Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vaxigrip suspension for injection in pre-filled syringe.Trivalent 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**

Per 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.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vaxigrip is indicated for the prevention of influenza disease caused by the two influenza A virus subtypes and the influenza B virus type 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).

The use of Vaxigrip should be based on official recommendations on vaccination against influenza.

4.2 Posology and method of administration

Posology
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 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 (see Sections 4.4, 4.6 and 5.1).

Method of administration
The preferred route of administration for this vaccine is intramuscular although it can also be given subcutaneously.
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 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.

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.

Hypersensitivity
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.

Concurrent illness
Vaccination should be postponed in patients with acute febrile illness until the fever is resolved.

Precautions for use
Vaxigrip should under no circumstances be administered intravascularly.

Thrombocytopenia and coagulation disorders
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
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.

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

As with any vaccine, vaccination with Vaxigrip 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).

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

Potassium and sodium content
Vaxigrip contains less than 1 mmol potassium (39 mg) and sodium (23 mg) per dose, i.e. essentially 'potassium-free' and 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Vaxigrip could be given at the same time as other vaccines if needed.

Data showing that Vaxigrip can be administered concomitantly with other vaccines are available for the following vaccines: a pneumococcal polysaccharide vaccine, a tetanus, diphtheria, pertussis, polio vaccine (Tdap-IPV, Repevax), and a zoster vaccine.
If Vaxigrip is given at the same time as other vaccines, separate injection sites and separate syringes should be used.
The immunological response may be reduced if the patient is undergoing immunosuppressant treatment.

4.6 Fertility, pregnancy and lactation

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

Vaxigrip 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 with the first trimester. Data from worldwide use of inactivated influenza vaccines, including Vaxigrip and Vaxigrip Tetra (quadrivalent 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 Vaxigrip and Vaxigrip Tetra were administered in pregnant women during the second or third trimester (116 exposed pregnancies and 119 live births for Vaxigrip, 230 exposed pregnancies and 231 live births for Vaxigrip Tetra).
Data from four clinical studies with 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) did 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.
Results of one reproductive study in rabbits conducted with Vaxigrip Tetra (60 µg of total amount HA/dose) can be extrapolated to Vaxigrip (45 µg of total amount HA /dose): this study did not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development or early post-natal development.

Breast-feeding
Vaxigrip may be used during breast-feeding.

Fertility
No fertility data are 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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Vaxigrip is based on data from 46 clinical studies in which approximately 17 900 participants from 6 months of age received Vaxigrip or Vaxigrip Tetra, and data from post-marketing surveillance.

Most of adverse reactions usually occurred within the first 3 days after vaccination and resolved spontaneously within 1 to 3 days after onset. The intensity of most these reactions was mild to moderate.
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.

Tabulated list of adverse reactions

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);

Not known (cannot be estimated from available data).

Adult and elderly

The safety profile is based on data:
- from clinical studies in more than 8 000 adults (5 064 for Vaxigrip, 3 040 for Vaxigrip Tetra) and more than 5 800 elderly over 60 years of age (4 468 for Vaxigrip, 1 392 for Vaxigrip Tetra),
- from worldwide post-marketing surveillance in the overall population.

In adults, the most frequently reported adverse reactions after vaccination were injection site pain (52.8%), headache (27.8%), myalgia (23.0%), malaise (19.2%).

In the elderly, the most frequently reported adverse reactions after vaccination were injection site pain (25.8%), headache (15.6%), myalgia (13.9%).

