SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VAXIGRIPTETRA, suspension for injection in pre-filled syringe

Quadrivalent influenza vaccine (split virion, inactivated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus (inactivated, split) of the following strains*:

A/Victoria/4897/2022 (H1N1)pdm09-like strain (A/Victoria/4897/2022, IVR-238).....
.....15 micrograms HA**

A/Croatia/10136RV/2023 (H3N2)-like strain (A/Croatia/10136RV/2023, X-425A).....
.....15 micrograms HA**

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

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

For one 0.5 mL dose

* propagated in fertilised hens' eggs from healthy chicken flocks

** haemagglutinin

This vaccine complies with the WHO recommendations (Northern Hemisphere) and EU decision for the 2025/2026 season.

For the full list of excipients, see section 6.1.

VAXIGRIPTETRA 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 in pre-filled syringe.

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

VAXIGRIPTETRA 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.
- passive protection of infants less than 6 months of age and born to women vaccinated during pregnancy (see Sections 4.4, 4.6 and 5.1).

The use of VAXIGRIPTETRA should be based on official recommendations.

4.2. Posology and method of administration

Posology

Based on clinical experience with the trivalent vaccine, annual revaccination with influenza vaccine is recommended given the duration of immunity provided by the vaccine and because circulating strains of influenza virus might change from year to year.

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 VAXIGRIPTETRA administration (active immunisation) have not been established. No data are available.
  Regarding passive protection, one 0.5 mL dose administered to a pregnant woman may protect infants from birth to almost 6 months of age; however, not all infants may be protected (see section 5.1).

Method of administration

The vaccine should be given by intramuscular or subcutaneous injection.

The preferred site for intramuscular injection is 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 the medicinal product

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

4.3. Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section 6.1 or to any component that may be present as traces such as eggs (ovalbumin, chicken proteins), neomycin, formaldehyde and octoxinol-9.

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

4.4. Special warnings and precautions for use

Traceability

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

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

VAXIGRIPTETRA should under no circumstances be administered intravascularly.

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

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.

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

As with any vaccine, vaccination with VAXIGRIPTETRA may not protect all vaccinees.

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

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

Interference with serological testing

See section 4.5.

VAXIGRIPTETRA contains potassium and sodium

This vaccine contains less than 1 mmol potassium (39 mg) and less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially “potassium-free” and “sodium-free”.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with VAXIGRIPTETRA.

VAXIGRIPTETRA can be given at the same time as other vaccines, based on clinical experience with Vaxigrip. Separate injection sites and separate needles should be used in case of concomitant administration.

The immunological response may be reduced if the patient is undergoing immunosuppressant treatment.

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the false-positive ELISA test results. The transient false positive results could be due to the IgM response by the vaccine.

4.6. Fertility, pregnancy and lactation

Pregnancy

Pregnant women are at high risk of influenza complications, including premature labour and delivery, hospitalisation, and death: pregnant women should receive an influenza vaccine.

VAXIGRIPTETRA can be used in all stages of pregnancy.

Larger datasets on safety of inactivated influenza vaccines are available for the second and third trimesters, than for the first trimester. Data from worldwide use of inactivated influenza vaccines, including VAXIGRIPTETRA and Vaxigrip (trivalent inactivated influenza vaccine), do not indicate any adverse foetal and maternal outcomes attributable to the vaccine. This is consistent with results observed in one clinical study where VAXIGRIPTETRA and Vaxigrip were administered in pregnant women during the second or third trimester (230 exposed pregnancies and 231 live births for VAXIGRIPTETRA and 116 exposed pregnancies and 119 live births for Vaxigrip).

Data from four clinical studies with the trivalent inactivated influenza vaccine (Vaxigrip) administered in pregnant women during the second or third trimester (more than 5,000 exposed pregnancies and more than 5,000 live births followed up to approximately 6 months post-partum) do not indicate any adverse foetal, newborn, infant and 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 foetal, 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.

For additional information, see Sections 4.8 and 5.1.

One animal study with VAXIGRIPTETRA did not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development or early post-natal development.

Breastfeeding

VAXIGRIPTETRA may be used during breastfeeding.

