-like strain (B/Brisbane/60/2008, wild type)

The virus strain is supplied as a primary seed virus by the NIBSC (National Institute for Biological Standards and Control, Potters Bar, UK), or by another designated WHO laboratory. The primary seed virus is propagated in embryonated SPF (specific pathogen-free) hens' eggs to generate a master seed virus (MSV). The working seed virus (WSV) is generated by the propagation of the MSV in embryonated SPF hens' eggs.

The WSV is diluted to a seed suspension and then inoculated in embryonated eggs. The inoculated eggs are incubated for approximately 3 days. After incubation, the eggs are cooled to 5 ± 3°C for 4 - 48 hours.

The allantoic fluid is harvested from the eggs and clarified using a centrifuge to remove cell and egg debris. The clarified allantoic fluid of the single harvest of a strain is separated in a zonal gradient centrifuge (0-60% sucrose). The virus containing fractions with approximately 47 to 35% m/m of sucrose are collected and inactivated by formaldehyde treatment in two stages, first for 18 hours to 3 days and secondly for 4 to 10 days. The inactivated fractions are pooled, filtered and diluted with PBS. The sucrose and formaldehyde is removed by ultrafiltration. The hemagglutinin and neuraminidase are solubilised by the addition of Polysorbate 80 and CTAB. The non-solubilised remainders of the virus particles are removed by centrifugation.

The CTAB and the Polysorbate 80 are removed from the supernatant by adsorption to an adequate quantity of Amberlite XAD-4 resin. After adsorption of the detergents, the Amberlite resin is removed by filtration. PBS is added and the final suspension is sterilised by filtration which is the Monovalent Bulk vaccine.
The manufacture of the drug product (=final lot) involves blending four monovalent bulks (one

per strain), and diluting the drug substance with buffers to produce the final (=quadrivalent) bulk. The final bulk is filled into single-dose syringes, using an Isolator filling machine to produce the final product.

15 CLINICAL TRIALS

15.1 Trial Design and Study Demographics

Immunogenicity

Table 3. - Summary of patient demographics for clinical trials in prophylaxis of influenza

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n*)	Mean age (Range)	Sex
INFQ3001	Randomized, double-blind and active-controlled study in which the quadrivalent (QIV) influenza vaccine was compared to two trivalent (TIV) influenza vaccines, containing the B-strain of either Yamagata (Yam) or Victoria (Vic) lineage	0.5 mL, intramuscular	1,980	QIV & TIV: Adults 41 Elderly 70	QIV adults: 44% male QIV elderly: 42% male TIV adults: 46% male (Vic) 39% male (Yam) TIV elderly: 44% male (Vic) 46% male (Yam)
*Total number of randomized subjects.					

In general, the demographics of subjects were similar in all vaccination groups.

Subjects at risk for complications of influenza due to their baseline health status were 13.8% of non-elderly adults and 45.2 % of elderly adults who were vaccinated with QIV, and 9.5% and 40.2% of the non-elderly adults and elderly adults vaccinated with TIV.

15.2 Study Results

Study INFQ3001 was a randomized, double-blind, active-controlled study in adult, stratified 1:1 for age into adults (≥ 18 to ≤ 60 years) and elderly (≥ 61 years) cohorts, to assess the safety and immunogenicity of INFLUVAC® TETRA (QIV) and its noninferiority to TIV INFLUVAC®. The number of subjects randomly assigned to the vaccine groups were 1,538 to QIV, 221 to the TIV formulation containing a B-strain of the Victoria lineage and 221 to the TIV formulation containing a B-strain of the Yamagata lineage. HI antibody response to each of the vaccine antigens were evaluated at 21 days post-vaccination.

Primary Efficacy Variables

The noninferiority of QIV to TIV with respect to the induced immunogenicity against the shared strains was tested by comparing the postvaccination geometric means of the HI titers against these strains between the quadrivalent formulation and the trivalent formulations (See Table 4).

For all four strains, the upper limit of the 95% confidence interval for the geometric mean ratio (GMR; TIV versus QIV) fell below the predefined noninferiority margin of 1.5, meaning that the noninferiority of QIV to TIV was demonstrated.

