AUSTRALIAN PRODUCT INFORMATION – VAXIGRIP TETRA® (INFLUENZA VIRUS HAEMAGGLUTININ) SUSPENSION FOR INJECTION

1 NAME OF THE MEDICINE

Inactivated quadrivalent influenza vaccine, split virion (Influenza virus haemagglutinin)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vaxigrip Tetra is formulated to contain the following four influenza strains*:

Active Substance	Quantity (per 0.5 mL dose)
A/Victoria/4897/2022 (H1N1)pdm09-like strain (A/Victoria/4897/2022, IVR-238)	15 micrograms HA**
A/Croatia/10136RV/2023 (H3N2)-like strain (A/Croatia/10136RV/2023, X-425A)	15 micrograms HA**
B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild type)	15 micrograms HA**
B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, wild type)	15 micrograms HA**

* propagated in fertilised hens' eggs from healthy chicken flocks

** haemagglutinin

The type and amount of viral antigens contained in Vaxigrip Tetra conform to the annual requirements of the Australian Influenza Vaccine Committee (AIVC) and the World Health Organisation (WHO) recommendations for the 2025 season.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.

The vaccine, after shaking gently, is a colourless opalescent liquid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Vaxigrip Tetra is indicated for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine for:

- active immunisation of adults, including pregnant women, and children from 6 months of age and older

- passive protection of infant(s) from birth to less than 6 months of age following vaccination of pregnant women (see Sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation and 5.1 Pharmacodynamic properties – clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

Vaxigrip Tetra should be given in accordance with the national recommendation as per the current Immunisation Handbook.

Given the antigenic variation in circulating influenza viruses and the duration of immunity provided by the vaccine, it is recommended to perform vaccination against influenza every year at the beginning of the risk period.

Individuals from 9 years of age: one injection of 0.5 mL dose.

Children from 6 months to 8 years of age:

- If the child has not previously been vaccinated: two 0.5 ml injections at least one month apart.
- If the child has been previously vaccinated: a single 0.5 ml injection.

Infants younger than 6 months of age:

No data are available regarding the safety and efficacy of Vaxigrip Tetra administration (active immunisation) in infants younger than 6 months of age.

Regarding passive protection, one 0.5-ml dose given to pregnant women may protect infants from birth to less than 6 months of age; however not all these infants will be protected (see Section 5.1 Pharmacodynamic properties – clinical trials)

Method of administration

The vaccine should be given by intramuscular or deep subcutaneous injection.

The preferred site of administration is into the deltoid muscle in adults and children ≥ 12 months of age. The preferred site for infants (6 months to < 12 months of age) is the anterolateral aspect of the

thigh. The vaccine should be administered into healthy well developed muscle and should not be injected into the gluteal region where there may be a risk of local neural, vascular and tissue injury.

Shake before use to distribute uniformly the suspension before administration.

Parenteral drug products should be inspected visually for particulate matter and/or discolouration prior to administration whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

The syringe is for single use only in one patient and must not be reused. Discard any remaining unused contents.

4.3 CONTRAINDICATIONS

Vaxigrip Tetra should not be given to individuals with a history of severe allergic reaction to any component of the vaccine (See Section 2 Qualitative and quantitative composition and Section 6.1 List of excipients). Vaxigrip Tetra should not be given to individuals with a history of severe allergic reaction after previous administration of Vaxigrip Tetra or a vaccine containing the same components.

Refer to Section 4.4 Special warnings and precautions for use for influenza vaccination for individuals with a known egg allergy.

Vaccination should be postponed in case of moderate or severe febrile or acute disease.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Vaxigrip Tetra should under no circumstances be administered intravenously.

Hypersensitivity

Prior to any vaccine injection, all known precautions should be taken to prevent hypersensitivity reactions. This includes a review of the individual's prior vaccination history with respect to possible hypersensitivity to the vaccine or similar vaccines. Adrenaline (epinephrine) injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be available to treat unexpected reactions (e.g. anaphylaxis).

Individuals with egg allergy, including a history of anaphylaxis, can be safely vaccinated with influenza vaccines. Refer to the current Immunisation Handbook for guidance on the use of influenza vaccines in individuals with egg allergy.

Vaxigrip Tetra may contain traces of formaldehyde and octoxinol 9 which are used during vaccine production, caution should be exercised when the vaccine is administered to individuals with hypersensitivity to either one of these products.

As each dose may contain undetectable traces of neomycin, which is used during vaccine production, caution should be exercised when the vaccine is administered to individuals with hypersensitivity to this antibiotic (and other antibiotics of the same class).

Neurological Disorders

Patients with a history of Guillain-Barré Syndrome (GBS) with an onset related in time to influenza vaccination may be at increased risk of again developing GBS, but whether vaccination specifically might increase the risk for recurrence is unknown. Because patients with a history of GBS have an increased likelihood of again developing the syndrome, the chance of them coincidentally developing the syndrome following influenza vaccination may be higher than in individuals with no history of GBS. If GBS has occurred within 6 weeks following previous influenza vaccination, the decision to give Vaxigrip Tetra should be based on careful consideration of the potential benefits and risks.

Immunosuppressive Treatments or Conditions

If Vaxigirip Tetra is administered to immunocompromised individuals, whether due to genetic defect, immunodeficiency disease, or immunosuppressive therapy, they may have a reduced immune response to vaccination. For current recommendation, refer to the current Immunisation Handbook.

Protection

As with any vaccine, vaccination with Vaxigrip Tetra may not protect 100% of recipients.

Regarding passive protection, not all infants younger than 6 months of age born to women vaccinated during pregnancy will be protected (see Section 5.1 Pharmacodynamic properties – clinical trials)

Influenza virus is remarkably unpredictable in that significant antigenic changes may occur from time to time. It is known that influenza vaccines, as now constituted, are not effective against all possible strains of influenza virus. Protection is limited to those strains of virus from which the vaccine is prepared or to closely related strains.