Fertility

There are no fertility data available in Humans. One animal study with VAXIGRIPTETRA did not indicate harmful effects on female fertility.

4.7. Effects on ability to drive and use machines

VAXIGRIPTETRA has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

The safety of VAXIGRIPTETRA was assessed in six clinical trials in which 3,040 adults from 18 to 60 years of age, 1,392 elderly over 60 years of age and 429 children from 9 to 17 years of age received one dose of VAXIGRIPTETRA, 884 children from 3 to 8 years of age received one or two doses of VAXIGRIPTETRA depending on their influenza vaccination history and 1614 children from 6 to 35 months of age received two doses (0.5 ml) of VAXIGRIPTETRA.

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

The most frequently reported adverse reaction after vaccination, in all populations, including the whole group of children from 6 to 35 months of age, was injection site pain (between 52.8% and 56.5% in children from 3 to 17 years of age and in adults, 26.8% in children from 6 to 35 months of age and 25.8% in elderly). In subpopulation of children less than 24 months of age, irritability (32.3%) was the most frequently reported adverse reaction.
In subpopulation children from 24 to 35 months of age, malaise (26.8%) is the most frequently reported adverse reaction.

The other most frequently reported adverse reactions after vaccination were:

- In adults: headache (27.8%), myalgia (23%) and malaise (19.2%),
- In elderly: headache (15.6%) and myalgia (13.9%),
- In children from 9 to 17 years of age: myalgia (29.1%), headache (24.7%), malaise (20.3%) and injection site swelling (10.7%),
- In children from 3 to 8 years of age: malaise (30.7%), myalgia (28.5%), headache (25.7%), injection site swelling (20.5%), injection site erythema (20.4%), injection site induration (16.4%), shivering (11.2%).
- For all children from 6 to 35 months of age: fever (20.4%) and injection site erythema (17.2%),
- In children less than 24 months of age: appetite lost (28.9%), crying abnormal (27.1%), vomiting (16.1%) and drowsiness (13.9%),
- In children from 24 months to 35 months of age: headache (11.9%) and myalgia (11.6%).

Adverse reactions were generally less frequent in the elderly than in adults and children.

Tabulated summary of adverse reactions

The data below summarize the frequencies of the adverse reactions that were recorded following vaccination with VAXIGRIPTETRA during clinical trials and worldwide post-marketing surveillance.

Adverse events are ranked under headings of frequency using the following convention:

Very common (≥1/10);

Common (≥1/100 to <1/10);

Uncommon (≥1/1,000 to <1/100);

Rare (≥1/10,000 to <1/1,000);

Very rare (<1/10,000).

Not known (cannot be estimated from available data): adverse reactions have been spontaneously reported following commercial use of VAXIGRIPTETRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Within each frequency grouping, the adverse reactions are presented in decreasing order of seriousness.

Adults and elderly

The safety profile presented below is based on:

- data from 3,040 adults from 18 to 60 years of age and 1,392 elderly over 60 years of age.
- data from worldwide post-marketing surveillance (*).

ADVERSE REACTIONS	FREQUENCY
Blood and lymphatic system disorders	
Lymphadenopathy (1)	Uncommon
Immune system disorders	
Hypersensitivity (1), allergic reactions such as angioedema (1), dermatitis allergic (1), pruritus generalised (1), urticaria (1), pruritus (2), erythema	Rare
Anaphylactic reactions	Not known*
Nervous system disorders	
Headache	Very common
Dizziness (3)	Uncommon
Paraesthesia, somnolence	Rare
Vascular disorders	
Hot flush (4)	Uncommon
Respiratory, thoracic and mediastinal disorders	
Dyspnoea (1)	Rare
Gastrointestinal disorders	
Diarrhoea, nausea (5)	Uncommon
Skin and subcutaneous tissue disorders	
Hyperhidrosis	Rare
Musculoskeletal and connective tissue disorders	
Myalgia	Very common
Arthralgia (1)	Rare
General disorders and administration site conditions	
Malaise (6) Injection site pain	Very common
Shivering, fever (2) Injection site erythema, injection site swelling, injection site induration	Common
Fatigue Injection site ecchymosis, injection site pruritus, injection site warmth	Uncommon
Asthenia, flu-like illness Injection site discomfort (1)	Rare

(1) In adults (2) Uncommon in elderly (3) Rare in adults
(4) In elderly (5) Rare in elderly (6) Common in elderly

Paediatric population

The safety profile presented below is based on:

- data from 429 children from 9 to 17 years of age who received one dose of VAXIGRIPTETRA and from 884 children from 3 to 8 years of age who received one or two doses of VAXIGRIPTETRA depending on their influenza vaccination history.
- data from worldwide post-marketing surveillance (*).

