PROFESSIONAL INFORMATION FOR VAXIGRIP TETRA

SCHEDULING STATUS S2

1. NAME OF THE MEDICINE

VAXIGRIP TETRA 2023 strains suspension for injection

Quadrivalent influenza vaccine (split virion, inactivated).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per 0,5 mL dose:

Active substance:

Split influenza virus, inactivated strains for 2023 Southern Hemisphere

A/Sydney/5/2021 (H1N1)pdm09 - like strain (A/Sydney/5/2021, SAN-013)……..... 15 micrograms*

A/Darwin/9/2021 (H3N2) - like strain (A/Darwin/9/2021, IVR-228)…….…….. 15 micrograms*

B/Austria/1359417/2021 - like strain (B/Michigan/01/2021, wild type)…….…. 15 micrograms*

B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, wild type).....……. 15 micrograms*

* Haemagglutinin

This vaccine complies with WHO Southern Hemisphere recommendations for the 2023 season.

Sugar free.

For the full list of excipients, see section 6.1.

VAXIGRIP TETRA may contain traces of eggs, such as ovalbumin, and of neomycin, formaldehyde and octoxinol-9, which are used during the manufacturing process (see section 4.3).

3. PHARMACEUTICAL FORM

Suspension for injection.

Colourless opalescent liquid and free from visible particulate matter, presented in a pre-filled syringe that contains one dose of 0,5 mL.

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 4.4, 4.6 and 5.1).

4.2 Posology and method of administration

Posology

Due to the variation of the influenza virus 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.

Adults: one dose of 0,5 mL.

Paediatric population:

- Children from 6 months to 17 years of age: one dose of 0,5 mL.

  For children less than 9 years of age who have not previously been vaccinated, a second dose of 0,5 mL should be given after an interval of at least 4 weeks.
- Infants less than 6 months of age: the safety and efficacy of VAXIGRIP TETRA administration (active immunisation) have not been established. No data are available.

  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).

Method of administration

The vaccine should be given 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 administering VAXIGRIP TETRA:

For instructions on preparation of VAXIGRIP TETRA before administration, see section 6.6.

4.3 Contraindications

VAXIGRIP TETRA should not be administered to subjects with a history of severe allergic reaction to egg proteins (eggs or egg products), to chicken proteins, to any component of the vaccine (i.e. as defined under sections 2 and 6.1 including manufacturing residuals) or a history of severe allergic reaction after previous administration of VAXIGRIP TETRA or a vaccine containing the same components.

Administration of VAXIGRIP TETRA should be postponed in subjects suffering from moderate or severe febrile disease or acute disease.

4.4 Special warnings and precautions for use

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

Vaccination with VAXIGRIP TETRA may not protect all vaccinees.

Regarding passive protection, not all infants less than 6 months of age born to women vaccinated during pregnancy will be protected (see section 5.1).

Influenza virus is remarkably unpredictable in that significant antigenic changes may occur from

time to time.

It is known that VAXIGRIP TETRA as constituted per annual seasonal composition, is not effective against all possible strains of influenza virus.

VAXIGRIP TETRA is intended to provide protection against those strains of virus from which the vaccine is prepared.

If VAXIGRIP TETRA is used in immunocompromised persons whether due to genetic, immunodeficiency disease, or immunosuppressive therapy, they may have a reduced immune response to vaccination.

Interference with serological testing

See section 4.5.

Do not administer VAXIGRIP TETRA by intravascular injection.

- The vaccine must be administered with caution to subjects with thrombocytopenia or a bleeding disorder, since bleeding may occur following an intramuscular administration to these subjects.
- Appropriate medical treatment and supervision should be readily available for immediate use in case of an anaphylactic reaction following the administration of the vaccine.
- As a precautionary measure, adrenaline (epinephrine) injection (1:1 000) must be immediately available in case of unexpected anaphylactic or serious allergic reactions.
- 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 falling injury and manage syncopal reactions.

4.5 Interaction with other medicines and other forms of interaction

No studies regarding the simultaneous administration of VAXIGRIP TETRA and other vaccines have been conducted.

Nevertheless, clinical data showing that VAXIGRIP can be administered concomitantly with other

vaccines are available for the following vaccines: Pneumococcal polysaccharide vaccine in elderly subjects, Tdap-IPV (Adacel QUADRA®) in adults aged ≥ 60 years and zoster vaccine (Zostavax®) in adults aged 50 years and older.

In addition, according to ACIP, there is no evidence that inactivated vaccines interfere with the immune response to other inactivated vaccines or to live vaccines. Any inactivated vaccine can be administered either simultaneously or at any time before or after a different inactivated vaccine or live vaccine.

VAXIGRIP TETRA should not be mixed with any other vaccines or medicines in the same syringe. Separate injection sites and separate syringes should be used in case of concomitant administration. Persons deficient in producing antibodies due to immunosuppressive therapy may have a reduced immune response to vaccination.

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV-1, hepatitis C and especially HTLV-1 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

One developmental and reproductive toxicity study conducted in rabbits with VAXIGRIP TETRA did not show any effects on mating performance, embryo-fetal development and early postnatal development.