Bleeding Disorders

As with other vaccines administered intramuscularly, the vaccine should be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these individuals.

Syncope

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent injury from fainting and manage syncopal reactions.

Use in the elderly

Annual influenza vaccination is recommended for individuals 65 years of age and over.

Paediatric use

Infants younger than 6 months of age:

No data are available regarding the safety and efficacy of Vaxigrip Tetra administration (active immunisation) in infants younger than 6 months of age. Regarding passive protection, one 0.5-ml dose given to pregnant women may protect infants from birth to less than 6 months of age; however not all these infants will be protected (see Sections 4.2 Dose and method of administration and 5.1 Pharmacodynamic properties – clinical trials)

Effects on laboratory tests

Interference of Vaxigrip Tetra with laboratory and/or diagnostic tests has not been studied.

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 can be used to disprove these results. The transient false positive reactions could be due to IgM response by the vaccine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No studies regarding the simultaneous administration of Vaxigrip Tetra and other vaccines have been conducted.

Nevertheless, clinical data showing that Vaxigrip (Inactivated Trivalent Influenza Vaccine (Split Virion) can be administered concomitantly with other vaccines are available for the following vaccines: 23-valent pneumococcal polysaccharide vaccine in elderly, dTpa-IPV (diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine) in adults aged ≥ 60 years, and zoster vaccine in adults aged 50 and older.

Vaxigrip Tetra can be given at the same time as other vaccines.

Separate injection sites and separate syringes should be used in case of concomitant administration.

Individuals deficient in producing antibodies due to immunosuppressive therapy may have a reduced immune response to vaccination.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no fertility data available in humans. One animal study with Vaxigrip Tetra did not indicate harmful effects on female fertility in rabbits.

Use in pregnancy (Category A)

One development and reproductive study conducted in rabbits with Vaxigrip Tetra did not indicate direct or indirect harmful effects with respect to pregnancy, embryo-fetal development or early post-natal development.

Data from studies involving large numbers of women (> 80,000) vaccinated during pregnancy with inactivated influenza vaccines do not indicate any adverse fetal and maternal outcomes attributable to the vaccine.

Data from four clinical studies conducted with Vaxigrip (trivalent influenza vaccine, TIV) administered to pregnant women during the second and third trimesters (more than 5,000 exposed pregnancies and more than 5,000 live births, followed up to approximately 6 months postpartum) did not indicate any adverse fetal, newborn, infant, or maternal outcomes attributable to the vaccine.

In three of these clinical studies conducted in South Africa and Nepal, there were no significant differences between the Vaxigrip (TIV) and placebo groups with regards to fetal, newborn, infant, or maternal outcomes (including miscarriage, stillbirth, premature birth, low birth weight).

In the fourth study conducted in Mali, there were no significant differences between the Vaxigrip (TIV) and control vaccine (quadrivalent meningococcal conjugate vaccine) groups with regards to prematurity rate, stillbirth rate, or rate of low birth weight/small for gestational age.

Data from a clinical study conducted in Finland with Vaxigrip Tetra administered in pregnant women during the second or third trimester (230 exposed pregnancies and 231 live births) did not indicate any adverse fetal or maternal outcomes attributable to the vaccine.

Vaxigrip Tetra can be administered in all stages of pregnancy based on the safety data from clinical studies and post-marketing experience. Larger datasets on safety of inactivated influenza vaccines are available for the second and third trimesters than for the first trimester. Data from worldwide use of inactivated influenza vaccines, including Vaxigrip Tetra and Vaxigrip (trivalent inactivated influenza vaccine), do not indicate any adverse fetal and maternal outcomes attributable to the vaccine. Because of the known adverse consequences of influenza infection in pregnant women, health authorities recommend vaccination of pregnant women.

Use in lactation

There are no data on the effect of the vaccine in breastfed newborns/infants of women vaccinated with Vaxigrip Tetra during breastfeeding period. Based on experience with inactivated influenza vaccines, Vaxigrip Tetra may be used during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Within each system organ class, the adverse events are ranked under headings of frequency, using the following convention:

Very common	≥ 1/10 (≥ 10%)
Common	≥ 1/100 and < 1/10 (≥ 1% and < 10%)
Uncommon	≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
Rare	≥ 1/10.000 and < 1/1000 (≥ 0.01% and < 0.1%)
Very rare	< 1/10.000 (< 0.01%)
Not known	Cannot be estimated from available data

Adverse event information is derived from clinical trials with Vaxigrip Tetra and from-worldwide post-marketing experience with Vaxigrip Tetra and Vaxigrip.

Clinical Trial Data

The safety of Vaxigrip Tetra was assessed in six randomised controlled clinical trials in which 3040 adults from 18 to 60 years of age, 1392 elderly over 60 years of age and 429 children from 9 to 17 years of age received one dose of Vaxigrip Tetra and 884 children from 3 to 8 years of age received one or two doses of Vaxigrip Tetra depending on their influenza vaccination history and 1614 children from 6 to 35 months of age received two doses (0.5 ml) of Vaxigrip Tetra.
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 mild.
The most frequently reported adverse reaction after vaccination, in all populations including the whole group of children from 6 to 35 months of age, was injection site pain (between 52.8% and 56.5% in children from 3 to 17 years of age and in adults, 26.8% in children from 6 to 35 months of age and 25.8% in elderly). In subpopulation of children less than 24 months of age, irritability (32.3%) was the most frequently reported adverse reaction.
In subpopulation children from 24 to 35 months of age, malaise (26.8%) is the most frequently reported adverse reaction.

