NEW ZEALAND DATA SHEET

INFLUVAC® TETRA (Saison 2019/2020)

1. Product Name

Influvac Tetra (Saison 2019/2020), 15/15/15/15 microgram haemagglutinin per 0.5 mL, Suspension for injection.

2. Qualitative and Quantitative Composition

Influvac Tetra (Saison 2019/2020) is a purified, inactivated influenza vaccine (surface antigen), containing the following four influenza strains:

- A/Brisbane/02/2018 (H1N1)pdm09-like strain
  (A/Brisbane/02/2018, IVR-190)
- A/Kansas/14/2017 (H3N2)-like strain
  (A/Kansas/14/2017, NYMC X-327)
- B/Colorado/06/2017-like strain
  (B/Maryland/15/2016, NYMC BX-69A)
- B/Phuket/3073/2013-like strain
  (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 of 60 micrograms. Each strain has been propagated in fertilised hens' eggs from healthy chickens.

This vaccine complies with the World Health Organisation (WHO) recommendation (northern hemisphere) and EU recommendation for the 2019/2020 season.

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 nanograms ovalbumin, 0.01 mg formaldehyde, 0.02 mg cetrimonium bromide, 1 mg sodium citrate, 0.2 mg sucrose, 1 nanograms 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.

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 (Saison 2019/2020) is indicated in adults and children 3 years of age and older at low risk of complications from influenza.

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 listed in section 6.1 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.

This medicine contains sodium, less than 1 mmol (23 mg) per dose, i.e. essentially 'sodium free'.

This medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium free'.

Use in the elderly

The safety and immunogenicity of Influvac Tetra was evaluated in adults ≥ 65 years in INFQ3001. Overall serological responses in elderly subjects were lower than those in younger adult subjects.

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.

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%).

b) Tabulated list of adverse reactions

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).

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 Local reaction: pain	Malaise, shivering, 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] 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

Provisional consent

This medicine has been given a provisional consent under Section 23 of the Medicines Act 1981. This means that there are specific conditions of use.

Provisional consent is to be granted for 1 year to address an urgent shortage in the market. The medicine may only be administered to patients who are not eligible to receive a PHARMAC-funded influenza vaccine during the 2020 influenza season.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of repeat dose and local toxicity, reproductive and developmental toxicity and safety pharmacology studies.

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
- 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 nanograms ovalbumin
- 0.01 mg formaldehyde
- 0.02 mg cetrimonium bromide
- 1 mg sodium citrate
- 0.2 mg sucrose
- 1 nanograms 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°C. 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 pre-filled syringe with 16 mm needle (glass, type I), in packs of 1 or 10.

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
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Ellerslie
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9. Date of First Approval

15 May 2020

10. Date of Revision of the Text

13 May 2020

Section Changed	Summary of new information
-	New data sheet
2	Influenza vaccine composition in line with NH2019
4.1	Amendments to the product indication for patients at low risk of complications from influenza.
5.1	Details of provisional consent