Pregnant women are at high risk of influenza complications, including premature labour and delivery, hospitalisation, and death; therefore, pregnant women should receive an influenza vaccine, whatever their stage of pregnancy during the influenza season.

VAXIGRIP TETRA can be administered in all stages of pregnancy based on the safety data from clinical studies and post-marketing experience with VAXIGRIP TETRA and with the Sanofi Pasteur

trivalent influenza vaccine, VAXIGRIP thiomersal free.

Data from worldwide use of inactivated influenza vaccines, including experience with use of VAXIGRIP TETRA and VAXIGRIP in countries where inactivated influenza vaccines are recommended in all stages of pregnancy, and 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.

Data from four clinical studies conducted with VAXIGRIP thiomersal free 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 post-partum), did not indicate any adverse fetal, newborn, infant or maternal outcomes attributable to the vaccine.

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

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

In these clinical studies, none of the serious adverse events reported in women, fetuses or infants were considered related to VAXIGRIP TETRA or VAXIGRIP.

Breastfeeding

There are no data on the effect of the vaccine in breastfed newborns/infants of women vaccinated with VAXIGRIP TETRA during the breastfeeding period.

Based on inactivated influenza vaccines experience, VAXIGRIP TETRA may be used during breastfeeding.

Fertility

There are no fertility data available in humans.

One animal study with VAXIGRIP TETRA did not indicate harmful effects on female fertility.

4.7 Effects on ability to drive and use machines

VAXIGRIP TETRA has no or negligible influence on the ability to drive a vehicle and use machines.

4.8 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 (frequent): ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %)

Uncommon (infrequent): ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %)

Rare: ≥ 1/10 000 and < 1/1 000 (≥ 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 (trivalent).

Data from clinical studies

The safety of VAXIGRIP TETRA was assessed in six randomised, controlled clinical trials in which 3 040 adults from 18 to 60 years of age, 1 392 elderly patients over 60 years of age and 429 children and adolescents from 9 to 17 years of age received one dose (0,5 mL) of VAXIGRIP TETRA, and 884 children from 3 to 8 years of age received one or two doses (0,5 mL) of VAXIGRIP TETRA and 1 614 children from 6 to 35 months of age received two doses (0,5 mL) of VAXIGRIP

TETRA. In all of these trials, the comparator vaccine was VAXIGRIP (trivalent).
In addition, a placebo was also used as comparator in the 6 to 35 months population.

The overall safety profile of VAXIGRIP TETRA was comparable to VAXIGRIP (trivalent). For all subjects, safety evaluations were performed during the first 21 days following vaccination, except for children 6 months to 8 years of age, where safety evaluations were performed during the first 28 days after any vaccination. Serious adverse reactions were collected during six months of follow-up. Most of the 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. (Grade I: Fever: ≥ 38,0 °C to ≤ 38,4 °C except for < 24 months of age: ≥ 38,0 °C to ≤ 38,5 °C / Injection site reactions: ≥ 25 to ≤ 50 mm except for children under 12 years old: < 25 mm / Other reactions: no interference with activity).

The most frequently reported adverse reaction after vaccination, in all populations, including the whole group of children from 6 months to 35 months of age, was injection site pain.
In the subpopulation of children less than 24 months of age, the most frequently reported adverse reaction was irritability and in the 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 in children.

Adults

In 3 randomised active-controlled studies, 3 040 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 VAXIGRIP.
The most frequently reported reactions following VAXIGRIP TETRA administration were injection site pain, headache, myalgia and malaise.

Side effects reported within 7 days after vaccination with VAXIGRIP TETRA in adults from 18 to 60 years of age

Nervous system disorders

Very common: headache

Musculoskeletal and connective tissue disorders

Very common: myalgia

General disorders and administration site conditions

Very common: injection site pain, malaise

Common: injection site erythema, injection site swelling, injection site induration, shivering, fever

Uncommon: injection site ecchymosis.

Side effects reported within 21 days after vaccination with VAXIGRIP TETRA in adults from 18 to 60 years of age

Blood and lymphatic system disorders

Uncommon: lymphadenopathy

Immune system disorders

Rare: hypersensitivity

Nervous system disorders

Rare: dizziness, paraesthesia, somnolence

Respiratory, thoracic and mediastinal disorders

Rare: dyspnoea

Gastrointestinal disorders

Uncommon: diarrhoea, nausea

Skin and subcutaneous tissue disorders

Rare: urticaria, angioedema, allergic dermatitis, erythema, hyperhidrosis, pruritus, generalised pruritus

Musculoskeletal and connective tissue disorders

Rare: arthralgia

General disorders and administration site conditions

Uncommon: injection site pruritus, injection site warmth, fatigue

Rare: injection site discomfort, influenza-like illness, asthenia.

Elderly patients

In 2 randomised, active-controlled studies, 1 392 elderly patients over 60 years of age received one dose (0,5 mL) of VAXIGRIP TETRA, and 502 received one dose (0,5 mL) of VAXIGRIP (trivalent). The most frequently reported reactions following VAXIGRIP TETRA administration were injection site pain, headache and myalgia.