The other most frequently reported adverse reactions after vaccination were:

- In adults: headache (27.8%), myalgia (23%) and malaise (19.2%),
- In elderly: headache (15.6%) and myalgia (13.9%),

- In children from 9 to 17 years of age: myalgia (29.1%), headache (24.7%), malaise (20.3%) and injection site swelling (10.7%),
- In children from 3 to 8 years of age: malaise (30.7%), myalgia (28.5%), headache (25.7%), injection site swelling (20.5%), injection site erythema (20.4%), injection site induration (16.4%), shivering (11.2%),
- In all children from 6 to 35 months of age: fever (20.4%) and injection site erythema (17.2%),
- In children less than 24 months of age: appetite lost (28.9%), crying abnormal (27.1%), vomiting (16.1%) and drowsiness (13.9%),
- In children from 24 to 35 months of age: headache (11.9%) and myalgia (11.6%).

Overall, adverse reactions were generally less frequent in the elderly than in adults and children.

Adults and elderly

The safety profile presented below is based on data from 3,040 adults from 18 to 60 years of age and 1,392 elderly over 60 years of age.

Table 1 - Adverse reactions in adults and elderly

ADVERSE REACTIONS	FREQUENCY
Blood and Lymphatic System Disorders	
Lymphadenopathy [1]	Uncommon
Immune System Disorders	
Hypersensitivity [1], allergic reactions such as erythema, urticaria [1], pruritus [2], pruritus generalised [1], dermatitis allergic [1], angioedema [1]	Rare
Nervous System Disorders	
Headache	Very common
Dizziness [3]	Uncommon
Somnolence, paresthaesia	Rare
Vascular disorders	
Hot flush [4]	Uncommon
Respiratory, thoracic and mediastinal disorders	
Dyspnoea [1]	Rare
Gastrointestinal Disorders	
Diarrhoea, nausea [5]	Uncommon
Skin and Subcutaneous System Disorders	
Hyperhidrosis	Rare
Musculoskeletal and Connective Tissue Disorders	
Myalgia	Very common
Arthralgia [1]	Rare
General Disorders and Administration Site Conditions	

Malaise [6] Injection site pain	Very common
Shivering, fever [2] Injection site erythema, injection site swelling, injection site induration	Common
Fatigue Injection site ecchymosis, injection site pruritus, injection site warmth	Uncommon
Asthenia, flu-like illness Injection site discomfort [1]	Rare

[1] In adults [2] Uncommon in elderly [3] Rare in adults [4] In elderly [5] Rare in elderly [6] Common in elderly

Paediatric population

The safety profile presented below is based on data from 429 children from 9 to 17 years of age who received one dose of Vaxigrip Tetra and from 884 children from 3 to 8 years of age who received one or two doses of Vaxigrip Tetra depending on their influenza vaccination history.

Table 2 - Adverse reactions in children from children from 9 to 17 years of age who received one dose of Vaxigrip Tetra and from 3 to 8 years who received one or two doses of Vaxigrip Tetra

ADVERSE REACTIONS	FREQUENCY
Blood and Lymphatic System Disorders	
Thrombocytopaenia [1]	Uncommon
Psychiatric disorders	
Moaning [2], restlessness [2]	Uncommon
Nervous System Disorders	
Headache	Very common
Dizziness [2]	Uncommon
Gastrointestinal Disorders	
Diarrhoea, vomiting [2], abdominal pain upper [2]	Uncommon
Musculoskeletal and Connective Tissue Disorders	
Myalgia	Very common
Arthralgia [2]	Uncommon
General Disorders and Administration Site Conditions	
Malaise, shivering [3] Injection site pain, injection site swelling, injection site erythema [3], injection site induration [3]	Very common
Fever Injection site ecchymosis	Common
Fatigue [2], Injection site warmth [2], injection site pruritus [4]	Uncommon

[1] Reported in one child of 3 years of age
[2] Reported in children from 3 to 8 years of age
[3] Common in children from 9 to 17 years of age
[4] Reported in children from 9 to 17 years of age

The safety profile presented below is based on data from 1,614 children from 6 to 35 months of age who received two doses of Vaxigrip Tetra.

Table 3 - Adverse reactions in children from 6 to 35 months of age who received two doses of Vaxigrip Tetra

ADVERSE REACTIONS	FREQUENCY
Immune System Disorders	
Hypersensitivity	Uncommon
Allergic reactions such as pruritus generalised, rash papular	Rare
Nervous System Disorders	
Headache [(1)]	Very common
Gastrointestinal Disorders	
Vomiting [(2)]	Very common
Diarrhoea	Uncommon
Musculoskeletal and Connective Tissue Disorders	
Myalgia [(3)]	Very common
General Disorders and Administration Site Conditions	
Irritability [(4)], appetite lost [(4)], crying abnormal [(5)], malaise [(3)], fever, drowsiness [(5)], injection site pain/tenderness, injection site erythema	Very common
Shivering [(1)] Injection site induration, injection site swelling, injection site ecchymosis	Common
Injection site rash, injection site pruritus , influenza like illness	Rare

[(1)] Reported in children ≥24 months of age
[(2)] Uncommon in children ≥24 months of age
[(3)] Rare in children <24 months of age
[(4)] Rare in children ≥24 months of age
[(5)] Reported in children <24 months of age

In children from 6 months to 8 years of age, the safety profile of Vaxigrip Tetra was similar after the first and the second injections with a trend of lower incidence of adverse reactions after the second injection compared to the first one in children from 6 to 35 months.

Other special populations

The safety profile of Vaxigrip Tetra observed in a limited number of subjects with co-morbidities enrolled in the clinical studies does not differ from the one observed in the overall population. In addition, studies conducted with Vaxigrip in renal transplant patients, and asthmatic patients showed no major differences in terms of safety profile of Vaxigrip in these populations.