ADVERSE REACTIONS	FREQUENCY
Blood and lymphatic system disorders	
Thrombocytopenia (1)	Uncommon
Immune system disorders	
Allergic including anaphylactic reactions	Not known*
Psychiatric disorders	
Moaning (2), restlessness (2)	Uncommon
Nervous system disorders	
Headache	Very common
Dizziness (2)	Uncommon
Gastrointestinal disorders	
Diarrhoea, vomiting (2), abdominal pain upper (2)	Uncommon
Musculoskeletal and connective tissue disorders	
Myalgia	Very common
Arthralgia (2)	Uncommon
General Disorders and administration site conditions	
Malaise, shivering (3) Injection site pain, injection site swelling, injection site erythema (3), injection site induration (3)	Very common
Fever Injection site ecchymosis	Common
Fatigue (2) Injection site warmth (2), injection site pruritus (4)	Uncommon

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

The safety profile presented below is based on:

- data from 1,614 children from 6 to 35 months of age who received two doses of VAXIGRIPTETRA.
- data from worldwide post-marketing surveillance (*).

ADVERSE REACTIONS	FREQUENCY
Immune System Disorders	
Hypersensitivity	Uncommon
Allergic reactions such as pruritus generalised, rash papular	Rare
Anaphylactic reactions	Not known*
Nervous System Disorders	
Headache [1]	Very common
Gastrointestinal Disorders	
Vomiting [2]	Very common
Diarrhoea	Uncommon
Musculoskeletal and Connective Tissue Disorders	
Myalgia [3]	Very common
General Disorders and Administration Site Conditions	
Irritability [4], appetite lost [4], crying abnormal [5], malaise [3], fever, drowsiness [5] Injection site pain/tenderness, injection site erythema	Very common
Shivering [1] Injection site induration, injection site swelling, injection site ecchymosis	Common
Influenza like illness Injection site rash, injection site pruritus	Rare

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

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

Adverse events

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

- ***Blood and lymphatic system disorders***

Transient thrombocytopenia [1], lymphadenopathy [1].

- ***Nervous system disorders***

Paraesthesia [1], Guillain-Barré Syndrome (GBS), neuritis, neuralgia, convulsions, encephalomyelitis.

- ***Vascular disorders***

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

[1] These adverse events were reported during clinical trials only in some age groups (see Tabulated summary of adverse reactions).

Other special populations

The safety profile of VAXIGRIPTETRA 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), the frequencies of local and systemic solicited reactions reported within 7 days following administration of the vaccine 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 VAXIGRIPTETRA (see sections 4.6 and 5.1), frequencies of local and systemic solicited reactions reported within 7 days following administration of VAXIGRIPTETRA were consistent with those reported for the adult population (with the exception of pregnant women) during clinical studies conducted with VAXIGRIPTETRA even though higher for some adverse reactions (injection site pain, malaise, shivering, headache, myalgia).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: “Agence nationale de sécurité du médicament et des produits de santé (ANSM) et réseau des Centres Régionaux de Pharmacovigilance - Site internet : https://signalement.social-sante.gouv.fr/.”

4.9. Overdose

Cases of administration of more than the recommended dose (overdose) have been reported with VAXIGRIPTETRA. When adverse reactions were reported, they were consistent with the safety profile of VAXIGRIPTETRA described in Section 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: INFLUENZA VACCINE, ATC code: J07BB02.

Mechanism of action

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

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

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

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

Annual revaccination with VAXIGRIPTETRA 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 change from year to year.