Table 1: Adverse reactions reported in adults and elderly

System Organ Class (SOC)/Adverse Reactions	Frequency
Blood and Lymphatic System Disorders	
Lymphadenopathy [1]	Uncommon
Transient thrombocytopenia	Not known*
Immune System Disorders	
Allergic reactions such as hypersensitivity [2], dermatitis atopic [2], urticaria [2, 3], oropharyngeal pain, asthma [1], rhinitis allergic [2], rhinorrhea [1], conjunctivitis allergic [2], pruritus [4], hot flush [5]	Uncommon
Allergic reactions such as angioedema [2, 3], swelling face, erythema, rash, flushing [5], oral mucosal eruption [5], paraesthesia oral [5], throat irritation, dyspnoea [2, 3], sneezing, nasal obstruction [2], upper respiratory tract congestion [2], ocular hyperaemia [2], dermatitis allergic [2], pruritus generalised [2]	Rare
Allergic reactions such as rash erythematous, anaphylactic reaction, shock	Not known*
Metabolism and Nutrition Disorders	
Decreased appetite	Rare
Nervous System Disorders	
Headache	Very common
Dizziness [4], somnolence [4]	Uncommon
Hypoaesthesia [2], paresthesia	Rare
Neuralgia, convulsions, encephalomyelitis, neuritis, Guillain Barré Syndrome	Not known*
Vascular disorders	
Vasculitis such as Henoch-Schonlein purpura, with transient renal involvement in certain cases	Not known*
Gastrointestinal Disorders	
Diarrhoea, nausea	Uncommon
Abdominal pain [2], vomiting	Rare
Skin and Subcutaneous System Disorders	
Hyperhidrosis [1]	Uncommon
Musculoskeletal and Connective Tissue Disorders	
Myalgia	Very common
Arthralgia [1]	Uncommon
General Disorders and Administration Site Conditions	
Injection site pain, malaise [6]	Very common
Fever [7], shivering, injection site erythema, injection site induration, injection site swelling	Common
Asthenia [1], fatigue, injection site ecchymosis, injection site pruritus, injection site warmth, injection site discomfort,	Uncommon
Flu-like symptoms, injection site exfoliation [5], injection site hypersensitivity [2]	Rare

[1] Rare in elderly
[2] Reported during clinical trials in adults
[3] Not known in elderly
[4] Rare in adults
[5] Reported during clinical trials in elderly
[6] Common in elderly
[7] Uncommon in elderly
(*) Adverse reactions reported post-marketing after use of Vaxigrip or Vaxigrip Tetra

Paediatric population
The safety profile is based on data:
- from clinical studies in 1 247 children from 3 to 8 years of age (363 for Vaxigrip, 884 for Vaxigrip Tetra) and in 725 children/adolescents from 9 to 17 years of age (296 for Vaxigrip, 429 for Vaxigrip Tetra),
- from one clinical study in 1 981 children from 6 to 35 months of age (367 for Vaxigrip, 1 614 for Vaxigrip Tetra),
- from worldwide post-marketing surveillance in the overall population.

Depending on immunization history, children from 6 months to 8 years of age received one or two doses of Vaxigrip or Vaxigrip Tetra. Children/adolescents from 9 to 17 years of age received one dose.

In children from 6 months to 8 years of age, the safety profile 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.

In children/adolescents from 9 to 17 years of age, the most frequently reported adverse reactions after vaccination were injection site pain (65.3%), myalgia (29.1%), headache (28.6%), malaise (20.3%), shivering (13.0%), injection site erythema (11.7%) and injection site swelling (11.4%).

In children from 3 to 8 years of age, the most frequently reported adverse reactions after any vaccination were injection site pain (59.1%), malaise (30.7%), injection site erythema (30.3%), myalgia (28.5%), headache (25.7%), injection site swelling (22.1%), injection site induration (17.6%), and shivering (11.2%).

In children from 6 to 35 months of age, the most frequently reported adverse reactions after any vaccination were injection site pain/tenderness (29.4%), fever (20.4%) and injection site erythema (17.2%).

- In subpopulation of children from 6 to 23 months of age, the most frequently reported adverse reactions after any vaccination were irritability (34.9%), crying abnormal (31.9%), appetite lost (28.9%), drowsiness (19.2%) and vomiting (17.0%).
- In subpopulation of children from 24 to 35 months of age, the most frequently reported adverse reactions after any vaccination was malaise (26.8%). myalgia (14.5%), headache (11.9%).

