Product Insert (PI) for Influenza vaccine

1. NAME OF THE MEDICINAL PRODUCT

Influvac Tetra, suspension for injection in vial
(influenza vaccine, surface antigen, inactivated).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

- A/Victoria/4897/2022 (H1N1)pdm09-like strain (A/Victoria/4897/2022, IVR-238)	15 micrograms HA **
- A/Darwin/9/2021 (H3N2)-like strain (A/Darwin/9/2021, SAN-010)	15 micrograms HA **
- B/Austria/1359417/2021-like strain (B/Austria/1359417/2021, BVR-26)	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 (northern hemisphere) and EU recommendation for the 2023/2024 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).

3. PHARMACEUTICAL FORM

Suspension for injection in vial.
A colourless clear liquid,

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 6 months 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 6 months 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.

Infants less than 6 months 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. The preferred sites for intramuscular injection are the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in children 6 months through 35 months of age, or the deltoid muscle in children from 36 months of age and adults.

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

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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.

As with other vaccines administered intramuscularly, Influvac Tetra should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

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.

Influvac Tetra is not effective against all possible strains of influenza virus. Influvac Tetra is intended to provide protection against those strains of virus from which the vaccine is prepared and to closely related strains.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

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

There is no information on administration/possible immune reference of Influvac Tetra with (childhood) vaccines. Therefore, Influvac Tetra should not be given at the same time with other (childhood) vaccines.

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 three clinical trials.
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 or trivalent influenza vaccine Influvac.
In a third study, the safety of Influvac Tetra was assessed in healthy children from 6 months to 35 months of age administered Influvac Tetra or a non-influenza vaccine control.

In both children studies, children from 6 months 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.
The most frequently reported general adverse reactions after vaccination observed in the clinical studies for Influvac Tetra in children from 6 months to 35 months of age were irritability/fussiness.

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

The rates of solicited systemic adverse reactions were similar in recipients of Influvac Tetra and the non-influenza vaccine, whereby the rates of solicited local adverse reactions were lower in recipients of Influvac Tetra.

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 Influvac Tetra and/or 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				
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 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 (6 months to 17 years of age) Adverse Reactions Reported with Influvac Tetra				
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[c], 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[f]			Generalised skin reactions including pruritus, urticaria or non-specific rash
Metabolism and nutrition disorders	Appetite loss[b]			
Gastrointestinal disorders	Nausea[c], abdominal pain[c], diarrhoea[e], vomiting[e]			
Psychiatric disorders	Irritability/fussiness[b]			
Musculoskeletal and connective tissue disorders	Myalgia[c]	Arthralgia[c]		
General disorders and administration site conditions	Fatigue[c], fever[f], malaise[c] Local reactions: pain, redness, swelling[d], induration[d]	Shivering[c] Local reaction: ecchymosis		

[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 in children 6 months to 5 years of age
[c] Reported in children 6 to 17 years of age
[d] Reported as common in children 6 to 35 months of age
[e] Reported as common in children 3 to 5 years of age
[f] Reported as common in children 3 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 national reporting system.

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:
Efficacy of Influvac Tetra in children 6 - 35 months of age:

The efficacy of Influvac Tetra was evaluated in a randomized, observer-blind, non-influenza vaccine-controlled study (INFQ3003) conducted during 3 influenza seasons 2017 to 2019 in Europe and Asia. Healthy subjects aged 6 - 35 months received two doses of Influvac Tetra (N=1005) or non-influenza control vaccine (N=995) approximately 28 days apart. The efficacy of Influvac Tetra was assessed for the prevention of reverse transcription polymerase chain reaction (RT-PCR) - confirmed influenza A and/or B disease due to any influenza strain. All RT-PCR-positive specimens were further tested for viability in cell culture and to determine whether the circulating viral strains matched those in the vaccine.

