AUSTRALIAN PRODUCT INFORMATION – VAXIGRIP TETRA INACTIVATED QUADRIVALENT INFLUENZA VACCINE (SPLIT VIRION), INFLUENZA VIRUS HAEMAGGLUTININ

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/Michigan/45/2015 (H1N1)pdm09-like virus (A/Michigan/45/2015 X-275)	15 micrograms HA**
A/Switzerland/8060/2017 (H3N2)-like virus A/ Brisbane/1/2018 X-311)	15 micrograms HA**
B/Phuket/3073/2013-like virus (B/Phuket/3073/2013; Yamagata lineage)	15 micrograms HA**
B/Colorado/06/2017-like virus (B/Maryland/15/2016 BX-69A; Victoria lineage)	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 2019 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 active immunisation of adults and children from 6 months of age and older 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.

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.

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 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.

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

Children less than 6 months of age: the safety and efficacy of Vaxigrip Tetra in children less than 6 months of age have not been established.

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. Vaxigrip Tetra should be given to a pregnant woman following an assessment of the risks and benefits. 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%)

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

In all of the trials, the comparator vaccine was Vaxigrip. In addition, a placebo was also used as comparator in the 6 to 35 months population. The overall safety profile of Vaxigirip Tetra was comparable to Vaxigrip.

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. In subpopulation of children less than 24 months of age, the most frequently reported adverse reaction was irritability and in subpopulation of children from 24 to 35 months of age, it was malaise.

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

Adults and elderly

In 3 randomised active controlled studies, 3040 adults from 18 to 60 years of age received one dose (0.5 mL) of Vaxigrip Tetra and 557 received one dose (0.5 mL) of Vaxigirip. The most frequently reported reactions following Vaxigrip Tetra administration were injection site pain, headache, myalgia and malaise.

In 2 randomised, active controlled studies, 1392 elderly over 60 years of age received one dose (0.5 mL) of Vaxigrip Tetra and 502 received one dose (0.5mL) of Vaxigrip. The most frequently reported reactions following Vaxigrip Tetra administration were injection site pain, headache and myalgia.

Table 1 and

Table 2 summarise the frequencies of solicited and unsolicited adverse reactions, respectively, that were recorded following vaccination with Vaxigrip Tetra in adults (18 to 60 years of age) and elderly (over 60 years of age).

Table 1 - Frequency of unsolicited adverse reactions within 7 days after vaccination with Vaxigrip Tetra in adults (18 to 60 years of age) and elderly (> 60 years of age)

	Adults (18 to 60 years) (N=3040)		**Elderly (> 60 years) (N=1392)**	
Subjects experiencing at least one:	**%**	**Frequency**	**%**	**Frequency**
General disorders and administration site conditions				
Local reactions				
Injection site pain	52.8	Very Common	25.8	Very Common
Injection site erythema	7.6	Common	7	Common
Injection site swelling	5.9	Common	3.5	Common
Injection site induration	5.7	Common	3	Common
Injection site ecchymosis	0.9	Uncommon	0.4	Uncommon
Systemic reactions				
Malaise	19.2	Very Common	9.3	Common
Shivering	6.2	Common	4.3	Common
Fever	1.3	Common	0.9	Uncommon
Nervous system disorders				
Headache	27.8	Very Common	15.6	Very Common
Musculoskeletal and connective tissue disorders				
Myalgia	23	Very Common	13.9	Very Common

Table 2 - Frequency of unsolicited adverse reactions within 21 days after vaccination with Vaxigrip Tetra in adults (18 to 60 years of age) and elderly (> 60 years of age)

	Adults (18 to 60 years) (N=3040)		Elderly (> 60 years) (N=1392)	
Subjects experiencing at least one:	**%**	**Frequency**	**%**	**Frequency**
General disorders and administration site conditions				
Local reactions				
Injection site pruritus	0.8	Uncommon	0.8	Uncommon
Injection site warmth	0.2	Uncommon	0.1	Uncommon
Injection site discomfort	<0.1	Rare	-	-
Systemic reactions				
Fatigue	0.4	Uncommon	0.2	Uncommon
Influenza like illness	<0.1	Rare	<0.1	Rare
Asthenia	<0.1	Rare	<0.1	Rare
Respiratory, Thoracic And Mediastinal Disorders				
Dyspnoea	<0.1	Rare	-	-
Gastrointestinal Disorders				
Diarrhoea	0.1	Uncommon	0.1	Uncommon
Nausea	0.1	Uncommon	<0.1	Rare
Nervous System Disorders				
Dizziness	<0.1	Rare	0.1	Uncommon
Paraesthesia	<0.1	Rare	<0.1	Rare
Somnolence	<0.1	Rare	<0.1	Rare
Vascular disorders				
Hot Flush	-	-	0.1	Uncommon
Skin And Subcutaneous Tissue Disorders				
Urticaria	<0.1	Rare	-	-
Angioedema	<0.1	Rare	-	-
Dermatitis allergic	<0.1	Rare	-	-
Erythema	<0.1	Rare	<0.1	Rare
Hyperhidrosis	<0.1	Rare	<0.1	Rare
Pruritus	<0.1	Rare	0.1	Uncommon
Pruritus generalised	<0.1	Rare	-	-

