Scheduling status: S2

1. NAME OF THE MEDICINE

INFLUVAC TETRA 2021, suspension for injection in pre-filled syringe

(influenza vaccine, surface antigen, inactivated).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus surface antigens (inactivated) (haemagglutinin and neuraminidase) of the following strains*:

- A/Victoria/2570/2019 (H1N1)pdm09-like strain	
(A/Victoria/2570/2019, IVR-215)	15 micrograms HA **
- A/Hong Kong/2671/2019 (H3N2)-like strain	
A/Hong Kong/2671/2019, IVR-208	15 micrograms HA **
- B/Washington/02/2019-like strain	
(B/Washington/02/2019, wild type)	15 micrograms HA **
- B/Phuket/3073/2013-like strain	
(B/Phuket/3073/2013, wild type)	15 micrograms HA **
	per 0.5 ml dose

* propagated in fertilised hens' eggs from healthy chicken flocks

** haemagglutinin.

This vaccine complies with the World Health Organisation (WHO) recommendation (southern hemisphere) and EU recommendation for the 2021 season.

For a full list of excipients see section 6.1.

Influvac Tetra may contain traces of eggs (such as ovalbumin, chicken proteins), formaldehyde, cetyltrimethylammonium bromide, polysorbate 80 or gentamicin, which are used during the manufacturing process (see section 4.3).

Contains sugar (0,0002 g).

3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.

A colourless clear liquid, filled in single-dose syringes.

Free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Prophylaxis of influenza, especially those who run an increased risk of associated complications.

Influvac Tetra is indicated in adults and children from 3 years of age.

The use of Influvac Tetra should be based on official recommendations.

4.2. Posology and method of administration

Posology

Adults: 0.5 ml.

Paediatric population

Children from 3 to 17 years of age: 0.5 ml.

Children less than 9 years of age, who have not previously been vaccinated with a seasonal influenza vaccine: 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.

Method of Administration

Immunisation should be carried out by intramuscular or deep subcutaneous injection.

Precautions to be taken before handling or administrating the medicinal product:

For instructions for preparation of the medicinal product before administration, see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section 6.1 or to any component that may be present as traces such as eggs (ovalbumin, chicken proteins), formaldehyde,

cetyltrimethylammonium bromide, polysorbate 80 or gentamicin.

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

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 less than 1 mmol sodium (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".

4.5. Interaction with other medicinal products 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 and maternal outcomes attributable to the vaccine.

Breast-feeding

Influvac Tetra may be used during breast-feeding.

Fertility

No 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 machines.

4.8. Undesirable effects

a. Summary of the safety profile

The safety of Influvac Tetra was assessed in two clinical trials in which healthy adults 18 years of age and older, and healthy children 3 to 17 years of age were administered Influvac Tetra or trivalent influenza vaccine Influvac. Children from 3 to 8 years of age received one or two doses of Influvac Tetra depending on their influenza vaccination history.

Most reactions usually occurred within the first 3 days following vaccination and resolved spontaneously within 1 to 3 days after onset. The intensity of these reactions was generally mild.

In all age groups, the most frequently reported local adverse reaction after vaccination observed in the clinical studies for Influvac Tetra was vaccination site pain.

The most frequently reported general adverse reactions after vaccination observed in the clinical studies for Influvac Tetra in adults and children from 6 to 17 years of age were fatigue and headache, and for children from 3 to 5 years of age drowsiness, irritability and loss of appetite.

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

b. Tabulated summary of adverse reactions

The following undesirable effects are considered at least possibly related to Influvac Tetra and have either been observed during the clinical trials with Influvac Tetra or are resulting from post-marketing experience with the trivalent influenza vaccine Influvac.

The following frequencies apply:

very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data).

Adults and elderly

Adverse Reactions Reported with Influvac Tetra/Influvac				
MedDRA System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Not Known[a] (cannot be estimated from the available data)**
Blood and lymphatic system				Transient thrombocytopenia, transient lymphadenopathy
Immune system disorders				Allergic reactions, in rare cases leading to shock, angioedema
Nervous system disorders	Headache[b]			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

Adverse Reactions Reported with Influvac Tetra/Influvac				
MedDRA System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Not Known[a] (cannot be estimated from the available data)**
				involvement
Skin and subcutaneous tissue disorders		Sweating		Generalised skin reactions including pruritus, urticaria or non-specific rash
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] Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure [b] In elderly adults (≥ 61 years) reported as common				

Paediatric population

Children (3 to 17 years of age) Adverse Reactions Reported with Influvac Tetra/Influvac				
MedDRA System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Not Known[a] (cannot be estimated from the available data)**
Blood and lymphatic system				Transient thrombocytopenia, transient lymphadenopathy
Immune system disorders				Allergic reactions, in rare cases leading to shock, angioedema
Nervous system disorders	Headache[d] Drowsiness[b]			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		Sweating[c]		Generalised skin reactions including pruritus, urticaria or non-specific rash
Metabolism and	Appetite loss[b]			

Children (3 to 17 years of age) Adverse Reactions Reported with Influvac Tetra/Influvac				
MedDRA System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Not Known[a] (cannot be estimated from the available data)**
nutrition disorders				
Gastrointestinal disorders	Gastrointestinal symptoms[d]	Diarrhoea[b], vomiting[b]		
Psychiatric disorders	Irritability[b]			
Musculoskeletal and connective tissue disorders	Myalgia[d]	Arthralgia[d]		
General disorders and administration site conditions	Fatigue[d], malaise[d] Local reactions: pain[c], redness[c], swelling[c], induration[c]	Fever[c], shivering[d] Local reaction: ecchymosis[c]		

[a] Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure

[b] Reported as a solicited symptom in children 3 to 5 years of age

[c] Reported as a solicited symptom in children 3 to 17 years of age

[d] Reported as a solicited symptom in children 6 to 17 years of age

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9. Overdose

Overdosage is unlikely to have any untoward effect.

