

**AUSTRALIAN PRODUCT INFORMATION**  
**INFLUVAC® TETRA (Influenza virus haemagglutinin)**  
**Suspension for Injection**

**1. NAME OF THE MEDICINE**

Quadrivalent Influenza Vaccine, surface antigen, inactivated (influenza virus haemagglutinin)

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Influvac Tetra is a purified, inactivated influenza vaccine (surface antigen), containing the following four influenza strains recommended for the 2019 influenza season:

- A/Michigan/45/2015 (H1N1)pdm09-like strain  
(A/Singapore/GP1908/2015, IVR-180)
- A/Switzerland/8060/2017 (H3N2)-like strain  
(A/Brisbane/1/2018, NYMC X-311)
- B/Colorado/06/2017-like strain (B/Victoria/2/87 lineage)  
(B/Maryland/15/2016, NYMC BX-69A)
- B/Phuket/3073/2013-like strain (B/Yamagata/16/88 lineage)  
(B/Phuket/3073/2013, wild type)

Each 0.5 mL dose contains 15 micrograms haemagglutinin per each of the above mentioned viral strains, for a combined total amount of 60 micrograms. Each strain has been propagated in fertilised hens' eggs from healthy chickens.

The type and amount of viral antigens in Influvac Tetra conform to the requirements of the Australian Influenza Vaccine Committee (AIVC) and the New Zealand Ministry of Health for the winter of 2019.

For the full list of excipients, see section **6.1 LIST OF EXCIPIENTS**.

**3. PHARMACEUTICAL FORM**

Influvac Tetra is a clear colourless liquid for injection in pre-filled syringes (glass, type I).

## 4. **CLINICAL PARTICULARS**

### **4.1 THERAPEUTIC INDICATIONS**

For the prevention of influenza caused by influenza virus, types A and B.

For full details regarding recommendations for influenza vaccination, please refer to the relevant National Immunisation Guidelines.

Influvac Tetra is indicated in adults (18 years of age and older).

### **4.2 DOSE AND METHOD OF ADMINISTRATION**

**Adults (18 years of age or older):** 0.5 mL dose

**Children and adolescents:** the safety and efficacy of Influvac Tetra in children have not been established.

Influvac Tetra should be administered in autumn before the beginning of the influenza season or as required by the epidemiological situation. Vaccination should be repeated every year.

#### ***Administration***

Influvac Tetra should be administered by intramuscular or deep subcutaneous injection, whereas the intramuscular route is preferred.

Influvac Tetra should not be administered intravenously.

Influvac Tetra should not be mixed with other injection fluids.

The syringe is for single use in one patient only, any remaining residue should be discarded.

#### ***Instructions for use/handling***

Influvac Tetra shaken well and inspected visually before use.

Please refer to the relevant National Immunisation Guidelines for full details on preparations and vaccine administration.

### **4.3 CONTRAINDICATIONS**

Hypersensitivity to the active substances, to any of the excipients and to residues of eggs (ovalbumin, chicken proteins), formaldehyde, cetrimonium bromide, polysorbate 80, or gentamicin.

Anaphylaxis following a previous dose of any influenza vaccine.

Immunisation should be postponed in patients with febrile illness or acute infection.

Refer to the relevant National Immunisation Guidelines for full details on contraindications and precautions.

#### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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.

Influvac Tetra should under no circumstances be administered intravascularly.

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.

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

Interference with serological testing: see subheading ***Effects on laboratory tests*** below.

##### ***Use in the elderly***

No data available.

##### ***Paediatric use***

The safety and efficacy of Influvac Tetra in children have not been established.

##### ***Effects on 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 false-positive ELISA test results. The transient false-positive reactions could be due to the IgM response by the vaccine.

#### **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

No interaction studies have been performed. If Influvac Tetra is given at the same time as other vaccines, immunisation 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.

#### **4.6 FERTILITY, PREGNANCY AND LACTATION**

##### ***Effects on fertility***

No animal or human fertility data are available.

## ***Use in pregnancy***

Category B2

Inactivated influenza vaccines 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 fetal or maternal outcomes attributable to the vaccine.

