**NEW ZEALAND DATA SHEET**

# INFLUVAC® TETRA

## 1. Product Name

Influvac Tetra, 60 microgram haemagglutinin per 0.5 mL, Suspension for injection

## 2. Qualitative and Quantitative Composition

Influvac Tetra is a purified, inactivated influenza vaccine (surface antigen), containing the following four influenza strains recommended for the 2018 influenza season:

- A/Michigan/45/2015 (H1N1)pdm09-like strain
  (A/Singapore/GP1908/2015, IVR-180)
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain
  (A/Singapore/INFIMH-16-0019/2016, NIB-104)
- B/Phuket/3073/2013-like strain
  (B/Phuket/3073/2013, wild type)
- B/Brisbane/60/2008-like strain
  (B/Brisbane/60/2008, wild type)

Each 0.5 mL dose contains 15 micrograms haemagglutinin per each of the above mentioned viral strains, for a combined total 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 2018.

For a full list of excipients, see section 6.1.

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.

## 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 and children 3 years of age and older.

## *4.2 Dose and method of administration*

### Dose

**Adults and children 3 years of age and older:** 0.5 mL

For children less than 9 years of age who have not previously been vaccinated, a second dose of 0.5 mL should be given after an interval of at least 4 weeks.

**Children less than 3 years of age:** the safety and efficacy of Influvac Tetra 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.

### Method of 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 and 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 should be 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. Please 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 section 4.5.

## *4.5 Interaction with other medicines and other forms of interaction*

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.

Interference with serological testing: 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.

## *4.6 Fertility, pregnancy and lactation*

### Pregnancy

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 foetal 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.

### Lactation

Influvac Tetra may be used during lactation.

### Fertility

No animal or human fertility data are available.

## *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 Undesirable effects*

### Clinical trial experience

#### *a) Summary of the safety profile*

In two clinical studies, healthy adults 18 years of age and older and healthy children 3 to 17 years of age were administered Influvac Tetra (1535 adults and 402 children) or trivalent influenza vaccine, Influvac (442 adults and 798 children).

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 in all age groups was pain at injection site (16.3% in adults 18 years of age and older, and 59.0% in children).

In adults 18 years of age and above, the most frequently reported general adverse reactions after vaccination 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%).

The following undesirable effects have been observed during the clinical trials with Influvac Tetra with the following frequencies:

very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100).

***b) Tabulated list of adverse reactions***

**Adults and elderly**

The safety profile presented below is based on data from 768 adults aged 18 - 60 years of age and 767 elderly aged 61 years or older.

| **Organ class** | **Very common ≥ 1/10** | **Common ≥ 1/100, <1/10** | **Uncommon ≥ 1/1,000, <1/100** |
|---|---|---|---|
| **Nervous system disorders** | Headache[a] | | |
| **Skin and subcutaneous tissue disorders** | | Sweating | |
| **Musculoskeletal and connective tissue disorders** | | Myalgia, arthralgia | |
| **General disorders and administration site conditions** | Fatigue<br>Local reaction: pain | Malaise, shivering,<br>Local reactions: redness, swelling, ecchymosis, induration | Fever |

[a]In elderly adults (≥ 61 years) reported as common

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

**Paediatric population**

The safety profile presented below is based on data from 133 children from 9 to 17 years of age who received one dose of Influvac Tetra and from 269 children from 3 to 8 years of age who received one or two doses of Influvac Tetra depending on their influenza vaccination history.

| **Organ class** | **Very common ≥ 1/10** | **Common ≥ 1/100, <1/10** |
|---|---|---|
| **Nervous system disorders** | Headache[a,d]<br>Drowsiness[a,c] | |
| **Skin and subcutaneous tissue disorders** | | Sweating[a,b] |
| **Metabolism and nutrition disorders** | Appetite loss[a,c] | |

| | | |
|---|---|---|
| **Gastrointestinal disorders** | Gastrointestinal symptoms[a,d] | Diarrhoea/ vomiting[a,c] |
| **Psychiatric disorders** | Irritability[a,c] | |
| **Musculoskeletal and connective tissue disorders** | Myalgia[a,d] | Arthralgia[a,d] |
| **General disorders and administration site conditions** | Fatigue[a,d], malaise[a,d] Local reactions: pain[a,b], redness[a,b], swelling[a,b], induration[a,b] | Fever[a,b] shivering[a,d] Local reaction: ecchymosis[b] |

[a]These reactions usually disappear within 1-3 days without treatment
[b] Reported as a solicited symptom in children 3 years to 17 years of age
[c] Reported as a solicited symptom in children 3 years to 5 years of age
[d] Reported as a solicited symptom in children 6 years to 17 years of age

### Post-marketing experience

Data for post-marketing exposure to Influvac Tetra are not yet available. However, note that the viral strains included in Influvac Tetra have all been included in the Influvac TIV vaccine in previous years. The following adverse reactions reported from post marketing surveillance of trivalent influenza vaccine Influvac may occur in patients receiving Influvac Tetra, next to the reactions which have also been observed during the clinical trials:

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

## *4.9 Overdose*

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

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

# 5. Pharmacological Properties

## *5.1 Pharmacodynamic properties*

Pharmacotherapeutic group: Influenza vaccine, ATC Code: J07BB02.