Table: Efficacy in children 6 – 35 months of age

	Influvac Tetra N=1005	Non-influenza control-vaccine N=995	Vaccine efficacy (95% CI)
Laboratory-confirmed influenza caused by:	n	n	
- **Any influenza A or B strain**	59	117	0.54 (0.37 - 0.66)
- **Culture confirmed vaccine matching strains**	19	56	0.68 (0.45 - 0.81)

Vaccine efficacy: proportion of influenza cases prevented by the vaccination
N=number of subjects vaccinated
n=number of influenza cases
CI=confidence interval

Immunogenicity of Influvac Tetra:

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 and Seroconversion rates

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)
Seroconversion Rates (95% confidence interval)			
A/H1N1	59.4% (55.8% , 62.9%)	65.5% (55.8% , 74.3%)	64.8% (55.0% , 73.8%)
A/H3N2	51.3% (47.7% , 54.9%)	61.6% (51.9% , 70.6%)	55.5% (45.7% , 64.9%)
B (Yamagata)[3]	59.2% (55.7% , 62.8%)	58.7% (48.9% , 68.1%)	40.9% (31.6% , 50.7%)
B (Victoria)[4]	70.2% (66.8% , 73.4%)	51.4% (41.6% , 61.1%)	66.4% (56.7% , 75.1%)

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)
Seroconversion Rates (95% confidence interval)			
A/H1N1	50.3% (46.7% , 54.0%)	56.6% (46.6% , 66.2%)	58.2% (48.4% , 67.5%)
A/H3N2	39.3% (35.8% , 42.9%)	44.4% (34.9% , 54.3%)	43.6% (34.2% , 53.4%)
B (Yamagata)[3]	49.9% (46.2% , 53.5%)	46.2% (36.5% , 56.2%)	30.0% (21.6% , 39.5%)
B (Victoria)[4]	53.6% (50.0% , 57.2%)	25.0% (17.2% , 34.3%)	55.6% (45.7% , 65.1%)

N= number of subjects included in immunogenicity 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: Seroconversion rates

Children 3 - 17 years of age	Influvac Tetra N=396	Influvac[1] N=389	Influvac[2] N=399
	Seroconversion Rates (95% confidence interval)		
A/H1N1	60.1% (55.1% , 65.0%)	61.8% (56.7% , 66.6%)	59.1% (54.1% , 64.0%)
A/H3N2	80.6% (76.3% , 84.3%)	82.4% (78.3% , 86.1%)	80.7% (76.5% , 84.5%)
B (Yamagata)[3]	79.3% (75.0% , 83.2%)	73.1% (68.4% , 77.5%)	28.1% (23.7% , 32.8%)
B (Victoria)[4]	76.5% (72.0% , 80.6%)	39.5% (34.6% , 44.6%)	72.7% (68.0% , 77.0%)

N= number of subjects included in immunogenicity 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

Children 6 months - 35 months of age:

In clinical study INFQ3003 the immunogenicity of Influvac Tetra was evaluated in terms of seroconversion rates across 3 influenza seasons.

Table: Seroconversion rates

Children 6 - 35 months of age	Influenza season NH 2017-2018[1] N=348	Influenza season NH 2018-2019[1] N=359	Influenza season SH 2019[1] N=225
	Seroconversion Rates (95% confidence interval)		
A/H1N1	74.4% (69.5% , 78.9%)	76.0% (71.3% , 80.4%)	69.8% (63.3% , 75.7%)
A/H3N2	92.5% (89.2% , 95.0%)	86.6% (82.7% , 90.0%)	86.2% (81.0% , 90.4%)
B (Yamagata)	35.5% (30.4% , 40.8%)	56.0% (50.7% , 61.2%)	16.9% (12.2% , 22.4%)
B (Victoria)	26.5% (21.9% , 31.5%)	65.2% (60.0% , 70.1%)	47.6% (40.9% , 54.3%)

N= number of subjects included in immunogenicity analysis
[1]containing recommended strains by WHO for respective season for quadrivalent vaccines

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
- 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.
Once the single-dose vial has been penetrated, the vaccine should be used promptly.

6.4 Special precautions for storage

Store in a refrigerator **(**2°C to 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 vial (glass, type I), with bromobutyl stopper, sealed with an aluminium cap, in 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.

MANUFACTURER

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