Efficacy of VAXIGRIPTETRA

Paediatric population

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

A randomized placebo controlled study was conducted in 4 regions (Africa, Asia, Latina America and Europe) over 4 influenza seasons, in more than 5,400 children from 6 to 35 months of age who received two doses (0.5 mL) of VAXIGRIPTETRA (N=2,722), or placebo (N=2,717) 28 days apart to assess VAXIGRIPTETRA 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 VAXIGRIPTETRA Efficacy against laboratory-confirmed influenza illness in children from 6 to 35 months of age

	VAXIGRIPTETRA (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 analysed (full set)
n: number of subjects fulfilling the item listed
CI: Confidence Interval

In addition, a predefined complementary analysis showed VAXIGRIPTETRA 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 VAXIGRIPTETRA 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 from 3 to 8 years of age, the efficacy of VAXIGRIPTETRA 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 VAXIGRIPTETRA“ below).

- Infants less than 6 months of age born to women vaccinated during pregnancy (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.

The efficacy in infants born to women who received a single 0.5 mL dose of VAXIGRIPTETRA during the second or third trimester of pregnancy has not been studied; however, the efficacy in infants born to women who received a single 0.5 mL dose of the trivalent inactivated influenza vaccine (Vaxigrip) during the second or third trimester of pregnancy has been demonstrated in clinical trials and can be extrapolated to VAXIGRIPTETRA.

The efficacy of the trivalent inactivated influenza vaccine (Vaxigrip) in infants born to women vaccinated during the first trimester of pregnancy has not been studied in these trials. If influenza vaccination is considered necessary during the first trimester of pregnancy, it should not be postponed (see section 4.6).

In randomised, controlled phase IV clinical studies conducted in Mali, Nepal and South Africa, approximately 5,000 pregnant women received Vaxigrip (trivalent influenza vaccine) and approximately 5,000 pregnant women received a placebo or control vaccine (quadrivalent meningococcal conjugate vaccine) during the second or third trimester of pregnancy. Vaccine efficacy against laboratory confirmed influenza illness 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). 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 Illness 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; 85.8)
	Vaxigrip	**Placebo**	
South Africa	1.8 (19/1,062)	3.6 (38/1,054)	50.4 (14.5; 71.2)

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

In the same randomised, controlled, phase IV clinical studies conducted in Mali, Nepal and South Africa, 4,530 of the 4,898 (92%) infants born to women who received Vaxigrip (trivalent influenza vaccine) during the second or third trimester of pregnancy, and 4,532 of the 4,868 (93%) infants born to pregnant women who received a placebo or control vaccine (quadrivalent meningococcal conjugate vaccine) during the second or third trimester of pregnancy (see table 3) were followed-up until approximately 6 months of age.

These studies confirmed the efficacy of Vaxigrip for the prevention of influenza in infants born to women vaccinated during these trimesters of pregnancy, from birth until approximately 6 months of age. Women in their first trimester of pregnancy were not included in these studies; the efficacy of Vaxigrip in infants born to women vaccinated during the first trimester of pregnancy could therefore not be evaluated.

Table 3: Influenza Attack Rates and Vaxigrip Efficacy against Laboratory-confirmed influenza illness in infants born to women vaccinated during pregnancy

	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; 57.8)
	Vaxigrip	**Placebo**	
Nepal	4.1 (74/1,820)	5.8 (105/1,826)	30.0 (5; 48)
South Africa	1.9 (19/1,026)	3.6 (37/1,023)	48.8 (11.6; 70.4)

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

The efficacy data indicate a waning protection over time, after birth, of the infants born to women vaccinated during pregnancy.

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

In the trial conducted in Mali, there is also a trend to higher efficacy of the trivalent inactivated influenza vaccine in infants during the first 4 months after birth, with lower efficacy within the 5th month and a marked fall during the 6th month where protection is no longer evident.

The prevention of influenza can only be expected if the infants are exposed to the strains included in the vaccine administered to the mother.

Immunogenicity of VAXIGRIPTETRA

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 assessed VAXIGRIPTETRA immune response 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 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 VAXIGRIPTETRA for HAI antibody GMT at Day 21. Another clinical study performed in children from 9 to 17 years of age described the immune response of VAXIGRIPTETRA.

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

VAXIGRIPTETRA induced a significant immune response against the 4 influenza strains contained in the vaccine.