Table 2: Adverse reactions reported in children and adolescents from 6 months to 17 years of age

System Organ Class (SOC)/ Adverse Reactions	Frequency			
	Children 6-35 months of age		Children 3-8 years of age	Children and adolescents 9-17 years of age
	6-23 months of age	24-35 months of age		
Blood and Lymphatic System Disorders				
- Lymphadenopathy	Not known*		Uncommon	Not known*
- Thrombocytopenia	Not known*		Uncommon	Not known*
Immune System Disorders				
- Allergic reactions such as:				
• Oropharyngeal pain	-		Uncommon	-
• Hypersensitivity	Uncommon		-	-
• Rash	-		Uncommon	Uncommon
• Urticaria	Not known*		Uncommon	Uncommon
• Pruritus	Not known*		Uncommon	Not known*
• Pruritus generalized, rash papular	Rare		-	-
• Rash erythematous, dyspnoea, anaphylactic reaction, angioedema, shock	Not known*		Not known*	Not known*
Metabolism and Nutrition Disorders				
- Decreased appetite	Very common	Rare	-	-
Psychiatric Disorders				
- Crying abnormal	Very common	-	-	-
- Irritability	Very common	Rare	-	-
- Restlessness	-		Uncommon	-
- Moaning	-		Uncommon	-
Nervous System Disorders				
- Headache	-	Very common	Very common	Very common
- Drowsiness	Very common	-	-	-
- Dizziness	-		Uncommon	Uncommon
- Neuralgia, neuritis and Guillain Barré Syndrome	-		Not known*	Not known*
- Paraesthesia, convulsions, encephalomyelitis	Not known*		Not known*	Not known*
Vascular Disorders				
- Vasculitis such as Henoch-Schonlein purpura, with transient renal involvement in certain cases	Not known*		Not known*	Not known*
Gastrointestinal Disorders				
- Diarrhoea	Common		Uncommon	Uncommon
- Abdominal pain	-		Uncommon	-
- Vomiting	Very common	Uncommon	Uncommon	-

System Organ Class (SOC)/ Adverse Reactions	Frequency			
	Children 6-35 months of age		Children 3-8 years of age	Children and adolescents 9-17 years of age
	6-23 months of age	24-35 months of age		
Musculoskeletal and Connective Tissue Disorders				
- Myalgia	Rare	Very common	Very common	Very common
- Arthralgia	-		Uncommon	-
General Disorders and Administration Site Conditions				
Injection site reactions				
- Injection site pain/tenderness, injection site erythema	Very common		Very common	Very common
- Injection site swelling	Common		Very common	Very common
- Injection site induration	Common		Very common	Common
- Injection site ecchymosis	Common		Common	Common
- Injection site pruritus	Rare		Uncommon	Uncommon
- Injection site warmth	-		Uncommon	Uncommon
- Injection site discomfort	-		-	Uncommon
- Injection site rash	Rare		-	-
Systemic reactions				
- Malaise	Rare	Very common	Very common	Very common
- Shivering	-	Common	Very common	Very common
- Fever	Very common		Common	Common
- Fatigue	-		Uncommon	Uncommon
- Asthenia	-		-	Uncommon
- Crying	-		Uncommon	-
- Influenza-like illness	Rare			-

(*) Adverse reactions reported post-marketing after use of Vaxigrip or Vaxigrip Tetra

Other special populations

Although only a limited number of subjects with co-morbidities were enrolled, studies conducted in patients with co-morbidities such as renal transplant or asthmatic patients, showed no major differences in terms of safety profile of Vaxigrip and Vaxigrip Tetra 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 the vaccine, were consistent with those reported for the adult population during clinical studies. In the study conducted in South Africa, local reactions were more frequent in the Vaxigrip group than in the placebo group in both HIV-negative and HIV-positive cohorts. There were no other significant differences in solicited reactions between Vaxigrip and placebo groups in both cohorts.