Pregnant women:

In clinical studies conducted in pregnant women in South Africa and Mali with Vaxigrip (TIV)(see Section 4.6 Fertility, Pregnancy and Lactation and Section 5.1 Pharmacodynamic properties – clinical trials), frequencies of local and systemic solicited reactions reported within 7 days following administration of Vaxigrip, were generally consistent with those reported for the adult population during clinical studies conducted with Vaxigrip; In the study conducted in South Africa, local reactions were more frequent in the Vaxigrip group than in the placebo group in both HIV-negative and HIV-positive cohorts.

There were no other significant differences in solicited reactions between Vaxigrip and placebo groups in both cohorts.

In one clinical study conducted in pregnant women in Finland with Vaxigrip Tetra (see Sections 4.6 Fertility, pregnancy and lactation and 5.1 Pharmacodynamic properties – Immunogenicity of Vaxigrip Tetra), frequencies of local and systemic solicited reactions reported within 7 days following administration of Vaxigrip Tetra were consistent with those reported for the non-pregnant adult population during clinical studies conducted with Vaxigrip Tetra even though higher for some adverse reactions (injection site pain, malaise, shivering, headache, myalgia). When higher frequencies were observed, this increase was also seen with Vaxigrip (TIV), used as comparator, suggesting a clinical study effect in this pregnant women population.

Post marketing experience

Immune system disorders

Not known: allergic including anaphylactic reactions

Nervous system disorders

Febrile convulsions

Skin and subcutaneous tissue disorders

Rash

The following adverse events were reported following commercial use of Vaxigrip. A causal relationship with Vaxigrip Tetra has not been established.

Blood and lymphatic system disorders

Transient thrombocytopenia*, lymphadenopathy*

Nervous system disorders

Paraesthesia*,-Guillain-Barré Syndrome (GBS), neuritis, neuralgia, convulsions, encephalomyelitis

Vascular disorders

Vasculitis, such as Henoch-Schönlein purpura, with transient renal involvement in certain cases.

* These adverse events were reported during clinical trials only in some age groups (see Section 4.8 Adverse effects (undesirable effects) – Clinical trial data).

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

Cases of administration of more than the recommended dose (overdose) have been reported with Vaxigrip Tetra. When adverse reactions were reported, the information was consistent with the known safety profile of Vaxigrip Tetra described in Section 4.8 Adverse effects (undesirable effects).

For information on the management of overdose, contact the Poisons Information Centre, on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02

Mechanism of action

Vaxigrip Tetra provides active immunisation against four influenza virus strains (two A subtypes and two B types) contained in the vaccine.

Vaxigrip Tetra induces humoral antibodies against the haemagglutinins within 2 to 3 weeks. These antibodies neutralise influenza viruses.

Specific levels of haemagglutination-inhibition (HAI) antibody titre post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the HAI antibody titres have been used as a measure of vaccine activity. In some human challenge studies, HAI antibody titres of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.

Since influenza viruses constantly evolve, the virus strains selected in the vaccine are reviewed annually by the WHO.

Annual revaccination with Vaxigrip Tetra has not been studied. However, based on clinical experience with TIV, annual influenza vaccination is recommended given the duration of immunity provided by the vaccine and because circulating strains of influenza virus change from year to year.

Clinical trials

Efficacy of Vaxigrip Tetra

Children aged from 6 to 35 months (active immunisation)

A randomised placebo controlled study was conducted in 4 regions (Africa, Asia, Latina America and Europe) over 4 influenza seasons, in more than 5400 children from 6 to 35 months of age who received two doses (0.5 ml) of Vaxigrip Tetra (N=2722), or placebo (NaCl 0.9%, N=2717) 28 days apart to assess Vaxigrip Tetra efficacy for the prevention of laboratory confirmed influenza illness caused by any strain A and/or B and caused by vaccine similar strains (as determined by sequencing).

Laboratory-confirmed influenza illness was defined as influenza like-illness (ILI) [occurrence of fever ≥ 38°C (that lasts at least 24 hours) concurrently with at least one of the following symptoms: cough, nasal congestion, rhinorrhoea, pharyngitis, otitis, vomiting, or diarrhoea] laboratory-confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) and/or viral culture.

Table 4 - Influenza attack rates and Vaxigrip Tetra efficacy against laboratory-confirmed influenza illness in children from 6 to 35 months of age

	Vaxigrip Tetra (N=2584)		**Placebo (N=2591)**		**Efficacy**
	n	**Influenza attack rate (%)**	**n**	**Influenza attack rate (%)**	**% (2-sided 95% CI)**
Laboratory-confirmed influenza illness caused by:					
• Any influenza A or B Type	122	4.72	255	9.84	52.03 (40.24, 61.66)
• Viral strains similar to those contained in the vaccine	26	1.01	85	3.28	69.33 (51.93; 81.03)
N=Number of children analysed (full set) n=number of subjects fulfilling the item listed CI=confidence interval					

In addition, a predefined complementary analysis showed Vaxigrip Tetra prevented 56.6% (95% CI: 37.0; 70.5) of severe laboratory-confirmed influenza illnesses due to any strain, and 71.7% (95% CI: 43.7; 86.9) of severe laboratory-confirmed influenza illnesses due to vaccine-similar

strains. Furthermore, subjects receiving Vaxigrip Tetra were 59.2% (95% CI: 44.4; 70.4) less likely to experience a medically attended influenza illness than subjects receiving placebo.

Severe laboratory-confirmed influenza illnesses were defined as ILI laboratory-confirmed by RT-PCR and/or viral culture with at least one of the following items:

- fever > 39.5°C for subjects aged < 24 months or ≥ 39.0°C for subjects aged ≥ 24 months,
- and/or at least one significant ILI symptom which prevents daily activity (cough, nasal congestion, rhinorrhoea, pharyngitis, otitis, vomiting, diarrhoea),
- and/or one of the following events: acute otitis media, acute lower respiratory infection (pneumonia, bronchiolitis, bronchitis, croup), inpatient hospitalisation.