Side effects reported within 7 days after vaccination with VAXIGRIP TETRA in elderly patients over 60 years of age

Nervous system disorders

Very common: headache

Musculoskeletal and connective tissue disorders

Very common: myalgia

General disorders and administration site conditions

Very common: injection site pain

Common: injection site erythema, injection site swelling, injection site induration, shivering, malaise

Uncommon: injection site ecchymosis, fever.

Side effects reported within 21 days after vaccination with VAXIGRIP TETRA in elderly patients over 60 years of age

Nervous system disorders

Uncommon: dizziness

Rare: paraesthesia, somnolence

Vascular disorders

Uncommon: hot flushes

Gastrointestinal disorders

Uncommon: diarrhoea

Rare: nausea

Skin and subcutaneous tissue disorders

Uncommon: pruritus

Rare: erythema, hyperhidrosis

General disorders and administration site conditions

Uncommon: injection site pruritus, injection site warmth, fatigue

Rare: asthenia, influenza-like illness.

Children and adolescents 9 to17 years of age

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 VAXIGRIP (trivalent).

The most frequently reported reactions following VAXIGRIP TETRA administration were injection site pain (54,5 %), myalgia (29,1 %), headache (24,7 %) malaise (20,3 %) and injection site swelling (10,7 %).

Side effects reported within 7 days after vaccination with VAXIGRIP TETRA in children and adolescents from 9 to 17 years of age

Nervous system disorders

Very common: headache

Musculoskeletal and connective tissue disorders

Very common: myalgia

General disorders and administration site conditions

Very common: injection site pain, injection site swelling, malaise

Common: injection site erythema, injection site induration, injection site ecchymosis, shivering, fever.

Side effects reported within 21 days after vaccination with VAXIGRIP TETRA in children and adolescents 9 to 17 years of age

Gastrointestinal disorders

Uncommon: diarrhoea

General disorders and administration site conditions

Uncommon: injection site pruritus.

Children from 3 to 8 years of age

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 (trivalent). 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 (56,5 %), 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 %).

Side effects reported within 7 days after any vaccination with VAXIGRIP TETRA in children from 3 to 8 years of age

Nervous system disorders

Very common: headache

Musculoskeletal and connective tissue disorders

Very common: myalgia

General disorders and administration site conditions

Very common: injection site pain, injection site swelling, injection site erythema, injection site induration, malaise, shivering

Common: injection site ecchymosis, fever.

Side effects reported within 28 days after any vaccination with VAXIGRIP TETRA in children from 3 to 8 years of age

Blood and lymphatic system disorders

Uncommon: thrombocytopenia

Psychiatric disorders

Uncommon: restlessness, moaning

Nervous system disorders

Uncommon: dizziness

Gastrointestinal disorders

Uncommon: diarrhoea, vomiting, upper abdominal pain

Musculoskeletal and connective tissue disorders

Uncommon: arthralgia

General disorders and administration site conditions

Uncommon: fatigue, injection site warmth.

Children from 6 to 35 months of age

In one study, 1 614 children from 6 to 35 months of age received 2 doses (0,5 mL) of VAXIGRIP TETRA, 1 612 received 2 doses (0,5 mL) of placebo and 367 received 2 doses (0,5 mL) of VAXIGRIP.

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 (26,8 %), fever (20,4 %) and injection site erythema (17,2 %).
- In subpopulation of children less than 24 months of age: irritability (32,3 %), appetite loss (28,9 %), abnormal crying (27,1 %), vomiting (16,1 %) and drowsiness (13,9 %).
- In a subpopulation of children from 24 to 35 months of age: malaise (26,8 %), headache (11,9 %) and myalgia (11,6 %).

Side effects reported within 7 days after any vaccination with VAXIGRIP TETRA compared to VAXIGRIP in children from 6 months to 35 months of age

Nervous system disorders

Very common: headache*

Gastrointestinal disorders

Very common: vomiting†

Musculoskeletal and connective tissue disorders

Very common: myalgia*

General disorders and administration site conditions

Very common: injection site pain/tenderness, injection site erythema, fever, malaise*, abnormal crying†, drowsiness†, irritability†, appetite loss†

Common: injection site swelling, injection site induration, ecchymosis, shivering*.

* Solicited, recorded for subjects ≥ 24 months.

† Solicited, recorded for subjects < 24 months.

Side effects within 28 days after any vaccination with VAXIGRIP TETRA compared to VAXIGRIP in children from 6 months to 35 months of age

Immune system disorders

Uncommon: hypersensitivity

Metabolism and nutrition disorders

Rare: decreased appetite[(a)]

Gastrointestinal disorders

Uncommon: diarrhoea, vomiting[(a)]

Skin and subcutaneous tissue disorders

Rare: generalised pruritus, papular rash

Musculoskeletal and connective tissue disorders

Rare: myalgia[(b)]

General disorders and administration site conditions

Rare: influenza-like illness, injection site pruritus, injection site rash, irritability[(a)], malaise[(b)].

[(a)] In children ≥ 24 months of age.

[(b)] 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.

Pregnant women:

In clinical studies conducted in pregnant women in South Africa and Mali with VAXIGRIP (see sections 4.6 and 5.1), frequencies of local and systemic solicited reactions reported within 7 days following administration of VAXIGRIP were consistent with those reported for the adult population during clinical studies conducted with VAXIGRIP. In the South Africa study, 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 and 5.1), frequencies of local and systemic solicited reactions reported within 7 days following

administration of VAXIGRIP TETRA were consistent with those reported for the nonpregnant 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, used as comparator, suggesting a clinical study effect in this pregnant women population.