In one clinical study conducted in pregnant women in Finland with Vaxigrip and Vaxigrip Tetra (see Sections 4.6 and 5.1), frequencies of reported local and systemic solicited reactions were consistent with those reported for the non-pregnant adult population during clinical studies conducted with Vaxigrip or Vaxigrip Tetra even though higher for some adverse reactions (injection site pain, injection site erythema, 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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: influenza vaccine, ATC code: J07BB02

Mechanism of action
Vaxigrip provides active immunisation against three influenza virus strains (two A subtypes and one B type) contained in the vaccine.

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

In infants less than 6 months of age born to women vaccinated with Vaxigrip during pregnancy, protection is due to transplacental transfer of these neutralizing antibodies.

Specific levels of haemagglutination-inhibition (HAI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the HAI antibody titers have been used as a measure of vaccine activity. In some human challenge studies, HAI antibody titers 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 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
Efficacy data of Vaxigrip are available in pregnant women and in infants less than 6 months of age born to vaccinated pregnant women (passive protection).
No efficacy studies were performed with Vaxigrip in children and adolescents from 9 to 17 years of age, in adults and in the elderly.
In children from 6 to 35 months of age and from 3 to 8 years of age (active immunisation), Vaxigrip efficacy is based on extrapolation of Vaxigrip Tetra efficacy.

- 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 hospitalization; however influenza vaccines are not indicated for active immunisation in this age group.

Efficacy in infants of women who received a single 0.5 mL dose of Vaxigrip during the second or third trimester of pregnancy has been demonstrated in clinical trials.

Efficacy of 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 randomized, controlled phase IV clinical studies conducted in Mali, Nepal and South Africa, approximately 5 000 pregnant women received Vaxigrip 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 3). 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 3: Influenza Attack Rates and Vaxigrip Efficacy against Laboratory-confirmed influenza in pregnant women

		Influenza Attack Rate (Any influenza A or B type) % (n/N)		**Vaxigrip Efficacy % (95% CI)**
		TIV	**Control***	
Mali		0.5 (11/2,108)	1.9 (40/2,085)	70.3 (42.2 to 85.8)
		TIV	**Placebo**	
South Africa		1.8 (19/1,062)	3.6 (38/1,054)	50.4 (14.5 to 71.2)

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

In the same randomized, controlled phase IV clinical studies conducted in Mali, Nepal and South Africa, 4530 of 4898 (92%) infants born to pregnant women who received Vaxigrip and 4 532 of 4 868 (93%) infants born to pregnant women who received a placebo or control vaccine (quadrivalent meningococcal conjugate vaccine) (see Table 4) during the second or third trimester of pregnancy, were followed up until approximately 6 months of age.

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

Table 4: Influenza Attack Rates and Vaxigrip Efficacy against Laboratory-confirmed influenza in infants following vaccination in pregnant women

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

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

The efficacy data indicate a waning 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 Vaxigrip in infants during the first 4 months after birth, with lower efficacy within the 5th month of surveillance and a marked fall within the 6th month where protection is no longer evident.

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.

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

In addition, a predefined complementary analysis showed Vaxigrip Tetra prevented 56.6% (95% CI: 37.0; 70.5) of severe laboratory-confirmed influenza illnesses due to any strain, and 71.7% (95% CI: 43.7; 86.9) of severe laboratory-confirmed influenza illnesses due to vaccine-similar strains. Furthermore, subjects receiving Vaxigrip Tetra were 59.2% (95% CI: 44.4; 70.4) less likely to experience a medically attended influenza illness than subjects receiving placebo.