Adults and elderly

A total of 832 adults from 18 to 60 years of age and 831 elderly over 60 years of age were assessed in terms of immune response after one dose of VAXIGRIPTETRA.

Immunogenicity results are presented in the tables below:

Table 4: Immunogenicity results in adults from 18 to 60 years of age and in elderly over 60 years of age

Antigen strain	18 to 60 years of age N=832	Over 60 years of age N=831
GMT (95% CI)		
A (H1N1) [(a)(b)]	608 (563; 657)	219 (199; 241)
A (H3N2)	498 (459; 541)	359 (329; 391)
B (Victoria)	708 (661; 760)	287 (265; 311)
B (Yamagata)	1715 (1607; 1830)	655 (611; 701)
SC % (95% CI) [(c)]		
A (H1N1) [(a)(b)]	64.1 (60.7; 67.4)	45.6 (42.1; 49.0)
A (H3N2)	66.2 (62.9; 69.4)	47.5 (44.1; 51.0)
B (Victoria)	70.9 (67.7; 74.0)	45.2 (41.8; 48.7)
B (Yamagata)	63.7 (60.3; 67.0)	42.7 (39.3; 46.2)
GMTR (95% CI) [(d)]		
A (H1N1) [(a)(b)]	9.77 (8.69; 11.0)	4.94 (4.46; 5.47)
A (H3N2)	10.3 (9.15; 11.5)	5.60 (5.02; 6.24)
B (Victoria)	11.6 (10.4; 12.9)	4.61 (4.18; 5.09)
B (Yamagata)	7.35 (6.66; 8.12)	4.11 (3.73; 4.52)

N= number of subjects with available data for the considered endpoint
GMT: Geometric Mean Titre; CI: Confidence Interval;
(a) N=833 for 18-60 years of age group
(b) N=832 for over 60 years of age group (c) 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
(d) GMTR: Geometric mean of individual titre ratios (post-/pre-vaccination titres)

Pregnant women and transplacental transfer

A total of 230 pregnant women received VAXIGRIPTETRA 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 VAXIGRIPTETRA are presented in table 5.

Table 5: Immunogenicity results by HAI method in pregnant women, 21 days post-vaccination with VAXIGRIPTETRA

Antigen Strain	VAXIGRIPTETRA N=216
GMT (95% CI)	
A (H1N1)*	525 (466; 592)
A (H3N2)*	341 (286; 407)
B1 (Victoria)*	568 (496; 651)
B2 (Yamagata)*	993 (870; 1134)

Antigen Strain	VAXIGRIPTETRA N=216
≥4-fold-rise n (%) [(a)]	
A (H1N1)*	38.0 (31.5; 44.8)
A (H3N2)*	59.3 (52.4; 65.9)
B1 (Victoria)*	61.1 (54.3; 67.7)
B2 (Yamagata)*	59.7 (52.9; 66.3)
GMTR (95% CI) [(b)]	
A (H1N1)*	3.81 (3.11; 4.66)
A (H3N2)*	8.63 (6.85; 10.9)
B1 (Victoria)*	8.48 (6.81; 10.6)
B2 (Yamagata)*	6.26 (5.12; 7.65)

* A/H1N1: A/Michigan/45/2015 (H1N1) pdm09-like virus;
A/H3N2: A/Hong Kong/4801/2014 (H3N2)-like virus;
B1: B/Brisbane/60/2008-like virus (B/Victoria lineage);
B2: B/Phuket/3073/2013-like virus (B/Yamagata lineage)
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)

Immunogenicity descriptive assessment by HAI method, at delivery, in blood sample of mother (BL03M) and in cord blood sample (BL03B) and of the transplacental transfer (BL03B/BL03M) are presented in table 6.