Children from 3 to 8 years of age (active immunisation)

Based on immune responses observed in children 3 to 8 years of age, the efficacy of Vaxigrip Tetra in this population is expected to be at least similar to the efficacy observed in children from 6 to 35 months (see "Children from 6 to 35 months of age" above and "Immunogenicity of Vaxigrip Tetra" below).

Pregnant women

There are no clinical efficacy data describing use of Vaxigrip Tetra in pregnant women. However, data are available on Vaxigrip (TIV) and cited below, and can be extrapolated to Vaxigrip Tetra.

In the randomised, controlled, phase IV, clinical studies conducted in Mali, Nepal, and South Africa, approximately 5,000 pregnant women received Vaxigrip (TIV) and approximately 5,000 pregnant women received placebo or control vaccine (quadrivalent meningococcal conjugate vaccine) during the second or third trimester of pregnancy. Vaccine efficacy against laboratory-confirmed influenza in pregnant women was evaluated as a secondary endpoint in all three studies.

The studies conducted in Mali and South Africa demonstrated the efficacy of Vaxigrip for the prevention of influenza in pregnant women (during pregnancy and for approximately 6 months post-delivery), following vaccination during these trimesters of pregnancy.

In the study conducted in Nepal, the efficacy of Vaxigrip (TIV) for the prevention of influenza in pregnant women following vaccination during these trimesters of pregnancy was not demonstrated.

Table 5 - Influenza Attack Rates and Vaxigrip Efficacy against Laboratory-confirmed influenza in pregnant women

	Influenza Attack Rate (Any influenza A or B type) % (n/N)		**Vaxigrip Efficacy % (95% CI)**
	TIV	**Control***	

Mali	0.5 (11/2,108)	1.9 (40/2,085)	70.3 (42.2 to 85.8)
	TIV	**Placebo**	
South Africa	1.8 (19/1,062)	3.6 (38/1,054)	50.4 (14.5 to 71.2)

* Meningococcal vaccine
N: Number of pregnant women included in analysis
n: number of subjects with laboratory confirmed influenza
CI: Confidence Interval

Infants younger than 6 months of age born to vaccinated pregnant women (passive protection)

Infants younger than 6 months of age are at high risk of influenza, resulting in high rates of hospitalization; however, influenza vaccines are not indicated for use in this age group.

There are no clinical efficacy data in infants born to women vaccinated with Vaxigrip Tetra during pregnancy; however, efficacy in infants younger than 6 months of age whose mothers received a single 0.5-ml dose of Vaxigrip (TIV) during the second or third trimester has been demonstrated in clinical trials in Nepal, Mali and South Africa and can be extrapolated to Vaxigrip Tetra. Efficacy of Vaxigrip (TIV) in infants younger than 6 months of age whose mothers were vaccinated during the first trimester has not been studied in these trials. Nevertheless, influenza vaccination during the first trimester should not be postponed (see Section 4.6 Fertility, pregnancy and lactation).

Table 6 - Influenza Attack Rates and Vaxigrip Efficacy against Laboratory-confirmed influenza in infants following vaccination in pregnant women

	Influenza Attack Rate (Any influenza A or B type) % (n/N)		**Vaxigrip Efficacy % (95% CI)**
	TIV	**Control***	
Mali	2.4 (45/1,866)	3.8 (71/1,869)	37.3 (7.6 to 57.8)
	TIV	**Placebo**	
Nepal	4.1 (74/1,820)	5.8 (105/1,826)	30.0 (5 to 48)
South Africa	1.9 (19/1,026)	3.6 (37/1,023)	48.8 (11.6 to 70.4)

* Meningococcal vaccine
N: Number of infants included in the analysis
n: number of subjects with laboratory-confirmed influenza
CI: Confidence Interval

The efficacy data indicate a waning of protection in infants born to vaccinated mothers over time after birth.

In the trial conducted in South Africa, vaccine efficacy was highest among infants 8 weeks of age or younger (85.8% [95% CI, 38.3 to 98.4]) and decreased over time; vaccine efficacy was 25.5% (95% CI, -67.9 to 67.8) for infants >8 to 16 weeks of age and 30.4% (95% CI, -154.9 to 82.6) for infants >16 to 24 weeks of age.

In the trial conducted in Mali, there is also a trend of higher efficacy of the trivalent inactivated influenza vaccine in infants during the first 4 months after birth (70.2% [95% CI, 35.7 to 87.6]), with lower efficacy within the fifth month of surveillance (60.7% [95% CI, 33.8 to 77.5]) and a marked fall within the sixth month (37.3% [95% CI, 7.6 to 57.8]).

The prevention of influenza disease can only be expected if the infant(s) are exposed to strains included in the vaccine administered to the mother.

Immunogenicity of Vaxigrip Tetra

Clinical studies performed in adults from 18 to 60 years of age, in elderly over 60 years of age, in children from 3 to 8 years of age and from 6 to 35 months of age assessed the non-inferiority of Vaxigirip Tetra versus Vaxigrip for HAI (hemagglutinin inhibition) Geometric Mean antibody Titre (GMT) at Day 21 (for adults) and at Day 28 (for children), HAI seroconversion rate (4-fold rise in reciprocal titre or change from undetectable [< 10] to a reciprocal titre of ≥ 40), and HAI GMTR (post-/pre-vaccination titres).

One clinical study performed in adults from 18 to 60 years of age and in children from 9 to 17 years of age described the immune response of Vaxigrip Tetra versus Vaxigrip for HAI GMT at Day 21. Another clinical study performed in children from 9 to 17 years of age described only the immune response of Vaxigrip Tetra.