	Adults (18 to 60 years) (N=3040)		Elderly (> 60 years) (N=1392)	
Musculoskeletal And Connective Tissue Disorders				
Arthralgia	<0.1	Rare	-	-
Blood And Lymphatic System Disorders				
Lymphadenopathy	0.1	Uncommon	-	-
Immune System Disorders				
Hypersensitivity	<0.1	Rare	-	-

Children from 9 to 17 years and 3 to 8 years

In a randomised, active controlled study and an uncontrolled study, 429 children and adolescents from 9 to 17 years of age received one dose (0.5 mL) of Vaxigrip Tetra and 55 received one dose (0.5 mL) of Vaxigirip. The most frequently reported reactions following Vaxigrip Tetra administration were injection site pain, myalgia, headache, malaise and injection site swelling.

In a randomised active controlled study 884 children from 3 to 8 years of age received one or two doses (0.5 mL) of Vaxigrip Tetra and 354 received one or two doses (0.5 mL) of Vaxigrip.

The safety profile of Vaxigrip Tetra was similar after the first and the second injections.

The most frequently reported reactions following Vaxigrip Tetra administration were injection site pain malaise, myalgia, headache, injection site swelling, injection site erythema, injection site induration and shivering.

Table 3 and Table 4 summarise the frequencies of the solicited and unsolicited adverse reactions, respectively, that were recorded following vaccination with Vaxigrip Tetra in children from 9 to 17 years of age and from 3 to 8 years of age.

Table 3 - Frequency of solicited adverse reactions within 7 days after any vaccination with Vaxigrip Tetra in children from 9 to 17 years of age (one dose) and from 3 to 8 years of age (one or two doses)

	9 to 17 years (N=429)		3 to 8 years (N=884)	
Subjects experiencing at least one:	**%**	**Frequency**	**%**	**Frequency**
General disorders and administration site conditions				
Local reactions				
Injection site pain	54.5	Very Common	56.5	Very Common
Injection site swelling	10.7	Very Common	20.5	Very Common

	9 to 17 years (N=429)		3 to 8 years (N=884)	
Injection site erythema	9.8	Common	20.4	Very Common
Injection site induration	6.8	Common	16.4	Very Common
Injection site ecchymosis	1.6	Common	5.8	Common
Systemic reactions				
Malaise	20.3	Very Common	30.7	Very Common
Shivering	3.7	Common	11.2	Very Common
Fever	2.3	Common	8.4	Common
Nervous system disorders				
Headache	24.7	Very Common	25.7	Very Common
Musculoskeletal and connective tissue disorders				
Myalgia	29.1	Very Common	28.5	Very Common

Table 4 - Frequency of unsolicited adverse reactions within 21 days (9 to 17 years of age- one dose) or 28 days (3 to 8 years of age- one to two dose) after any vaccination with Vaxigrip Tetra

	9 to 17 years (N=429)		3 to 8 years (N=884)	
Subjects experiencing at least one:	**%**	**Frequency**	**%**	**Frequency**
General disorders and administration site conditions				
Injection site pruritus	0.2	Uncommon	-	-
Fatigue	-	-	0.6	Uncommon
Injection site warmth	-	-	0.3	Uncommon
Gastrointestinal Disorders				
Diarrhoea	0.2	Uncommon	0.5	Uncommon
Vomiting	-	-	0.2	Uncommon
Abdominal pain upper	-	-	0.1	Uncommon
Psychiatric disorders				
Restlessness	-	-	0.2	Uncommon
Moaning	-	-	0.1	Uncommon
Nervous System Disorders				
Dizziness	-	-	0.2	Uncommon
Musculoskeletal And Connective Tissue Disorders				

Arthralgia	-	-	0.1	Uncommon
Blood and Lymphatic System Disorders				
Thrombocytopenia	-	-	0.1	Uncommon

Children from 6 to 35 months

In one study, 1614 children from 6 to 35 months of age received 2 doses (0.5 mL) of Vaxigrip Tetra, 1612 received 2 doses (0.5 mL) of placebo (NaCl 0.9%) and 367 received 2 doses (0.5 mL) of Vaxigirip.

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.

The most frequently reported reactions following Vaxigrip Tetra, administration were:

- For all children from 6 to 35 months of age: injection site pain/tenderness, fever and injection site erythema,
- In subpopulation of children less than 24 months of age: irritability, appetite lost, crying abnormal, vomiting and drowsiness,
- In subpopulation of children from 24 months to 35 months of age: malaise, headache and myalgia.