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, and two B strains (one from each lineage; B/(Victoria) and B/(Yamagata)). Influvac Tetra, manufactured according to the same process as 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.

An immune response is generally obtained within 2 to 3 weeks. The duration of postvaccinal immunity to homologous strains or to strains closely related to the vaccine strains varies but is usually 6-12 months.

Pharmacodynamic effects:

Immunogenicity of Influvac Tetra compared to trivalent Influvac:

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

In both studies the immune response elicited by Influvac Tetra against the three strains in common was non-inferior to trivalent influenza vaccine Influvac. Influvac Tetra elicited a superior immune response against the additional B strain included in Influvac Tetra compared to trivalent influenza vaccine Influvac.

Adults 18 years of age and older:

In clinical study INFQ3001, 1,535 adults of 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 – 60 years of age	Influvac Tetra N=768	Influvac[1] N=112	Influvac[2] N=110
	GMT (95% confidence interval)		
A/H1N1	272.2 (248.0 , 298.8)	304.4 (235.1 , 394.1)	316.0 (245.1 , 407.3)
A/H3N2	442.4 (407.6 , 480.2)	536.5 (421.7 , 682.6)	417.0 (323.7 , 537.1)
B (Yamagata)[3]	162.5 (147.8 , 178.7)	128.7 (100.3 , 165.2)	81.7 (60.7 , 109.9)
B (Victoria)[4]	214.0 (195.5 , 234.3)	85.1 (62.6 , 115.6)	184.7 (139.0 , 245.3)

Elderly 61 years of age and older	Influvac Tetra N=765	Influvac[1] N=108	Influvac[2] N=110
	GMT (95% confidence interval)		
A/H1N1	127.2 (114.9 , 140.9)	142.4 (107.6 , 188.3)	174.2 (135.9 , 223.3)
A/H3N2	348.5 (316.8 , 383.5)	361.5 (278.3 , 469.6)	353.4 (280.7 , 445.0)
B (Yamagata)[3]	63.7 (57.7 , 70.4)	57.4 (43.6 , 75.7)	27.3 (20.7 , 36.0)
B (Victoria)[4]	109.4 (98.1 , 122.0)	48.0 (34.6 , 66.6)	106.6 (79.7 , 142.8)

N= number of subjects included in efficacy analysis

[1]containing A/H1N1, A/H3N2 and B (Yamagata lineage)

[2]containing A/H1N1, A/H3N2 and B (Victoria lineage)

[3]recommended B strain by WHO for the season 2014-2015 NH for trivalent vaccines

[4]additional recommended B strain by WHO for season 2014-2015 NH for quadrivalent vaccines

Paediatric population

Children 3 - 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 of age	Influvac Tetra N=396	Influvac[1] N=389	Influvac[2] N=399

	GMT (95% confidence interval)		
A/H1N1	546.2 (487.1 , 612.6)	605.6 (536.3 , 83.8)	633.1 (562.8 , 712.2)
A/H3N2	1161.5 (1035.8 , 1302.5)	1075.4 (947.7 , 1220.3)	1306.4 (1162.5 , 1468.1)
B (Yamagata)[3]	280.8 (246.2 , 320.1)	269.0 (232.8 , 310.7)	38.3 (31.9 , 46.1)
B (Victoria)[4]	306.7 (266.0 , 353.6)	104.5 (86.8 , 125.8)	361.4 (311.0 , 420.0)

N= number of subjects included in efficacy analysis

[1]containing A/H1N1, A/H3N2 and B (Yamagata lineage)

[2]containing A/H1N1, A/H3N2 and B (Victoria lineage)

[3]recommended B strain by WHO for the season 2016-2017 NH for trivalent vaccines

[4]additional recommended B strain by WHO for season 2016-2017 NH for quadrivalent vaccines

The European Medicines Agency has deferred the obligation to submit the results of studies with Influvac Tetra in one or more subsets of the paediatric population.

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

Potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, sodium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate and water for injections.

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.

6.4 Special precautions for storage

Store in a refrigerator **(**2°C - 8°C**)**. 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 / without needle (clear glass, type I). The glass syringe is closed at one end with a rubber plunger and at the other end with a rubber tip cap. The plunger consists of a grey coloured bromobutyl rubber compound. The plunger rod consists of polypropylene and is screwed into the rubber plunger. Each syringe can only be used once.

Pack of 1 or 10. *Not all pack sizes may be marketed.*

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use.

Shake before use. Inspect visually prior to administration.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place

219 Golf Club Terrace

Constantia Kloof, 1709

South Africa

8. REGISTRATION NUMBER

52/30.1/0094

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

11 August 2020

10. DATE OF REVISION OF THIS TEXT

11 August 2020