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

- fever >39.5°C for subjects aged <24 months or ≥39.0°C for subjects aged ≥24 months,
- and/or at least one significant ILI symptom which prevents daily activity (cough, nasal congestion, rhinorrhoea, pharyngitis, otitis, vomiting, diarrhoea),
- and/or one of the following events: acute otitis media, acute lower respiratory infection (pneumonia, bronchiolitis, bronchitis, croup), inpatient hospitalization. - *Children from 3 to 8 years of age (active immunisation):*

Based on immune responses of Vaxigrip Tetra observed in children 3 to 8 years of age, the efficacy of Vaxigrip 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 (active immunisation)*" above and "Immunogenicity" below).

Immunogenicity
Clinical studies performed in adults from 18 to 60 years of age, in elderly over 60 years of age, in children from 3 to 8 years of age and from 6 to 35 months of age described Vaxigrip (TIV) and Vaxigrip Tetra (QIV) immune response for HAI Geometric mean antibody titer (GMT) at Day 21 (for adults) and at Day 28 (for children), HAI seroconversion rate (4-fold rise in reciprocal titer or change from undetectable [<10] to a reciprocal titer of ≥40), and HAI GMTR (post-/pre-vaccination titers).

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

One clinical study performed in pregnant women described the immune response of Vaxigrip Tetra and 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 maternal blood, of cord blood and the ratio of cord blood/maternal blood, at delivery.

Overall, Vaxigrip induced an immune response to the 3 influenza strains contained in the vaccine.

In children from 3 years of age, in adults including pregnant women and in the elderly, Vaxigrip was as immunogenic as Vaxigrip Tetra for the strains in common.

Antibody persistence was assessed in adults, elderly and children from 6 to 35 months of age. The duration of post-vaccinal induced immunity lasted at least 12 months.

- Adults and elderly
In one clinical study, the immune response was described in adults from 18 to 60 years of age and elderly over 60 years of age who received one 0.5-mL dose of Vaxigrip or Vaxigrip Tetra.

The immunogenicity results by HAI method in adults from 18 to 60 years of age and elderly over 60 years of age are presented in Table 6.

Table 6: Immunogenicity results in adults from 18 to 60 years of age and in elderly over 60 years of age, 21 days after vaccination with Vaxigrip or Vaxigrip Tetra

	Adults from 18 to 60 years of age			**Elderly over 60 years of age**		
Antigen Strain	**Alternative TIV [a] (B Victoria) N=140**	**Licensed TIV [b] (B Yamagata) N=138**	**QIV N=832**	**Alternative TIV [a] (B Victoria) N=138**	**Licensed TIV [b] (B Yamagata) N=137**	**QIV N=831**
	GMT (95% CI)					
A (H1N1) [c][d]	685 (587; 800)		608 (563;657)		268 (228; 314)	219 (199; 241)
A (H3N2) [c]	629 (543; 728)		498 (459; 541)		410 (352; 476)	359 (329; 391)
B (Victoria)	735 (615; 879)	-	708 (661; 760)	301 (244; 372)	-	287 (265; 311)
B (Yamagata)	-	1735 (1490; 2019)	1715 (1607; 1830)	-	697 (593; 820)	655 (611; 701)
	SC % [e] **(95% CI)**					
A (H1N1) [c][d]	65.1 (59.2; 70.7)		64.1 (60.7; 67.4)		50.2 (44.1; 56.2)	45.6 (42.1; 49.0)
A (H3N2)[c]	73.4 (67.8; 78.5)		66.2 (62.9; 69.4)		48.5 (42.5; 54.6)	47.5 (44.1; 51.0)
B (Victoria)	70.0 (61.7; 77.4)	-	70.9 (67.7; 74.0)	43.5 (35.1; 52.2)	-	45.2 (41.8; 48.7)
B (Yamagata)	-	60.9 (52.2; 69.1)	63.7 (60.3;67.0)	-	38.7 (30.5; 47.4)	42.7 (39.3; 46.2)
	GMTR [f] **(95% CI)**					
A (H1N1) [c][d]	10.3 (8.35; 12.7)		9.77 (8.69; 11.0)		6.03 (4.93; 7.37)	4.94 (4.46; 5.47)
A (H3N2) [c]	14.9 (12.1; 18.4)		10.3 (9.15; 11.5)		5.79 (4.74; 7.06)	5.60 (5.02; 6.24)
B (Victoria)	11.4 (8.66; 15.0)	-	11.6 (10.4; 12.9)	4.60 (3.50; 6.05)	-	4.61 (4.18; 5.09)
B (Yamagata)	-	6.08 (4.79; 7.72)	7.35 (6.66;8.12)	-	4.11 (3.19; 5.30)	4.11 (3.73; 4.52)