One clinical study performed in pregnant women described the immune response of Vaxigrip Tetra versus Vaxigrip (TIV) for HAI GMT at Day 21, HAI seroconversion rate, and HAI GMTR after one dose administered during the second or third trimester of pregnancy. In this study, the transplacental transfer was evaluated using HAI GMTs of maternal blood, of cord blood and of ratio cord blood/maternal blood, at delivery.

Vaxigrip Tetra induced a significant immune response to the 4 influenza strains contained in the vaccine.
In children from 3 years of age, in adults including pregnant women and the elderly, Vaxigrip Tetra was as immunogenic as Vaxigrip for the strains in common. Vaxigrip Tetra elicited a superior immune response against the additional B strain included in Vaxigrip Tetra compared to Vaxigrip.

Adults and elderly

A randomised, active controlled non-inferiority study was conducted to assess the immunogenicity of Vaxigrip Tetra compared to Vaxigrip. A total of 1114 adults from 18 to 60

years of age and 1111 elderly over 60 years of age were randomised to receive either one dose of Vaxigrip Tetra or one dose of Vaxigrip (one of two formulations of comparator vaccine (TIV), each containing a B strain that corresponds to one of the two B strains in Vaxigirip Tetra (a B strain of the Yamagata lineage and a B strain of the Victoria lineage)

The immunogenicity of Vaxigrip Tetra was assessed 21 days after injection by HAI method in all subjects (832 adults from 18 to 60 years of age and 831 elderly over 60 years of age) and by seroneutralisation (SN) method in subsets of subjects (150 adults from 18 to 60 years of age and 150 elderly over 60 years of age).

Immunogenicity results in adults from 18 to 60 years of age and in elderly over 60 years of age for Vaxigrip Tetra are presented in Table 7 and Table 8, respectively.

Table 7 - Immunogenicity results by HAI and SN methods in adults from 18 to 60 years, 21 days post-vaccination with Vaxigrip Tetra

	HAI Method (N= 832)	**SN Method (N=150)**
	GMT (95% CI)	**GMT (95% CI)**
A (H1N1)[c]	608 (563;657)	3540 (2997; 4183)
A (H3N2)	498 (459; 541)	215 (182; 254)
B (Victoria)	708 (661; 760)	1143 (952; 1373)
B (Yamagata)	1715 (1607; 1830)	1825 (1463; 2277)
	SC % (95% CI)[a]	**≥4-fold-rise n(%) [d]**
A (H1N1) [c]	64.1 (60.7; 67.4)	61.3 (53.0; 69.2)
A (H3N2)	66.2 (62.9; 69.4)	47.3 (39.1; 55.6)
B (Victoria)	70.9 (67.7; 74.0)	70.0 (62.0; 77.2)
B (Yamagata)	63.7 (60.3;67.0)	67.3 (59.2; 74.8)
	GMTR (95% CI)[b]	**GMTR (95% CI) [b]**
A (H1N1) [c]	9.77 (8.69; 11.0)	13.4 (9.61; 18.6)
A (H3N2)	10.3 (9.15; 11.5)	4.6 (3.81; 5.56)
B (Victoria)	11.6 (10.4; 12.9)	11.9 (9.24; 15.2)
B (Yamagata)	7.35(6.66; 8.12)	12.8 (9.64; 17.0)

N : number of subjects with available data for the considered endpoint

GMT : Geometric Mean Titre; CI: Confidence Interval

(a) SC: Seroconversion or significant increase : for subjects with a pre-vaccination titre <10 (1/dil), proportion of subjects with a post vaccination titre ≥40 (1/dil) and for subjects with a pre-vaccination titre ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titre

(b) GMTR: Geometric mean of individual titre ratios (post-/pre-vaccination titres)

(c) N=833 for HAI method,

(d) For subjects with a pre-vaccination titre <10 (1/dil), proportion of subjects with a post vaccination titre ≥40 (1/dil) and for subjects with a pre-vaccination titre ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination

Table 8 - Immunogenicity results by HAI and SN methods in elderly over 60 years of age, 21 days post-vaccination with Vaxigrip Tetra

	HAI Method (N=831)	**SN Method (N=150)**
	GMT (95% CI)	**GMT (95% CI)**
A (H1N1) [(c)]	219 (199; 241)	988 (763; 1279)
A (H3N2)	359 (329; 391)	179 (151; 212)
B (Victoria)	287 (265; 311)	509 (414; 625)
B (Yamagata)	655 (611; 701)	572 (465; 704)
	SC % (95% CI)[a]	**≥4-fold-rise n (%) [d]**
A (H1N1) [(c)]	45.6 (42.1; 49.0)	54.7(46.3; 62.8)
A (H3N2)	47.5 (44.1; 51.0)	33.3(25.9; 41.5)
B (Victoria)	45.2 (41.8; 48.7)	42.7 (34.6; 51.0)
B (Yamagata)	42.7 (39.3; 46.2)	41.6 (33.6; 50.0)
	GMTR (95% CI)[b]	**GMTR (95% CI) [b]**
A (H1N1) [(c)]	4.94 (4.46; 5.47)	7.19 (5.59; 9.24)
A (H3N2)	5.60 (5.02; 6.24)	3.67 (3.00; 4.50)
B (Victoria)	4.61 (4.18; 5.09)	4.46 (3.60; 5.53)
B (Yamagata)	4.11 (3.73; 4.52)	4.68 (3.67; 5.96)

N : number of subjects with available data for the considered endpoint

GMT : Geometric Mean Titre; CI: Confidence Interval

(a) SC: Seroconversion or significant increase for subjects with a pre-vaccination titre <10 (1/dil), proportion of subjects with a post vaccination titre ≥40 (1/dil) and for subjects with a pre-vaccination titre ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titre

(b) GMTR: Geometric mean of individual titre ratios (post-/pre-vaccination titres)

(c) N=832 for HAI method

(d) For subjects with a pre-vaccination titre <10 (1/dil), proportion of subjects with a post vaccination titre ≥40 (1/dil) and for subjects with a pre-vaccination titre ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titre

The same trend as that described using HAI method was observed using SN method for both adult and elderly population.