Table 6: Immunogenicity descriptive assessment by HAI method of VAXIGRIPTETRA, at delivery

Antigen Strain	VAXIGRIPTETRA N=178
BL03M (Maternal blood) GMT (95% CI)	
A (H1N1)*	304 (265; 349)
A (H3N2)*	178 (146; 218)
B1 (Victoria)*	290 (247; 341)
B2 (Yamagata)*	547 (463; 646)
BL03B (Cord blood) GMT (95% CI)	
A (H1N1)*	576 (492; 675)
A (H3N2)*	305 (246; 379)
B1 (Victoria)*	444 (372; 530)
B2 (Yamagata)*	921 (772; 1099)
Transplacental transfer: BL03B/BL03M§ GMT (95% CI)	
A (H1N1)*	1.89 (1.72; 2.08)
A (H3N2)*	1.71 (1.56; 1.87)
B1 (Victoria)*	1.53 (1.37; 1.71)
B2 (Yamagata)*	1.69 (1.54; 1.85)

N: number of subjects with available data for the considered endpoint: women who received VAXIGRIPTETRA, delivered at least 2 weeks after injection and with available cord blood and mother blood at the time of delivery.
* A/H1N1: A/Michigan/45/2015 (H1N1) pdm09-like virus;
A/H3N2: A/Hong Kong/4801/2014 (H3N2)-like virus;

B1: B/Brisbane/60/2008-like virus (B/Victoria lineage)
B2: B/Phuket/3073/2013-like virus (B/Yamagata lineage)
§ If a mother has X babies, her titres values is counted X times

At delivery, the higher level of antibodies in the cord sample compared to the maternal blood sample is consistent with transplacental antibody transfer from mother to the foetus following vaccination of women with VAXIGRIPTETRA 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 in studies conducted in Mali, Nepal, and South Africa (see subsection Efficacy of VAXIGRIPTETRA).

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 VAXIGRIPTETRA, the immune response against the 4 strains contained in the vaccine was similar to the immune response induced in adults from 18 to 60 years of age.

- Children from 6 months to 8 years of age:

A total of 863 children from 3 to 8 years of age received either one or two doses of VAXIGRIPTETRA depending on their previous influenza vaccination history.

Children who received a one- or two-dose schedule of VAXIGRIPTETRA presented a similar immune response following the last dose of each schedule.

In addition to the VAXIGRIPTETRA efficacy, the immunogenicity of two 0.5 mL doses of VAXIGRIPTETRA was assessed 28 days after the last injection of VAXIGRIPTETRA by HAI method in 341 children from 6 to 35 months of age.

Immunogenicity results are presented in the table below:

Table 7: Immunogenicity results in children from 6 months to 8 years of age

Antigen strain	6-35 months of age N=341	3-8 years of age N=863
GMT (95% CI)		
A (H1N1)	641 (547; 752)	971 (896; 1052)
A (H3N2)	1071 (925; 1241)	1568 (1451; 1695)
B (Victoria)	623 (550; 706)	1050 (956; 1154)
B (Yamagata) [(a)]	1010 (885; 1153)	1173 (1,078; 1,276)
SC % (95% CI) [(b)]		
A (H1N1)	90.3 (86.7; 93.2)	65.7 (62.4; 68.9)
A (H3N2)	90.3 (86.7; 93.2)	64.8 (61.5; 68.0)
B (Victoria)	98.8 (97.0; 99.7)	84.8 (82.3; 87.2)
B (Yamagata) [(a)]	96.8 (94.3; 98.4)	88.5 (86.2; 90.6)
GMTR (95% CI) [(c)]		
A (H1N1)	36.6 (30.8; 43.6)	6.86 (6.24; 7.53)
A (H3N2)	42.6 (35.1; 51.7)	7.49 (6.72; 8.35)
B (Victoria)	100 (88.9; 114)	17.1 (15.5; 18.8)
B (Yamagata) [(a)]	93.9 (79.5; 111)	25.3 (22.8; 28.2)

N=number of subjects with available data for the considered endpoint
GMT: Geometric Mean Titre; CI: Confidence Interval;
(a) N=862 for 3-8 years of age group
(b) 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
(c) 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 VAXIGRIPTETRA).

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of repeat dose and local toxicity, reproductive and developmental toxicity and safety pharmacology studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Buffer Solution:

- Sodium chloride
- Potassium chloride
- Disodium phosphate dihydrate
- Potassium dihydrogen phosphate
- Water for injections

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life

1 year

6.4. Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the syringe in the outer carton in order to protect from light.

6.5. Nature and contents of container

0.5 mL of suspension in pre-filled syringe (type I glass) with attached needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) – box of 1, 10 or 20.