Table 4. - Noninferiority of QIV versus TIV against shared strains based on geometric mean HI titers at 21 days post-vaccination in adults 18 years of age – Per-Protocol Sample – Study INFQ3001

Strain	QIV		TIV		TIV/QIV
	N	GMT	N	GMT	Adjusted GMR (95% CI)
A (H1N1)	1511	186.6	433	220.9[a]	1.18 (1.023, 1.370)
A (H3N2)	1524	393.1	436	413.5[a]	1.06 (0.928, 1.213)
B-Victoria	1521	152.9	215	142.0[b]	0.88 (0.726, 1.071)[d]
B-Yamagata	1520	102.1	215	86.1[c]	0.82 (0.677, 0.998)[e]

QIV contained 2014/2015 northern hemisphere virus like strains A/California/7/2009 (H1N1)pdm09; A/Texas/50/2012 (H3N2); B/Massachusetts/2/2012-like virus (TIV(Yam)); and B/Brisbane/60/2008-like virus (TIV(Vic)).Per-protocol sample: all subjects who were included in the full analysis sample without major protocol violations.
Adjusted GMR and 95% CI were calculated using analysis of variance on the log-transformed titers at the Day 22 visit with age group, country, center, and vaccine group included as factors in the model.
N = Number of subjects with non-missing data; CI = confidence interval; GMT = geometric mean titer; GMR = geometric mean ratio; HI = hemagglutinin inhibition; Vic = Victoria B strain; Yam = Yamagata B strain.
Noninferiority of QIV to TIV could be concluded if for all four strains the upper limit of the 95% CI fell below 1.5.
a HI titer data of the two trivalent formulations were pooled for the two A-strains.
b Data for B Vic
c Data for B Yam
d TIV(Vic)/QIV
e TIV(Yam)/QIV

Secondary Efficacy Variables

The secondary efficacy objective of study INFQ3001 was to demonstrate the superiority of QIV to TIV with respect to the induced immunogenicity against the alternate-lineage B-strains. This was tested by comparing the post-vaccination geometric means of the HI titers against the alternate-lineage B-strains between the QIV and the two TIV formulations (See Table 5).

For both B-strain lineages, the GMT of the TIV group was less than half of the GMT in the QIV group: 64.1 versus 153.1 (B-Victoria lineage) and 47.2 versus 101.9 (B-Yamagata lineage). Both differences were statistically significant ($P < 0.0001$, both comparisons). Thus, the HI antibody responses elicited by the B-strain antigens were superior to the antibody responses elicited by cross-reactivity antigens of the alternate B-strain lineages. The results for the per-protocol (PP) subject sample were similar to the full analysis (FA) subject sample.

Table 5. - Superiority of QIV versus TIV against the alternate lineage B-Strains based on the postvaccination geometric mean HI titers – Full Analysis Sample – Study INFQ3001

Strain	QIV		TIV		TIV/QIV	
	N	GMT	N	GMT	Adjusted GMR (95%	P value

					CI)	
B-Victoria	1526	153.1	218	TIV $_{(Yam)}$ 64.1	$TIV_{(Yam)}$/QIV 0.41 (0.334, 0.493)	< 0.0001
B-Yamagata	1525	101.9	220	TIV $_{(Vic)}$ 47.2	$TIV_{(Vic)}$/QIV 0.45 (0.374, 0.552)	< 0.0001

The superiority of QIV to TIV for induced immunogenicity against the alternate-lineage B strains was tested by comparing the Day 22 GMT HI titers against the alternate-lineage B strains between the quadrivalent formulation and the two trivalent formulations, using an ANOVA for the log-transformed titers, with age group and center as factors in the model. Both comparisons will be done at the two-sided significance level 0.05.

QIV contained 2014/2015 northern hemisphere virus like strains A/California/7/2009 (H1N1)pdm09; A/Texas/50/2012 (H3N2); B/Massachusetts/2/2012-like virus (TIV(Yam)); and B/Brisbane/60/2008-like virus (TIV(Vic)). Per-protocol sample: all subjects who were included in the full analysis sample without major protocol violations. N = Number of subjects with non-missing data; CI = confidence interval; GMT = geometric mean titer; GMR = geometric mean ratio; HI = hemagglutinin inhibition; Vic = Victoria B strain; Yam = Yamagata B strain.

15.3 Comparative Bioavailability Studies

Not applicable.

16 MICROBIOLOGY

Not applicable.

17 NON-CLINICAL TOXICOLOGY

Specific pre-clinical studies have not been conducted for quadrivalent seasonal influenza vaccine, however for the toxicological characteristics of the vaccine formulation, reference is made below to study results obtained with trivalent and monovalent seasonal influenza vaccine.