Data from post-marketing experience

Immune system disorders

Not known: allergic reactions, including anaphylactic reactions.

Adverse events

The following adverse events were reported following commercial use of VAXIGRIP (trivalent). A causal relationship with VAXIGRIP TETRA has not been established.

Blood and lymphatic system disorders

Transient thrombocytopenia*, lymphadenopathy*

Immune system disorders

Severe allergic reactions: shock

Allergic reactions: rash, generalised erythema

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 with VAXIGRIP TETRA only in some age

groups (see “Data from clinical studies” above).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or
- SAHPRA via the “Adverse Drug Reactions Reporting Form” found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

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.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 30.2 Antigens

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02.

5.1 Pharmacodynamic properties

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 postvaccination 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 the trivalent vaccine, annual influenza vaccination is recommended given the duration of immunity provided by the vaccine and because circulating strains of influenza virus changes from year to year.

Efficacy of VAXIGRIP TETRA

Paediatric population

Children from 6 to 35 months of age (active immunisation)

A randomised placebo-controlled study was conducted in 4 regions (Africa, Asia, Latin America and Europe) over 4 influenza seasons (Southern Hemisphere 2014, Northern Hemisphere 2014 – 2015, Southern Hemisphere 2015, Northern Hemisphere 2015 – 2016), in more than 5 400 children from 6 to 35 months of age who received two doses (0,5 mL) of VAXIGRIP TETRA (N = 2 722), or placebo (N = 2 717) 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 1: Influenza attack rates and VAXIGRIP TETRA efficacy against laboratory-confirmed influenza illness in children from 6 to 35 months of age

		VAXIGRIP TETRA (N = 2 584)		Placebo (N = 2 591)	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 (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 above “Children from 6 to 35 months of age” and below “Immunogenicity”).

Pregnant women

There are no clinical efficacy data describing use of VAXIGRIP TETRA in pregnant women.

In randomised, controlled phase IV clinical studies conducted in Mali, Nepal and South Africa, approximately 5 000 pregnant women received VAXIGRIP (trivalent influenza thiomersal-free vaccine) 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 following vaccination during these trimesters of pregnancy (see Table 2 below). In the study conducted in Nepal, the efficacy of VAXIGRIP for the prevention of influenza in pregnant women following vaccination during these trimesters of pregnancy was not demonstrated.

Table 2: 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)**
	VAXIGRIP	**Control***	
Mali	0,5 (11/2 108)	1,9 (40/2 085)	70,3 (42,2 to 85,8)
	VAXIGRIP	**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 less than 6 months of age born to vaccinated pregnant women (passive protection) Infants less than 6 months of age are at high risk of influenza, resulting in high rates of hospitalisation; however, influenza vaccines are not indicated for active immunisation in this age group.
There are no clinical efficacy data in infants born to women vaccinated with VAXIGRIP TETRA during pregnancy.
Efficacy in infants of women who received a single 0,5 mL dose of VAXIGRIP TETRA during the second or third trimester of pregnancy has not been studied; however, efficacy in infants of women who received a single 0,5 mL dose of VAXIGRIP during the second or third trimester has been demonstrated in clinical trials and can be extrapolated to VAXIGRIP TETRA.
Efficacy of the trivalent inactivated influenza vaccine VAXIGRIP in infants following vaccination of pregnant women during the first trimester has not been studied in these trials. Necessary influenza vaccination during the first trimester should not be postponed (see section 4.6).

In the randomised, controlled, phase IV clinical studies conducted in Mali, Nepal and South Africa, the efficacy of VAXIGRIP thiomersal free, for the prevention of influenza in infants younger than 6 months of age following vaccination of women during the second or third trimester of pregnancy, was confirmed (see Table 3 below).

Table 3: 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)**
	VAXIGRIP	**Control***	
Mali	2,4 (45/1 866)	3,8 (71/1 869)	37,3 (7,6 to 57,8)
	VAXIGRIP	**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 protection of the infants born to vaccinated mothers by 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

Clinical studies performed in adults from 18 to 60 years of age, in elderly patients over 60 years of age and in children 3 to 8 years of age and from 6 to 35 months of age assessed the non-inferiority of VAXIGRIP TETRA versus VAXIGRIP (trivalent) for HAI 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 GMT ratio (post-/prevaccination 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 (trivalent) for HAI geometric mean antibody titre (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 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 mother blood, of cord blood and of ratio cord blood/mother blood, at delivery.

VAXIGRIP TETRA induced a significant immune response to the 4 influenza strains contained in the vaccine.
VAXIGRIP TETRA elicited a superior immune response against the additional B strain included in VAXIGRIP TETRA compared to VAXIGRIP (trivalent).

Adults and elderly patients

A total of 1 114 adults from 18 to 60 years of age and 1 111 elderly patients over 60 years of age were randomised to receive either one dose of VAXIGRIP TETRA or one dose of VAXIGRIP (trivalent). The immunogenicity of VAXIGRIP TETRA was assessed 21 days after injection by the haemagglutination inhibition (HAI) method in all subjects.