0.5 mL of suspension in pre-filled syringe (type I glass) equipped with a plunger stopper (elastomer bromobutyl) and a tip cap.

- Box of 1, 10 or 20 pre-filled syringe(s) without needle(s).
- Box of 1 or 10 pre-filled syringe(s) with separate needle(s) with safety shield.

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.

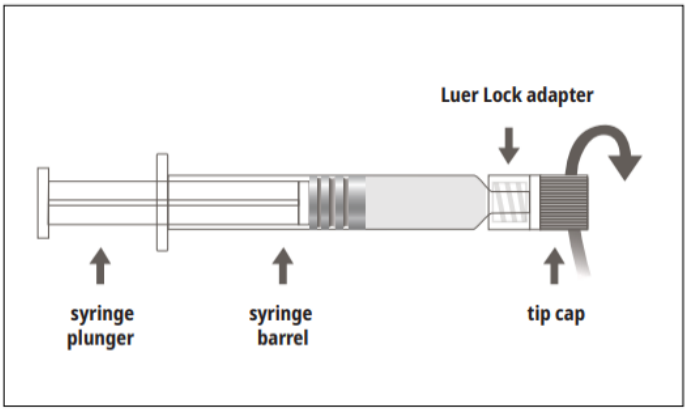
Preparation for administration:

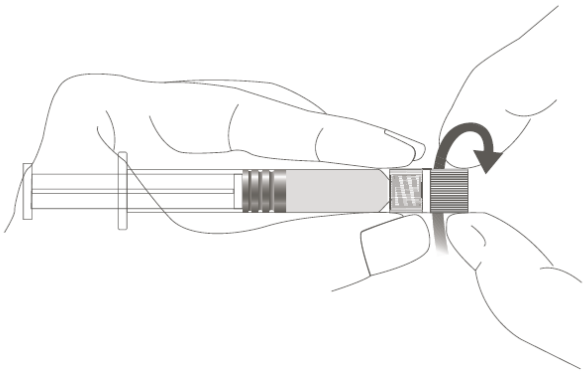
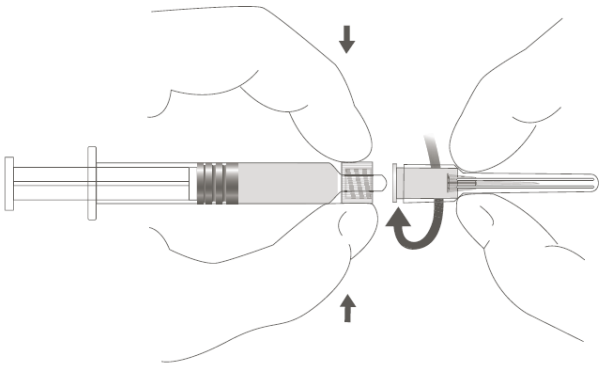
The syringe with suspension for injection should be visually inspected prior to administration. In the event of any foreign particulate matter, leakage, premature activation of the plunger or faulty tip seal, discard the pre-filled syringe.

The syringe is intended for single use only and must not be reused.

Instructions for use of Luer Lock pre-filled syringe

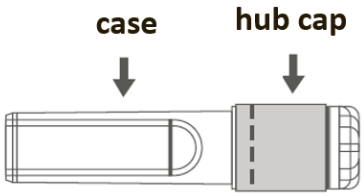
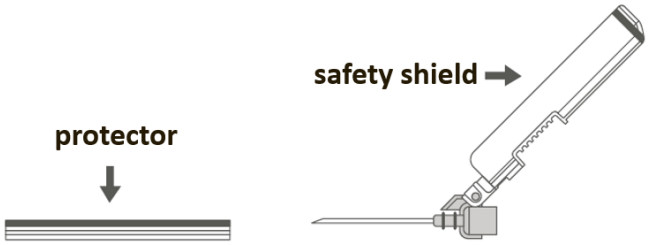
Picture A: Luer Lock syringe with Rigid Tip Cap