Pregnant women and transplacental transfer

In a randomised, controlled clinical study conducted in Finland, a total of 230 pregnant women received Vaxigrip Tetra and 116 pregnant women received Vaxigrip (TIV) during the second or third trimester of pregnancy (from 20 to 32 weeks of pregnancy).

Immunogenicity results by HAI method, in pregnant women 21 days after vaccination with Vaxigrip Tetra or Vaxigrip (TIV) are presented in Table 9.

Immunogenicity descriptive assessment by HAI method, at delivery, in blood sample of mother (BL03M), in cord blood sample (BL03B) and of the transplacental transfer (BL03B/ BL03M) are presented in Table 9.

At delivery, the level of antibodies in the cord sample compared to the mother sample was almost doubled for the A/H1N1 strain and increased between 1.5 and 1.7 times for the A/H3N2, B/Brisbane, and B/Phuket strains, supporting that there is transplacental antibody transfer from mother to the newborn, following vaccination of women with Vaxigrip Tetra or Vaxigrip (TIV) during the second or third trimester of pregnancy.

These data are consistent with the passive protection demonstrated in infants from birth to approximately 6 months of age following vaccination of women during the second or third trimester of pregnancy with Vaxigrip (TIV) in studies conducted in Mali, Nepal, and South Africa.

Table 9 - Immunogenicity results by HAI method in pregnant women, 21 days post-vaccination with Vaxigrip Tetra and at delivery

Antigen Strain	Pregnant Women N=216	At Delivery N*=178
	GMT (95% CI)	**BL03M [c] GMT (95% CI)**
A (H1N1)*	525 (466; 592)	304 (265 ; 349)
A (H3N2) *	341 (286; 407)	178 (146 ; 218)
B1 (Victoria) *	568 (496; 651)	290 (247 ; 341)
B2 (Yamagata) *	993 (870; 1134)	547 (463 ; 646)
	≥4-fold-rise n (%) [a]	**BL03B [d] GMT (95% CI)**
A (H1N1) *	38.0 (31.5; 44.8)	576 (492 ; 675)
A (H3N2) *	59.3 (52.4; 65.9)	305 (246 ; 379)
B1 (Victoria) *	61.1 (54.3; 67.7)	444 (372 ; 530)
B2 (Yamagata) *	59.7 (52.9; 66.3)	921 (772 ; 1099)
	GMTR (95% CI) [b]	**Transplacental transfer: BL03B/BL03M [e] GMT (95% CI)**
A (H1N1) *	3.81 (3.11; 4.66)	1.89 (1.72 ; 2.08)
A (H3N2) *	8.63 (6.85; 10.9)	1.71 (1.56 ; 1.87)
B1 (Victoria) *	8.48 (6.81; 10.6)	1.53 (1.37 ; 1.71)
B2 (Yamagata) *	6.26 (5.12; 7.65)	1.69 (1.54 ; 1.85)

Antigen Strain	Pregnant Women N=216	At Delivery N*=178
N: number of subjects with available data for the considered endpoint N*: number of subjects with available data for the considered endpoint: women who received QIV or TIV, delivered at least 2 weeks after injection and with available cord blood and mother blood at the time of delivery *A/H1N1: A/Michigan/45/2015 (H1N1) pdm09-like virus; A/H3N2: A/Hong Kong/4801/2014 (H3N2)-like virus; B1: B/Brisbane/60/2008-like virus (B/Victoria lineage): B2: B/Phuket/3073/2013-like virus (B/Yamagata lineage) GMT: Geometric Mean Titer; CI: Confidence Interval (a) SC: Seroconversion or significant increase: for subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥40 (1/dil) and for subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titer (b) GMTR: Geometric mean of individual titer ratios (post-/pre-vaccination titers) (c) BL03M: Blood sample of mother at delivery (d) BL03B: Cord blood sample at delivery (e) If a mother has X babies, her titers values is counted X times		

Children from 3 to 8 years of age:

A randomised, active controlled study was conducted to assess the immunogenicity of Vaxigrip Tetra compared to Vaxigrip. A total of 1242 children 3 to 8 years of age were randomised to receive either one or two doses of Vaxigrip Tetra or of Vaxigrip (control vaccine) depending on their previous influenza vaccination history.

The immunogenicity of Vaxigrip Tetra was assessed 28 days after receipt of the last injection of Vaxigrip Tetra by HAI method in all subjects and by SN method in subsets of subjects.

Children who received a one-or two-dose schedule of Vaxigrip Tetra presented a similar immune response following the last dose of the respective schedule.

Table 10 - Immunogenicity results by HAI and SN methods in children from 3 to 8 years of age, 28* days post vaccination with Vaxigrip Tetra

	HAI Method (N=863)	**SN Method (N=431)**
	GMT (95% CI)	**GMT (95% CI)**
A (H1N1)	971 (896; 1052)	3499 (3138; 3902)
A (H3N2)	1568 (1451; 1695)	475 (430; 525)