Table 4: Immunogenicity results by HAI method in adults from 18 to 60 years, 21 days postvaccination with VAXIGRIP TETRA or VAXIGRIP (trivalent)

Antigen strain	**VAXIGRIP TETRA N = 832**	**Alternative VAXIGRIP [(a)] (B Victoria) N = 140**	**Licensed VAXIGRIP [(b)] (B Yamagata) N = 138**
GMT (95 % CI)			
A (H1N1) [(c)(d)]	608 (563; 657)	685 (587; 800)	
A (H3N2) [(c)]	498 (459; 541)	629 (543; 728)	

B (Victoria)	708 (661; 760)	735 (615; 879)	204 (170; 243)
B (Yamagata)	1 715 (1 607; 1 830)	689 (556; 854)	1 735 (1 490; 2 019)
SC % (95 % CI) [e]			
A (H1N1) [c][d]	64,1 (60,7; 67,4)	65,1 (59,2; 70,7)	
A (H3N2) [c]	66,2 (62,9; 69,4)	73,4 (67,8; 78,5)	
B (Victoria)	70,9 (67,7; 74,0)	70,0 (61,7; 77,4)	38,4 (30,3; 47,1)
B (Yamagata)	63,7 (60,3; 67,0)	42,1 (33,9; 50,8)	60,9 (52,2; 69,1)
GMTR (95 % CI) [f]			
A (H1N1) [c][d]	9,77 (8,69; 11,0)	10,3 (8,35; 12,7)	
A (H3N2) [c]	10,3 (9,15; 11,5)	14,9 (12,1; 18,4)	
B (Victoria)	11,6 (10,4; 12,9)	11,4 (8,66; 15,0)	3,03 (2,49; 3,70)
B (Yamagata)	7,35 (6,66; 8,12)	3,22 (2,67; 3,90)	6,08 (4,79; 7,72)

N: Number of subjects with available data for the considered endpoint.

GMT: Geometric mean titre.

GMTR: Geometric mean titre ratio.

CI: Confidence interval.

SC: Seroconversion.

SI: Significant increase.

(a) Alternative VAXIGRIP containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).

(b) 2014-2015 licensed VAXIGRIP containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 (Yamagata lineage).

(c) Pooled TIV group includes participants vaccinated with either Alternative VAXIGRIP or licensed VAXIGRIP, N = 278.

(d) N = 833 for VAXIGRIP TETRA group.

(e) 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.

(f) Geometric mean of individual ratios (post-/prevaccination titres).

Table 5: Immunogenicity results by HAI method in elderly patients over 60 years of age, 21 days postvaccination with VAXIGRIP TETRA or VAXIGRIP (trivalent)

Antigen strain	VAXIGRIP TETRA N = 831	Alternative VAXIGRIP [a] (B Victoria) N = 138	Licensed VAXIGRIP [b] (B Yamagata) N = 137
GMT (95 % CI)			
A (H1N1) [c][d]	219 (199; 241)	268 (228; 314)	
A (H3N2) [c]	359 (329; 391)	410 (352; 476)	
B (Victoria)	287 (265; 311)	301 (244; 372)	121 (101; 147)
B (Yamagata)	55 (611; 701)	351 (294; 420)	697 (593; 820)
SC % (95% CI) [e]			
A (H1N1) [c][d]	45,6 (42,1; 49,0)	50,2 (44,1; 56,2)	
A (H3N2) [c]	47,5 (44,1; 51,0)	48,5 (42,5; 54,6)	
B (Victoria)	45,2 (41,8; 48,7)	43,5 (35,1; 52,2)	21,2 (14,7; 29,0)
B (Yamagata)	42,7 (39,3; 46,2)	28,3 (20,9; 36,5)	38,7 (30,5; 47,4)
GMTR (95 % CI) [f]			
A (H1N1) [c][d]	4,94 (4,46; 5,47)	6,03 (4,93; 7,37)	
A (H3N2) [c]	5,60 (5,02; 6,24)	5,79 (4,74; 7,06)	
B (Victoria)	4,61 (4,18; 5,09)	4,60 (3,50; 6,05)	1,99 (1,70; 2,34)
B (Yamagata)	4,11 (3,73; 4,52)	2,04 (1,71; 2,43)	4,11 (3,19; 5,30)

N: Number of subjects with available data for the considered endpoint.

GMT: Geometric mean titre.

CI: Confidence interval.

(a) Alternative TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).

(b) 2014-2015 licensed TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 (Yamagata lineage).

(c) Pooled TIV group includes participants vaccinated with either alternative TIV or licensed TIV, N = 275.

(d) N = 832 for QIV group.

(e) 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.

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

Pregnant women and transplacental transfer

A randomised, controlled clinical study was conducted in Finland in pregnant women to describe the immune response of VAXIGRIP TETRA compared to VAXIGRIP, 21 days after vaccination and to evaluate the transplacental transfer of antibody from mother to newborn from the cord blood after 1 dose of VAXIGRIP TETRA or of VAXIGRIP.

A total of 230 pregnant women received VAXIGRIP TETRA and 116 pregnant women received VAXIGRIP 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 TETRA, are presented in table 6 below.