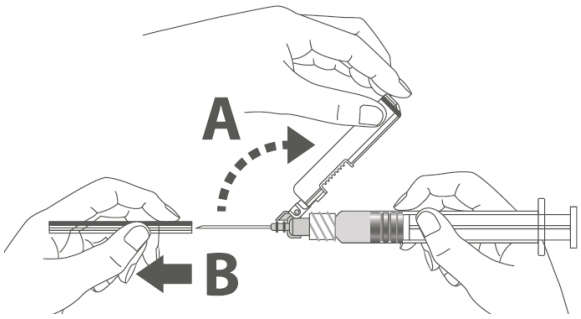
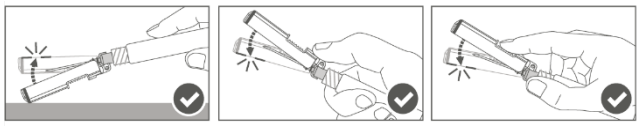
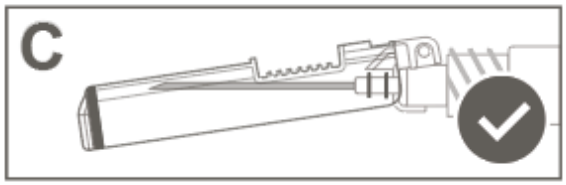
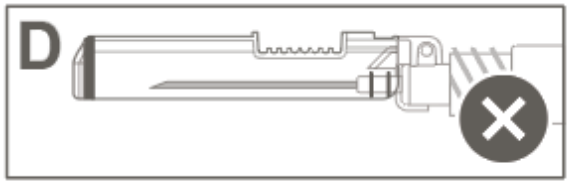


Step 1: Holding the Luer Lock adapter in one hand (avoid holding the syringe plunger or barrel), unscrew the tip cap by twisting it.	
Step 2: To attach the needle to the syringe, gently twist the needle into the Luer Lock adapter of the syringe until slight resistance is felt.	

<Instructions for use of Safety Needle with Luer Lock pre-filled syringe:

Follow Steps 1 and 2 above to prepare the Luer Lock syringe and needle for attachment.

Picture B: Safety Needle (inside case)	**Picture C: Safety Needle Components (prepared for use)**
	

Step 3: Pull the safety needle's case straight off. The needle is covered by the safety shield and protector.	
Step 4: **A:** Move the safety shield away from the needle and toward the syringe barrel to the angle shown. **B:** Pull the protector straight off.	
Step 5: After injection is complete, lock (activate) the safety shield using one of the three (3) **one-handed** techniques illustrated: surface, thumb or finger activation. Note: Activation is verified by an audible and/or tactile "click."	
Step 6: Visually inspect the safety shield activation. The safety shield should be **fully locked (activated)** as shown in Figure C. Figure D shows the safety shield is **NOT fully locked (not activated).**	 
Caution: Do not attempt to unlock (deactivate) the safety device by forcing the needle out of the safety shield.>	

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

7. MARKETING AUTHORISATION HOLDER

SANOFI WINTHROP INDUSTRIE
82 AVENUE RASPAIL
94250 GENTILLY

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 300 677 2 7: 0.5 mL of suspension in pre-filled syringe (type I glass) with attached needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) – box of 1.
- 34009 300 677 3 4: 0.5 mL of suspension in pre-filled syringe (type I glass) with attached needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) – box of 10.
- 34009 300 677 4 1: 0.5 mL of suspension in pre-filled syringe (type I glass) with attached needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) – box of 20.
- 34009 300 677 5 8: 0.5 mL of suspension in pre-filled syringe (type I glass) without needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) and a tip cap – box of 1.
- 34009 300 677 7 2: 0.5 mL of suspension in pre-filled syringe (type I glass) without needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) and a tip cap – box of 10.
- 34009 300 677 8 9: 0.5 mL of suspension in pre-filled syringe (type I glass) without needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) and a tip cap – box of 20
- 34009 302 967 6 9: 0.5 mL of suspension in pre-filled syringe (type I glass) with separate needle with safety shield, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) and a tip cap. Box of 1.
- 34009 302 967 7 6: 0.5 mL of suspension in pre-filled syringe (type I glass) with separate needle with safety shield, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) and a tip cap. Box of 10.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed later by the holder]

10. DATE OF REVISION OF THE TEXT

[to be completed later by the holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.