Health authorities recommend vaccination for all pregnant women at any stage of pregnancy, particularly those who will be in the second or third trimester during the influenza season.

## ***Use in lactation***

Influvac Tetra may be used during lactation.

## **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

Influvac Tetra has no or negligible influence on the ability to drive and use of machines.

## **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

### **a) Clinical Trial Experience**

Safety data regarding the use of Influvac Tetra are based on a clinical study in healthy adults 18 years of age and older: Influvac Tetra was administered to 1535 subjects and trivalent influenza vaccine Influvac to 442 subjects.

Similar rates of solicited adverse reactions were observed in recipients of Influvac Tetra and trivalent influenza vaccine Influvac.

The most frequently reported local adverse reaction after vaccination with Influvac Tetra was pain at injection site (16.3%).

The most frequently reported general adverse reactions after vaccination with Influvac Tetra were fatigue (11.2%) and headache (10.3%).

In children aged 6 to 17 years, the most frequently reported general adverse reactions after vaccination were headache (24.0%) and fatigue (23.6%).

In children aged 3 to 5 years, the most frequently reported general adverse reaction after vaccination was irritability (21.0%).

**Table 1: Percentage of Solicited Injection-Site Reactions and Systemic Adverse Events in Adults After Vaccination with Influvac Tetra (Safety Analysis Set)**

	<b>Adults 18 years of age and older (Safety sample)</b>	<b>Adults 61 years of age and older (Safety sample)</b>
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	Influvac Tetra <sup>c</sup> N=768	TIV <sup>a,b</sup> N=222  (Pooled data: TIV-1: B Victoria N=110, TIV-2: B Yamagata N=112)	Influvac Tetra <sup>c</sup> N=767	TIV <sup>a,b</sup> N=219  (Pooled data: TIV-1: B Victoria N=111, TIV-2: B Yamagata N=108)
<b>Injection-site reactions</b>				
Pain	24.9%	18.5%	7.6%	5.9%
Redness	2.6%	4.1%	3.5%	0.9%
Swelling	5.2%	6.3%	4.8%	3.2%
Ecchymosis	2.7%	3.2%	2.8%	1.8%
Induration	5.0%	6.8%	3.9%	2.3%
<b>Systemic reactions</b>				
Headache	12.4%	13.1%	8.1%	7.3%
Myalgia	7.3%	5.9%	7.5%	5.0%
Arthralgia	4.6%	3.2%	5.8%	2.3%
Malaise	5.9%	7.7%	6.4%	4.6%
Shivering	3.1%	2.7%	4.7%	2.7%
Fatigue	11.9%	12.6%	10.6%	6.8%
Sweating	4.4%	5.0%	5.9%	4.1%
Fever	0.1%	0%	0.9%	0.9%

N is the number of subjects in the safety analysis set

<sup>a</sup> 2014-2015 Influvac TIV containing 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/Brisbane/60/2008 (wild type) (TIV<sub>(vic)</sub>) (market formulation)

<sup>b</sup> 2014-2015 Influvac TIV containing 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) TIV<sub>(yam)</sub> non-licensed formulation

<sup>c</sup> 2014-2015 Influvac Tetra 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) TIV<sub>(yam)</sub> , B/Brisbane/60/2008 (wild type) (TIV<sub>(vic)</sub>) non-licensed formulation

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

### Adverse Reactions Reported From Post-Marketing Surveillance

There has been no post-marketing exposure to Influvac Tetra. However, as all three of the influenza strains of trivalent influenza vaccine Influvac are included in Influvac Tetra, the following adverse reactions reported from post marketing surveillance of trivalent influenza vaccine Influvac may occur also in vaccines receiving Influvac Tetra, next to the reactions which have also been observed during the clinical trial:

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:

Generalised skin reactions including pruritus, urticaria or non-specific rash

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

#### **4.9 OVERDOSE**

Given the nature of the product and mode of administration the probability of overdosage is negligible.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### ***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 trivalent influenza vaccine Influvac, induces humoral antibodies against the haemagglutinins. These antibodies neutralise influenza viruses with matching antigens which has entered the body during infection.