Table 6: Immunogenicity results by HAI method in pregnant women, 21 days postvaccination with VAXIGRIP TETRA or VAXIGRIP

Antigen strain	**VAXIGRIP TETRA N = 216**	**VAXIGRIP (B Victoria) N = 109**
GMT (95 % CI)		
A (H1N1)*	525 (466; 592)	638 (529; 769)
A (H3N2)*	341 (286; 407)	369 (283; 483)
B1 (Victoria)*	568 (496; 651)	697 (569; 855)
B2 (Yamagata)*	993 (870; 1 134)	529 (415; 674)
≥ 4-fold rise n (%) [(a)]		
A (H1N1)*	38,0 (31,5; 44,8)	41,3 (31,9; 51,1)

A (H3N2)*	59,3 (52,4; 65,9)	62,4 (52,6; 71,5)
B1 (Victoria)*	61,1 (54,3; 67,7)	60,6 (50,7; 69,8)
B2 (Yamagata)*	59,7 (52,9; 66,3)	38,5 (29,4; 48,3)
GMTR (95 % CI) [(b)]		
A (H1N1)*	3,81 (3,11; 4,66)	5,26 (3,66; 7,55)
A (H3N2)*	8,63 (6,85; 10,9)	9,23 (6,56; 13,0)
B1 (Victoria)*	8,48 (6,81; 10,6)	9,62 (6,89; 13,4)
B2 (Yamagata)*	6,26 (5,12; 7,65)	3,40 (2,68; 4,32)

N: Number of subjects with available data for the considered endpoint.

GMT: Geometric mean titre.

CI: Confidence interval.

* 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): this strain was included in the VAXIGRIP composition;

B2: B/Phuket/3073/2013 - like virus (B/Yamagata lineage): this strain was not included in the VAXIGRIP composition.

(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).

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 7 below.

Table 7: Immunogenicity descriptive assessment by HAI method of VAXIGRIP TETRA or VAXIGRIP (trivalent) at delivery

Antigen strain	**VAXIGRIP TETRA** **N = 178**	**VAXIGRIP (B Victoria)** **N = 89**
BL03M† **GMT (95 % CI)**		
A (H1N1)*	304 (265; 349)	411 (332; 507)
A (H3N2)*	178 (146; 218)	186 (137; 250)
B1 (Victoria)*	290 (247; 341)	371 (299; 461)
B2 (Yamagata)*	547 (463; 646)	367 (281; 479)
BL03B** **GMT (95 % CI)**		
A (H1N1)*	576 (492; 675)	751 (605; 932)
A (H3N2)*	305 (246; 379)	324 (232; 452)
B1 (Victoria)*	444 (372; 530)	608 (479; 772)
B2 (Yamagata)*	921 (772; 1 099)	539 (389; 748)
Transplacental transfer: BL03B/BL03M§ **GMT (95 % CI)**		
A (H1N1)*	1,89 (1,72; 2,08)	1,83 (1,64; 2,04)
A (H3N2)*	1,71 (1,56; 1,87)	1,75 (1,55; 1,97)
B1 (Victoria)*	1,53 (1,37; 1,71)	1,64 (1,46; 1,85)
B2 (Yamagata)*	1,69 (1,54; 1,85)	1,47 (1,28; 1,69)

N: Number of subjects with available data for the considered endpoint: women who received VAXIGRIP TETRA or VAXIGRIP, delivered at least 2 weeks after injection and with available cord blood and mother blood at the time of delivery.

GMT: Geometric mean titre;

CI: Confidence interval.

* 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): this strain was included in the VAXIGRIP composition;

B2: B/Phuket/3073/2013 - like virus (B/Yamagata lineage): this strain was not included in the VAXIGRIP composition.

† BL03M: Blood sample of mother at delivery.

** BL03B: Cord blood sample at delivery.

§ If a mother has X babies, her titre value is counted X times.

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 (trivalent) 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 (trivalent) in studies conducted in Mali, Nepal and South Africa (see section 5.1).

Paediatric 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 6 months to 8 years of age

A total of 1 242 children 3 to 8 years of age were randomised to receive either one or two doses of VAXIGRIP TETRA or of VAXIGRIP (trivalent) (control vaccine) depending on their previous influenza vaccination history.

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 8: Immunogenicity results by HAI method in children from 3 to 8 years of age, 28 days after the last injection of VAXIGRIP TETRA or VAXIGRIP