Repeated dose toxicity was investigated in male and female rabbits using a seasonal monovalent (trivalent) vaccine, which also included an adjuvanted influenza vaccine. General conclusion of this study is that the seasonal influenza vaccine used in this study did not show any systemic toxicity, when given as 3 subsequent vaccinations over the course of 4 weeks. Reproductive and developmental toxicity was investigated using trivalent seasonal vaccine. No unusual results were obtained, and the safety of the vaccine in this respect was confirmed. Given the similarity of the quadrivalent vaccine with the trivalent (or monovalent) vaccine that was used for these studies, it is considered justified to extrapolate the results from the trivalent to the quadrivalent vaccine.

18 SUPPORTING PRODUCT MONOGRAPHS

1) INFLUVAC® influenza vaccine, surface antigen, inactivated, Suspension for Injection Each 0.5 mL pre-filled syringe contains neuraminidase and 15 mcg hemagglutinin of each virus strain as recommended by the WHO and NACI. Submission control 212659, Product Monograph, BGP Pharma ULC. May 1, 2018.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[D]INFLUVAC® TETRA
Quadrivalent influenza vaccine, surface antigen, inactivated suspension for injection in pre-filled syringes

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

Serious Warnings and Precautions

- **INFLUVAC® TETRA should not be used in individuals who are allergic to eggs, previous doses of the flu vaccine, or any components of the flu vaccine.**

What is INFLUVAC® TETRA used for?

- INFLUVAC® TETRA is a vaccine used to prevent adults of 18 years of age and older from developing influenza (the flu).

How does INFLUVAC® TETRA work?

Like other influenza vaccines, INFLUVAC® TETRA causes the body to produce antibodies against the virus. This means that when your body is exposed to the flu virus, your body is able to defend itself. The antibodies stop the attacking virus. You cannot catch influenza from INFLUVAC® TETRA since it only contains portions of the inactivated virus, and not the whole live virus. Your body takes 10 to 21 days to produce antibodies after vaccination. Therefore, if you are exposed to influenza immediately before or after your vaccination, you could still develop the illness. The vaccine will not protect you against the common cold, even though some of the symptoms are similar to influenza. Influenza viruses change all the time, so different vaccines may be made every year. To stay protected against influenza, you need to be re-vaccinated every year before the winter season.

It is particularly important for some groups of people to be vaccinated. These include people with certain medical conditions, elderly people, people who are likely to be exposed to the infection and people on certain medications. If you are in doubt as to whether you should be vaccinated, talk to your local health care professionals.

INFLUVAC® TETRA complies with the World Health Organization (WHO) and National Advisory Committee on Immunization (NACI) recommendations for vaccination in the northern hemisphere for the 2018/2019 season.

What are the ingredients in INFLUVAC® TETRA?

Medicinal ingredients: The medicinal ingredient is surface antigens neuraminidase and hemagglutinin of the following viruses as recommended by WHO and the NACI: an A/California/7/2009 (H1N1)pdm09-like virus, an A/Texas/50/2012 (H3N2)-like virus, a B/Massachusetts/2/2012-like virus, a B/Brisbane/60/2008-like virus.

Non-medicinal ingredients: Calcium chloride dihydrate, disodium phosphate dihydrate, magnesium chloride hexahydrate, potassium chloride, potassium dihydrogen

phosphate, sodium chloride, water for injection and trace amounts of cetyltrimethyl ammonium bromide, chicken protein, eggs, formaldehyde, gentamicin sulphate (or neomycin sulphate, polymyxin B sulphate), hydrocortisone, polysorbate 80, sodium citrate, sucrose and tylosine tartrate.

INFLUVAC® TETRA comes in the following dosage forms:
INFLUVAC® TETRA comes in a 0.5 mL pre-filled syringe for injection, containing neuraminidase and 15 mcg hemagglutinin of each of the following virus strains:
- A/California/7/2009 (H1N1)pdm09- like strain (A/California/7/2009, X-181)
- A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012, X-223A)
- B/Massachusetts/2/2012-like strain (B/Massachusetts/2/2012, BX-51B)
- B/Brisbane/60/2008-like strain (B/Brisbane/60/2008, wild type)