	HAI Method (N=863)	SN Method (N=431)
B (Victoria)	1050 (956; 1154)	905 (788; 1039)
B (Yamagata)[(c)]	1173 (1078; 1276)	731 (638; 838)
	SC % (95% CI)[a]	**≥4-fold-rise n(%) [d]**
A (H1N1)	65.7 (62.4; 68.9)	60.3(55.5; 65.0)
A (H3N2)	64.8 (61.5; 68.0)	52.0 (47.1; 56.8)
B (Victoria)	84.8 (82.3; 87.2)	*80.3 (76.2; 83.9)*
B (Yamagata)[(c)]	88.5 (86.2; 90.6)	84.7 (80.9; 88.0)
	GMTR (95% CI)[b]	**GMTR (95% CI) [b]**
A (H1N1)	6.86 (6.24; 7.53)	8.45 (7.20; 9.92)
A (H3N2)	7.49 (6.72; 8.35)	5.03 (4.46; 5.68)
B (Victoria)	17.1 (15.5; 18.8)	13.6 (11.9; 15.5)
B (Yamagata)[(c)]	25.3 (22.8; 28.2)	19.3 (16.8; 22.1)

*28 days for primed subjects and 56 days for unprimed subjects in the SN method

N : number of subjects with available data for the considered endpoint

GMT : Geometric Mean Titre; CI: Confidence Interval

(a) SC: Seroconversion or significant increase : f or subjects with a pre-vaccination titre <10 (1/dil), proportion of subjects with a post vaccination titre ≥40 (1/dil) and for subjects with a pre-vaccination titre ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titre

(b) GMTR: Geometric mean of individual titre ratios (post-/pre-vaccination titres)

(c) N=862 for HAI method

(d) For subjects with a pre-vaccination titre <10 (1/dil), proportion of subjects with a post vaccination titre ≥40 (1/dil) and for subjects with a pre-vaccination titre ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titre

Children from 9 to 17 years of age:

In a total of 429 children from 9 to 17 years of age who received one dose of Vaxigrip Tetra the immune response against the 4 strains contained in the vaccine was similar to the immune response induced in adults 18 to 60 years of age.

Children from 6 months to 35 months of age:

In addition to the Vaxigrip Tetra efficacy, the immunogenicity of two 0.5ml of doses of Vaxigrip Tetra (N=341) compared to two 0.5ml of doses of Vaxigrip (N=369) was assessed 28 days after receipt of the last injection of Vaxigrip Tetra by HAI method in children 6 to 35 months of age and by SN method in subsets of subjects.

Table 11 - Immunogenicity results by HAI and SN methods in children from 6 to 35 months of age, 28* days post vaccination with Vaxigrip Tetra

	HAI Method (N=341)	**SN Method (N=169)**
	GMT (95% CI)	**GMT (95% CI)**
A (H1N1)	641 (547; 752)	2207 (1767; 2756)
A (H3N2)	1071 (925; 1241)	516 (432; 617)
B (Victoria)	623 (550; 706)	494 (415; 587)
B (Yamagata)	1010 (885; 1153)	371 (308; 447)
	SC % (95% CI)[a]	**≥4-fold-rise n (%) [c]**
A (H1N1)	90.3 (86.7; 93.2)	77.5 (70.5; 83.6)
A (H3N2)	90.3 (86.7; 93.2)	84.6 (78.3; 89.7)
B (Victoria)	98.8 (97.0; 99.7)	98.2 (94.9; 99.6)
B (Yamagata)	96.8 (94.3; 98.4)	97.0 (93.2; 99.0)
	GMTR (95% CI)[b]	**GMTR (95% CI) [b]**
A (H1N1)	36.6 (30.8; 43.6)	73.3 (50.0; 108)
A (H3N2)	42.6 (35.1; 51.7)	16.1 (12.9; 20.1)
B (Victoria)	100 (88.9; 114)	66.8 (55.7; 80.1)
B (Yamagata)	93.9 (79.5; 111)	44.4 (36.5; 53.9)

*28 days for primed subjects and 56 days for unprimed subjects in the SN method

N : number of subjects with available data for the considered endpoint

GMT : Geometric Mean Titre; CI: Confidence interval

(a) SC: Seroconversion or significant increase : for subjects with a pre-vaccination titre <10 (1/dil), proportion of subjects with a post vaccination titre ≥40 (1/dil) and for subjects with a pre-vaccination titre ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titre

(b) GMTR :Geometric mean of individual titre ratios (post-/pre-vaccination titres)

(c) For subjects with a pre-vaccination titre <10 (1/dil), proportion of subjects with a post vaccination titre ≥40 (1/dil) and for subjects with a pre-vaccination titre ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titre

These immunogenicity data provide supportive information in addition to vaccine efficacy data available in this population.

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Vaxigrip Tetra has not been tested for genotoxic potential

Carcinogenicity

Vaxigrip Tetra has not been tested for carcinogenic potential

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Buffer Solution:

- Sodium chloride
- Potassium chloride
- Dibasic sodium phosphate dihydrate
- Monobasic Potassium phosphate
- Water for injections

No adjuvant and no preservative are added.

Vaxigrip Tetra may contain traces of ovalbumin (≤ 0.05 micrograms), neomycin (≤ 10.1 picograms), formaldehyde (≤ 30 micrograms) and octoxinol-9 (≤ 222.5 micrograms), which are used during the manufacturing process (see Section 4.4 Special warnings and precautions for use).

6.2 INCOMPATIBILITIES

This vaccine must not be mixed with other vaccines or medicinal products.

6.3 SHELF LIFE

Vaxigrip Tetra has a shelf life of 12 months when stored at 2°C to 8°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Discard if vaccine has been frozen. In the absence of photostability studies, this vaccine should be protected from light.

6.5 NATURE AND CONTENTS OF CONTAINER

0.5 mL of suspension in pre-filled syringe with one separate needle or no needle provided per syringe – pack size of 1 or 10*.

Vaxigrip Tetra pre-filled syringe is not made with natural rubber latex.

*Not all pack sizes or presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedures.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure and CAS number

Not applicable/defined for vaccines.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

sanofi-aventis australia pty ltd
12 – 24 Talavera Road
Macquarie Park NSW 2113
Australia
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

20 May 2019

10 DATE OF REVISION

16 January 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Post-marketing section updated to include rash