Antigen strain	**QIV N = 863**	**Alternative VAXIGRIP** [a] **(B Victoria) N = 176**	**Licensed VAXIGRIP** [b] **(B Yamagata) N = 168**
GMT (95 % CI)			
A (H1N1) [c]	971 (896; 1 052)	1 141 (1 006; 1 295)	
A (H3N2) [c]	1 568 (1 451; 1 695)	1 746 (1 551; 1 964)	
B (Victoria) [d]	1 050 (956; 1 154)	1 120 (921; 1 361)	170 (125; 232)
B (Yamagata) [e] [f]	1 173 (1 078; 1 276)	217 (171; 276)	1 211 (1 003; 1 462)
SC % (95 % CI) [g]			
A (H1N1) [c]	65,7 (62,4; 68,9)	65,7 (60,4; 70,7)	
A (H3N2) [c]	64,8 (61,5; 68,0)	67,7 (62,5; 72,6)	
B (Victoria) [d]	84,8 (82,3; 87,2)	90,3 (85,0; 94,3)	38,5 (31,1; 46,2)
(Yamagata) [e] [f]	88,5 (86,2; 90,6)	46,0 (38,4; 53,7)	89,9 (84,3; 94,0)
GMTR (95 % CI) [h]			
A (H1N1) [c]	6,86 (6,24; 7,53)	7,65 (6,54; 8,95)	
A (H3N2) [c]	7,49 (6,72; 8,35)	7,61 (6,69; 9,05)	
B (Victoria) [d]	17,1 (15,5; 18,8)	17,8 (14,5; 22,0)	3,52 (2,93; 4,22)
B (Yamagata) [e] [f]	25,3 (22,8; 28,2)	4,60 (3,94; 5,37)	30,4 (23,8; 38,4)

N: Number of subjects with available data for the considered endpoint.

GMT: Geometric mean titre.

CI: Confidence interval.

(a) Alternative VAXIGRIP containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).

(b) 2014-2015 licensed VAXIGRIP containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 (Yamagata lineage).

(c) Pooled VAXIGRIP group includes participants vaccinated with either alternative VAXIGRIP or licensed VAXIGRIP, N = 344.

(d) N = 169 for VAXIGRIP (B Yamagata) group.

(e) N = 862 for VAXIGRIP TETRA group.

(f) N = 175 for VAXIGRIP (B Victoria) group.

(g) 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.

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

Table 9: Immunogenicity results by SN method in children from 3 to 8 years of age, 28 days after the last injection of VAXIGRIP TETRA or VAXIGRIP

Antigen strain	**QIV N = 431**	**Alternative VAXIGRIP (a) (B Victoria) N = 86**	**Licensed VAXIGRIP (b) (B Yamagata) N = 83**
GMT (95 % CI)			
A (H1N1) [c] [d]	3 499 (3 138; 3 902)	4 462 (3 778; 5 268)	
A (H3N2) [c]	475 (430; 525)	542 (467; 629)	
B (Victoria)	905 (788; 1 039)	980 (722; 1 329)	203 (139; 298)
B (Yamagata)	731 (638; 838)	131 (94,4; 181)	952 (709; 1 279)
≥ 4-fold rise n (%) [e]			
A (H1N1) [c] [d]	60,3(55,5; 65,0)	60,9 (53,2; 68,3)	
A (H3N2) [c]	52,0 (47,1; 56,8)	52,1 (44,3; 59,8)	
B (Victoria)	80,3 (76,2; 83,9)	89,5 (81,1; 95,1)	41,0 (30,3; 52,3)
B (Yamagata)	84,7 (80,9; 88,0)	39,5 (29,2; 50,7)	86,7 (77,5; 93,2)
GMTR (95 % CI) [f]			

A (H1N1) [c] [d]	8,45 (7,20; 9,92)	8,21 (6,37; 10,6)	
A (H3N2) [c]	5,03 (4,46; 5,68)	5,45 (4,50; 6,61)	
B (Victoria)	13,6 (11,9; 15,5)	15,6 (12,1; 20,1)	3,51 (2,78; 4,44)
B (Yamagata)	19,3 (16,8; 22,1)	3,87 (3,12; 4,81)	25,2 (18,1; 35,1)

*: 28 days for primed subjects and 56 days for unprimed subjects.

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

GMT: Geometric mean titre.

(a) Alternative VAXIGRIP containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).

(b) 2014-2015 licensed VAXIGRIP containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 (Yamagata lineage).

(c) Pooled VAXIGRIP group includes participants vaccinated with either alternative VAXIGRIP or licensed VAXIGRIP, N = 169.

(d) N = 431 for VAXIGRIP TETRA group.

(e) 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.

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

Children from 6 to 35 months of age

In addition to the VAXIGRIP TETRA efficacy, the immunogenicity of two 0,5 mL doses of VAXIGRIP TETRA (N = 341) compared to two 0,5 mL doses of VAXIGRIP (N = 369) was assessed 28 days after receipt of the last injection of VAXIGRIP TETRA by haemagglutination inhibition (HAI) method in children 6 to 35 months of age and by seroneutralisation (SN) method in subsets of subjects.

Table 10: Immunogenicity results by HAI method in children from 6 to 35 months of age, 28 days after the last injection of VAXIGRIP TETRA or VAXIGRIP

Antigen strain	**QIV N = 341**	**Alternative VAXIGRIP** [a] **(B Victoria) N = 172**	**Licensed VAXIGRIP** [b] [c] **(B Yamagata) N = 178**