Do not use INFLUVAC® TETRA if:
- INFLUVAC® TETRA vaccine is made in eggs; therefore this vaccine should not be given to anyone with allergies and especially severe allergies (anaphylactic reactions) to chicken eggs or egg products.
- INFLUVAC® TETRA should not be given to people who have allergies to the active substances, to any of the excipients and to residues of eggs, chicken protein, formaldehyde, cetyltrimethylammonium bromide, polysorbate 80, or gentamicin. For a complete listing of excipients, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- Anyone who has experienced allergic reactions to a previous dose of influenza vaccine SHOULD NOT be vaccinated with INFLUVAC® TETRA.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive INFLUVAC® TETRA. Talk about any health conditions or problems you may have, including if you:
- BEFORE you use INFLUVAC® TETRA talk to your doctor or pharmacist if: you are allergic to eggs or egg-products; you are allergic to any of the following: formaldehyde, cetyltrimethylammonium bromide, polysorbate 80 or gentamicin; you have a fever, or you think you may be getting a fever; you had a serious reaction to any flu vaccine in the past; you have any known allergies; you have experienced any health problems; you are pregnant; you are currently on any medication (i.e., immunosuppressants, theophylline, anticoagulants such as warfarin).
- Fainting, feeling faint or other stress related reactions can occur following, or even before, any needle injection. Therefore, tell your doctor or nurse if you have experienced this kind of reaction with a previous injection.

Other warnings you should know about:
See above.

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 INFLUVAC® TETRA:
- Immunosuppressants.

How to take INFLUVAC® TETRA:

INFLUVAC® TETRA should only be given by a health care professional.

Usual dose:
One dose of 0.5 mL pre-filled syringe containing neuraminidase and 15 mcg hemagglutinin per viral strain as recommended by WHO and NACI.

Adults: 0.5 mL, single dose.
INFLUVAC® TETRA comes as a 0.5 mL suspension, ready for intramuscular or deep subcutaneous injection. Allow the vaccine to reach room temperature before use. Shake well before use.

Overdose:
Overdosage is unlikely to have any bad effect.

If you think you have taken too much INFLUVAC® TETRA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Not applicable.

What are possible side effects from using INFLUVAC® TETRA?

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

Occasionally people have side effects with influenza vaccines. The most common of these are fever, feeling unwell, shivering, tiredness, headache, sweating, muscle or joint pain, and warmth. Skin reactions include redness, swelling, pain, ecchymosis (blue/black staining of the skin), a hardening of the skin at the injection site and itching.

These reactions will normally disappear without treatment in a day or two.

Rarely, neuralgia (nerve pain), paresthesia (numbness and tingling), convulsions (seizures) and temporary thrombocytopenia (a blood disorder) have been reported. In rare cases, allergic reactions may lead to shock.

Very rarely, vasculitis (inflammation of blood vessels) temporarily affecting the kidneys, neurological disorders (affecting the nerves and brain) such as encephalomyelitis, neuritis and Guillain Barré syndrome have been reported.

Allergic reactions (this might include but is not limited to breathing or swallowing difficulties, or swelling in the face or skin), and temporary enlargement of the lymph nodes have been reported.

If you think that you have a side effect not mentioned here, please tell your doctor or pharmacist.

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	Stop taking drug

	Only if severe	In all cases	and get immediate medical help
COMMON			
Fever	X		
Feeling unwell	X		
Shivering	X		
Tiredness	X		
Headache	X		
Sweating	X		
Muscle or joint pain	X		
Skin Reactions			
Redness	X		
Swelling	X		
Pain	X		
Ecchymosis (blue/ black staining of the skin)	X		
Reddening of the skin at the injection site	X		
UNCOMMON			
Nerve pain		X	
Numbness and tingling		X	
Convulsions (seizures)		X	
Temporary thrombocytopenia (a blood disorder)		X	
Allergic reactions		X	
Inflammation of blood vessels temporarily affecting the kidneys		X	
Brain disorders		X	
Guillain Barré syndrome		X	

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 BGP Pharma ULC 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 (https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html) and send it to your local Health Unit.

Storage:
Store INFLUVAC® TETRA at 2 to 8°C (in a refrigerator).

Do not freeze. Store in the original package in order to protect from light.

Do not use after the expiry date.

This vaccine is effective against this year's 2018/2019 influenza virus.

Keep out of reach and sight of children.

If you want more information about INFLUVAC® 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.mylan.ca, or by calling 1-844-596-9526.

This leaflet was prepared by BGP Pharma ULC.

Last Revised MAR 01 2019