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.

Seroprotection is obtained within 2-3 weeks. The duration of post-vaccination immunity to homologous strains or to strains closely related to the vaccine strains varies but is usually between 6-12 months.

### **Clinical trials**

#### Immunogenicity of quadrivalent Influvac Tetra compared to trivalent Influvac:

A clinical study performed in adults 18 years of age and older (INFQ3001) assessed the safety and immunogenicity of quadrivalent Influvac Tetra and its non-inferiority to trivalent influenza vaccine Influvac. The immunogenicity was assessed using HI Geometric mean antibody titer (GMT) at Day 22.

This study found the immune response elicited by Influvac Tetra against the three viral strains in common was non-inferior to Influvac.

Table 2: Post-vaccination GMT of HI

Adults 18 years of age and older	Influvac Tetra N=1533	Influvac <sup>1</sup> N=440
GMT (95% confidence interval)		
A/H1N1	186.2 (173.3;200.0)	221.6 (194.1;253.1)
A/H3N2	392.8 (368.7;418.4)	411.9 (364.3;465.8)
B (Yamagata) <sup>2</sup>	101.9 (94.8;109.7)	86.6 (71.5;105.0)
B (Victoria) <sup>3</sup>	153.1 (142.3;164.7)	140.7 (114.5;172.8)

<sup>1</sup>containing A/H1N1, A/H3N2 and B (Yamagata lineage) or B (Victoria lineage)

<sup>2</sup>recommended B strain by WHO for the season 2014-2015 NH for trivalent vaccines

<sup>3</sup>additional recommended B strain by WHO for season 2014-2015 NH for quadrivalent vaccines

Additionally, Influvac Tetra elicited a superior immune response against the additional B strain included in Influvac Tetra compared to trivalent Influvac.

### **5.2 PHARMACOKINETIC PROPERTIES**

Not applicable

### **5.3 PRECLINICAL SAFETY DATA**

#### **Genotoxicity**

No genotoxicity studies have been conducted with Influvac Tetra

#### **Carcinogenicity**

No carcinogenicity studies have been conducted with Influvac Tetra

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Each 0.5 mL dose contains 0.10 mg potassium chloride, 0.10 mg monobasic potassium phosphate, 0.67 mg dibasic sodium phosphate dihydrate, 4.0 mg sodium chloride, 0.067 mg calcium chloride dihydrate, 0.05 mg magnesium chloride hexahydrate and q.s. to 0.5 mL water for injections.

Influvac Tetra antigens have been produced from eggs and are inactivated by formaldehyde treatment. Each 0.5 mL may also contain not more than 100 ng ovalbumin, 0.01 mg formaldehyde, 0.02 mg cetrimonium bromide, 1 mg sodium citrate, 0.2 mg sucrose, 1 ng gentamicin sulfate, traces of tylosine tartrate, hydrocortisone and polysorbate 80, which are used during the manufacturing process.

### **6.2 INCOMPATIBILITIES**

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

See section **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

### **6.3 SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

The expiry date can be found on the packaging.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Keep out of the sight and reach of children

Store between 2 and 8 degrees Celsius. Refrigerate. Do not freeze. Store in the original package in order to protect from light.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

Single-dose 0.5 mL pre-filled glass syringe, available in packs of 1 or 10:

- with 16 mm needle                      AUST R 292237
- with 25 mm needle                     AUST R 292238\*
- without needle                         AUST R 281035\*

\* Presentation not currently marketed

### **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

Any unused medicine or waste material should be disposed of immediately.



## **6.7 PHYSICOCHEMICAL PROPERTIES**

Not applicable

## **7. MEDICINE SCHEDULE (POISONS STANDARD)**

Schedule 4 – Prescription Only Medicine

## **8. SPONSOR**

Mylan Health Pty Ltd  
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## **9. DATE OF FIRST APPROVAL**

02 November 2017

## **10. DATE OF REVISION**

28 November 2018

Version 3.0