GMT (95 % CI)			
A (H1N1)	641 (547; 752)	637 (500; 812)	628 (504; 781)
A (H3N2)	1 071 (925; 1 241)	1 021 (824; 1 266)	994 (807; 1 224)
B (Victoria)	623 (550; 706)	835 (691; 1 008)	10,0 (8,27; 12,1)
B (Yamagata) [(d)]	1 010 (885; 1 153)	39,9 (31,2; 51,0)	1 009 (850; 1 198)
SC % (95 % CI) [(e)]			
A (H1N1)	90,3 (86,7; 93,2)	87,2 (81,3; 91,8)	90,4 (85,1; 94,3)
A (H3N2)	90,3 (86,7; 93,2)	88,4(82,6; 92,8)	87,6 (81,9; 92,1)
B (Victoria)	98,8 (97,0; 99,7)	99,4 (96,8; 100,0)	2,2 (0,6; 5,7)
B (Yamagata)	96,8 (94,3; 98,4)	33,9 (26,9; 41,5)	99,4 (96,9; 100,0)
GMTR (95 % CI) [(f)]			
A (H1N1)	36,6 (30,8; 43,6)	35,3 (27,4; 45,5)	40,6 (32,6; 50,5)
A (H3N2)	42,6 (35,1; 51,7)	44,1 (33,1; 58,7)	37,1 (28,3; 48,6)
B (Victoria)	100 (88,9; 114)	114 (94,4; 138)	1,52 (1,40; 1,64)
B (Yamagata)	93,9 (79,5; 111)	4,34 (3,62; 5,20)	111 (91,3; 135)

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

GMT: Geometric mean titre.

CI: Confidence interval.

(a) Alternative VAXIGRIP containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).

(b) 2014-2015 licensed VAXIGRIP containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2) and B/Massachusetts/2/2012 (Yamagata lineage).

(c) Dose of 0,5 mL.

(d) N = 171 for Alternate VAXIGRIP (B Victoria) group.

(e) 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.

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

These immunogenicity data provide supportive information in addition to vaccine efficacy data

available in this population (see “Efficacy of VAXIGRIP TETRA”).

Table 11: Immunogenicity results by SN method in children from 6 to 35 months of age, 28 days after the last injection of VAXIGRIP TETRA or VAXIGRIP

Antigen strain	QIV N = 169	Alternative VAXIGRIP [a] (B Victoria) N = 86	Licensed VAXIGRIP [b] (B Yamagata) N = 88
GMT (95 % CI)			
A (H1N1) [c]	2 207 (1 767; 2 756)	2 824 (2 142; 3 723)	2 280 (1 725; 3 013)
A (H3N2)	516 (432; 617)	574 (441; 748)	643 (491; 841)
B (Victoria)	494 (415; 587)	907 (690; 1 191)	18,9 (14,5; 24,7)
B (Yamagata)	371 (308; 447)	20,6 (16,0; 26,5)	440 (334; 579)
≥ 4-fold rise n (%) [d]			
A (H1N1) [c]	77,5 (70,5; 83,6)	72,6 (61,8; 81,8)	84,1 (74,8; 91,0)
A (H3N2)	84,6 (78,3; 89,7)	78,8 (68,6; 86,9)	84,1 (74,8; 91,0)
B (Victoria)	98,2 (94,9; 99,6)	98,8 (93,6; 100,0)	31,8 (22,3; 42,6)
B (Yamagata)	97,0 (93,2; 99,0)	27,1 (18,0; 37,8)	95,5 (88,8; 98,7)
GMTR (95 % CI) [e]			
A (H1N1) [c]	73,3 (50,0; 108)	70,7 (40,1; 125)	96,6 (59,3; 157)
A (H3N2)	16,1 (12,9; 20,1)	12,8 (9,36; 17,4)	16,5 (11,9; 22,7)
B (Victoria)	66,8 (55,7; 80,1)	98,3 (73,4; 132)	2,96 (2,46; 3,56)
B (Yamagata)	44,4 (36,5; 53,9)	2,57 (2,16; 3,06)	54,1 (41,4; 70,7)

*: 28 days for primed subjects and 56 days for unprimed subjects.

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

GMT: Geometric mean titre.

(a) Alternative VAXIGRIP containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).

(b) 2014-2015 licensed TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 (Yamagata lineage).

(c) N = 85 for alternate VAXIGRIP.

(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.

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

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed.

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

Buffer saline solution containing:

- sodium chloride
- potassium chloride
- disodium phosphate dihydrate
- potassium dihydrogen phosphate
- water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, VAXIGRIP TETRA must not be mixed with other medicines in the same syringe (see section 4.5).

6.3 Shelf life

1 year.

6.4 Special precautions for storage

Store in a refrigerator between 2 °C and 8 °C. Shake before use.

Do not freeze.

Do not use after the expiry date indicated on the label or the package.

Keep the syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

Type I clear, colourless glass single-dose pre-filled syringe with a black bromobutyl or chlorobutyl plunger-stopper without or with a (25 G 5/8) needle.

Pack sizes: 1, 10 or 20.

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 to distribute the suspension uniformly before administration.

Inspect the vaccine visually for particulate matter and/or discolouration prior to administration. If either of these conditions exists, the vaccine should not be administered.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park

Building 1, 5th Floor

90 Bekker Road

Vorna Valley, Midrand, 2196

Tel: 011 256 3700

8. REGISTRATION NUMBER

51/30.1/0838

9. DATE OF FIRST AUTHORISATION

Registration date: 20 March 2019

10. DATE OF REVISION OF THE TEXT

February 2023