Table 5 - Frequency of solicited adverse reactions within 7 days after any vaccination with Vaxigrip Tetra compared to placebo in children from 6 to 35 months of age

	Vaxigrip Tetra (N=1614)		**Placebo (N=1612)**	
Subjects experiencing at least one:	**%**	**Frequency**	**%**	**Frequency**
General disorders and administration site conditions				
Local reactions				
Injection site pain /tenderness	26.8	Very common	21.6	Very Common
Injection site swelling	7.6	Common	4.1	Common
Injection site erythema	17.2	Very Common	12.9	Very Common
Injection site induration	9.1	Common	4.9	Common
Injection site ecchymosis	4.2	Common	3.3	Common
Systemic reactions				
Malaise*	26.8	Very Common	24.5	Very Common
Shivering*	5.6	Common	7.0	Common
Fever	20.4	Very Common	18.2	Very Common
Crying abnormal[#]	27.1	Very Common	29.7	Very Common

	Vaxigrip Tetra (N=1614)		Placebo (N=1612)	
Drowsiness[#]	13.9	Very Common	14.2	Very Common
Irritability[#]	32.3	Very Common	33.3	Very Common
Appetitive lost[#]	28.9	Very Common	28.4	Very Common
Gastrointestinal Disorders				
Vomiting #	16.1	Very Common	17.2	Very Common
Nervous system Disorders				
Headache*	11.9	Very Common	11.4	Very Common
Musculoskeletal and connective tissue disorders				
Myalgia*	11.6	Very Common	9.3	Common

*Solicited recorded for subjects ≥ 24 months

#Solicited recorded for subjects < 24 months

Table 6 - Frequency of unsolicited adverse reactions within 28 days after any vaccination with Vaxigrip Tetra compared to placebo in children from 6 to 35 months of age

	Vaxigrip Tetra (N=1614)		Placebo (N=1612)	
Subjects experiencing at least one:	**%**	**Frequency**	**%**	**Frequency**
General disorders and administration site conditions				
Influenza like illness	< 0.1	Rare	0	-
Injection site pruritus	< 0.1	Rare	0	-
Injection site rash	< 0.1	Rare	0	-
Irritability[*]	< 0.1	Rare	0	-
Malaise[#]	< 0.1	Rare	0	-
Gastrointestinal Disorders				
Diarrhoea	0.5	Uncommon	0.6	Uncommon
Vomiting[*]	0.2	Uncommon	0.2	Uncommon
Skin and Subcutaneous Tissue Disorders				
Pruritus generalised	< 0.1	Rare	0	-
Rash papular	< 0.1	Rare	<0.1	Rare
Immune system Disorders				
Hypersensitivity	0.1	Uncommon	0	-
Metabolism and nutrition disorders				

Decrease appetite*	< 0.1	Rare	0.2	Uncommon
Musculoskeletal And Connective Tissue Disorders				
Myalgia#	< 0.1	Rare	0	-

*In children ≥24 months of age

#In children < 24 months of age

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.

In the South Africa and Mali studies conducted in pregnant women with Vaxigrip (thiomersal free) (see Section 4.6 Fertility, Pregnancy and Lactation), 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; when higher frequencies were noted, the differences were limited and may be explained by the pregnant status of the study subjects. In the South Africa study, local reactions were more frequent in the Vaxigrip group than in the placebo group in both HIV-uninfected and HIV-infected cohorts. There were no other significant differences in solicited reactions between Vaxigrip and placebo groups in both cohorts.

Post marketing experience

There are no safety data from post-marketing experience with Vaxigrip Tetra.

However, the following adverse reactions have been reported with Vaxigrip during clinical trials or from post-marketing experience and may occur in people receiving Vaxigrip Tetra.

Immune system disorders

Severe allergic reactions: shock

Allergic reactions: rash, generalised erythema

Nervous system disorders

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

Vascular disorders

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

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 (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

4.9 OVERDOSE

Not documented for Vaxigrip Tetra. Cases of administration of more than the recommended dose (overdose) have been reported with Vaxigrip. When adverse reactions were reported, the information was consistent with the known safety profile of Vaxigrip.

For information on the management of overdose, contact the Poisons Information Centre, on 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

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 $\geq$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

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 7 - 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:

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).

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.

Vaxigrip Tetra induced a significant immune response to the 4 influenza strains contained in the vaccine.

In children from 3 years of age and in adults and 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 8** and Table 9, respectively.

Table 8 - 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 9 - 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.

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 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)
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 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 attached needle, or with one separate 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.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Australia
sanofi-aventis australia pty ltd
Talavera Corporate Centre – Building D
12 – 24 Talavera Road
Macquarie Park NSW 2113
Australia
Tel: 1800 818 806

New Zealand
Sanofi-aventis new Zealand limited
Level 8
56 Cawley St
Ellerslie Auckland
New Zealand
Tel: 0800 283 684

9 DATE OF FIRST APPROVAL

20 May 2019

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New registration