### 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.

### Pharmacodynamic effects

***Immunogenicity of quadrivalent Influvac Tetra compared to trivalent Influvac***

Clinical studies performed in adults 18 years of age and older (INFQ3001) and children 3 to 17 years of age (INFQ3002) assessed the safety and immunogenicity of quadrivalent Influvac Tetra and its non-inferiority to trivalent influenza vaccine Influvac. The post-vaccination immunogenicity was assessed using HI Geometric mean antibody titer (GMT).

The studies found the immune response elicited by Influvac Tetra against the three viral strains in common was non-inferior to trivalent Influvac. Additionally, Influvac Tetra elicited a superior immune response against the additional B strain included in Influvac Tetra compared to trivalent Influvac.

#### Adults 18 years of age and older

In clinical study INFQ3001, 1535 adults 18 years of age and older received a single dose of Influvac Tetra and 442 subjects received a single dose of trivalent Influvac.

**Table: Post-vaccination GMT**

| **Adults 18 years of age and older** | **Influvac Tetra N=1533** | **Influvac TIV[1] 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)[2]** | 101.9 (94.8; 109.7) | 86.6 (71.5; 105.0) |
| **B (Victoria)[3]** | 153.1 (142.3; 164.7) | 140.7 (114.5; 172.8) |

[1]containing A/H1N1, A/H3N2 and B (Yamagata lineage) (N=220) or B (Victoria lineage) (N=220)
[2]recommended B strain by WHO for the season 2014-2015 NH for trivalent vaccines
[3]additional recommended B strain by WHO for season 2014-2015 NH for quadrivalent vaccines
N = number of patients

#### Paediatric population

*Children 3 to 17 years of age*

In clinical study INFQ3002, 402 children of 3 to 17 years of age received one or two doses of Influvac Tetra and 798 children received one or two doses of trivalent Influvac based on their influenza vaccination history.

**Table: Post-vaccination GMT**

| **Children 3-17 years** | **Influvac Tetra N=396** | **Influvac TIV[1] N=788** |
|---|---|---|
| | **GMT (95% confidence interval)** | |
| **A/H1N1** | 546.2 (487.1; 612.6) | 619.4 (569.2; 673.9) |
| **A/H3N2** | 1161.5 (1035.8; 1302.5) | 1186.7 (1088.9; 1293.3) |
| **B (Yamagata)[2]** | 280.8 (246.2; 320.1) | 269.0 (232.8; 310.7) |
| **B (Victoria)[3]** | 306.7 (266.0; 353.6) | 361.4 (311.0; 420.0) |

[1]containing A/H1N1, A/H3N2 and B (Yamagata lineage) (N=389) or B (Victoria lineage) (N=399)
[2]recommended B strain by WHO for the season 2016-2017 NH for trivalent vaccines
[3]additional recommended B strain by WHO for season 2016-2017 NH for quadrivalent vaccines
N = number of patients

## *5.2 Pharmacokinetic properties*

Not applicable.

## *5.3 Preclinical safety data*

### Genotoxicity

No genotoxicity studies have been conducted with Influvac Tetra.

### Carcinogenesis

No carcinogenesis 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, 0.5 mg dibasic sodium phosphate, 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 is 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.

## *6.3 Shelf life*

1 year from the date of manufacture.

## *6.4 Special precautions for storage*

Keep out of the sight and reach of children.

Store between 2 and 8℃. Refrigerate. Do not freeze .

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

### *6.5 Nature and contents of container*

0.5 mL suspension for injection in prefilled syringe with / without 16 mm or 25 mm needle (glass, type I), in packs of 1 or 10.

Not all presentations and pack sizes may be marketed.

### *6.6 Special precautions for disposal*

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

## 7. Medicines Schedule

Prescription Medicine

## 8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

## 9. Date of First Approval

19 October 2017

## 10. Date of Revision of the Text

19 December 2017

| Section Changed | Summary of new information |
|---|---|
| 1 | Clarified strength of product. |
| 4.1 | Extended indication to children 3 years of age and older. |
| 4.2 | Included dosing for children 3 years of age and older. Editorial changes. |
| 4.3 | Revised to refer to correct sections of the national immunisation guidelines. |
| 4.8 | Section revised to include paediatric information. |
| 5.1 | Section revised to include paediatric information. |
| 6.5 | Needle lengths added. |