

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 2020 influenza season:

- A/Brisbane/02/2018 (H1N1)pdm09-like strain (A/Brisbane/02/2018, IVR-190)
- A/South Australia/34/2019 (H3N2)-like strain (A/South Australia/34/2019, IVR-197)
- B/Washington/02/2019-like strain (B/Victoria lineage) (B/Washington/02/2019, wild type)
- B/Phuket/3073/2013-like strain (B/Yamagata 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 2020 southern hemisphere influenza season.

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 and children from 3 years of age and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

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.

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 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.

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.

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 (See Section **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). Overall serological responses in elderly subjects were lower than those in younger adult subjects.

Paediatric Use

The safety and efficacy of Influvac Tetra in children under 3 years of age 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

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)

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 in all age groups (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

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

	Adults 18 years of age and older (Safety sample)		Adults 61 years of age and older (Safety sample)	
	Influvac Tetra ^c N=768	TIV ^{a,b} N=222 (Pooled data: TIV-1: B Victoria N=110, TIV-2: B Yamagata N=112)	Influvac Tetra ^c N=767	TIV ^{a,b} N=219 (Pooled data: TIV-1: B Victoria N=111, TIV-2: B Yamagata N=108)
Injection-site reactions				
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%
Systemic reactions				
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

a 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_(vic)) (market formulation)

b 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_(yam) non-licensed formulation

c 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_(yam), B/Brisbane/60/2008 (wild type) (TIV_(vic)) non-licensed formulation

Table 2: Percentage of Solicited Injection-Site Reactions and Systemic Adverse Events in Children 3-17 years After Vaccination with Influvac Tetra (Safety Analysis Set)

Age group	Solicited Reaction	Influvac Tetra ^c N=402	TIV ^{a,b} N=798 (Pooled data: TIV-1: B Victoria N=404, TIV-2: B Yamagata N=394)
Injection-site reactions			
3-17 years	Pain	59.0%	52.5%
	Redness	19.4%	16.6%
	Swelling	13.4%	10.7%
	Ecchymosis	6.5%	4.5%
	Induration	11.4%	10.1%
Systemic reactions			
3-17 years	Fever	4.2%	2.6%
	Sweating	4.2%	3.9%
6-17 years	Headache	24.0%	20.9%
	Fatigue	23.6%	22.1%
	Gastro-intestinal symptoms	14.8%	10.0%
	Myalgia	14.8%	15.3%
	Arthralgia	6.1%	4.9%
	Malaise	14.8%	12.3%
	Shivering	4.4%	3.5%
3-5 years	Irritability	21.0%	17.8%
	Drowsiness	15.9%	12.7%
	Diarrhea/Vomiting	6.8%	7.3%
	Loss of appetite	13.1%	11.1%

N is the number of subjects in the safety analysis set

^a 2016-2017 Influvac TIV with alternative B strain Tetra containing A/California/7/2009 (H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, and B/Phuket/3073/2013-like virus

^b 2016-2017 marketed Influvac TIV containing A/California/7/2009 (H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, and B/Brisbane/60/2008-like virus

^c 2016-2017 Influvac Tetra containing A/California/7/2009 (H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, B/Brisbane/60/2008-like virus and B/Phuket/3073/2013-like virus

Note: *Reactogenicity data of the two trivalent formulations pooled; RR = Relative Risk QIV vs TIV.

Note: Two sided 95 % CI. For the adjusted RR this is obtained based on the Mantel-Haenszel method.

Note: ** Adjusted for center and age/priming (9-17 years, 3-8 years primed and 3-8 years unprimed)

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 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 Suspected Adverse Effects

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 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:

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 3: 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)

¹containing A/H1N1, A/H3N2 and B (Yamagata lineage) (N = 220) or B (Victoria lineage) (N = 220)

²recommended B strain by WHO for the season 2014-2015 NH for trivalent vaccines

³additional recommended B strain by WHO for season 2014-2015 NH for quadrivalent vaccines

N = number of patients

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 4: 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)

¹containing A/H1N1, A/H3N2 and B (Yamagata lineage) (N=389) or B (Victoria lineage) (N=399)

²recommended B strain by WHO for the season 2016-2017 NH for trivalent vaccines

³additional 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

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 cetrimeron 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)

S4 (Prescription Only Medicine)

8 SPONSOR

Mylan Health Pty Limited

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Phone: 1800 314 527

9 DATE OF FIRST APPROVAL

02/11/2017

10 DATE OF REVISION

22/11/2019

Summary Table of Changes

Section Changed	Summary of New Information
2	Updated strain composition for 2020 influenza season

InfluvacTetra_pi\Nov19/00