N: number of subjects with available data for the considered endpoint
GMT: Geometric Mean Titer; CI: Confidence Interval

1. Alternative TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Brisbane/60/2008 (Victoria lineage)
2. 2014-2015 licensed TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 (Yamagata lineage)
3. Pooled TIV group includes participants vaccinated with either alternative TIV or licensed TIV, N= 278 for adults and N=275 for elderly
4. N=833 for QIV group in adults; N=832 for QIV group in elderly
5. SC: Seroconversion or significant increase: for subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥40 (1/dil) and for subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titer

6. GMTR: Geometric mean of individual titer ratios (post-/pre-vaccination titers)

- Pregnant women and transplacental transfer

In one clinical study, a total of 116 pregnant women received Vaxigrip and 230 pregnant women received Vaxigrip Tetra 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 or Vaxigrip Tetra are presented in Table 7.

Table 7: Immunogenicity results by HAI method in pregnant women, 21 days after vaccination with Vaxigrip or Vaxigrip Tetra

Antigen Strain	TIV (B Victoria) N=109	QIV N=216
	GMT (95% CI)	
A (H1N1)*	638 (529; 769)	525 (466; 592)
A (H3N2)*	369 (283; 483)	341 (286; 407)
B1 (Victoria)*	697 (569; 855)	568 (496; 651)
B2 (Yamagata)*	-	993 (870; 1134)
	≥4-fold-rise n (%) [(a)]	
A (H1N1)*	41.3 (31.9; 51.1)	38.0 (31.5; 44.8)
A (H3N2)*	62.4 (52.6; 71.5)	59.3 (52.4; 65.9)
B1 (Victoria)*	60.6 (50.7; 69.8)	61.1 (54.3; 67.7)
B2 (Yamagata)*	-	59.7 (52.9; 66.3)
	GMTR (95% CI) [(b)]	
A (H1N1)*	5.26 (3.66; 7.55)	3.81 (3.11; 4.66)
A (H3N2)*	9.23 (6.56; 13.0)	8.63 (6.85; 10.9)
B1 (Victoria)*	9.62 (6.89; 13.4)	8.48 (6.81; 10.6)
B2 (Yamagata)*	-	6.26 (5.12; 7.65)

N: number of subjects with available data for the considered endpoint
GMT: Geometric Mean Titer; 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 TIV composition;*
B2: B/Phuket/3073/2013-like virus (B/Yamagata lineage)*: this strain was not included in the TIV composition.*

1. SC: Seroconversion or significant increase: for subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥40 (1/dil) and for subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titer
2. GMTR: Geometric mean of individual titer ratios (post-/pre-vaccination titers)

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 8.

Table 8:Immunogenicity descriptive assessment by HAI method of Vaxigrip or Vaxigrip Tetra, at delivery

	Antigen Strain	TIV (B Victoria) N=89	QIV N=178	
		BL03M (Maternal blood) GMT (95% CI)		
	A (H1N1)*	411 (332; 507)	304 (265; 349)	
	A (H3N2)*	186 (137; 250)	178 (146; 218)	
	B1 (Victoria)*	371 (299; 461)	290 (247; 341)	
	B2 (Yamagata)*	-	547 (463; 646)	
		BL03B (Cord		

		blood) **GMT (95% CI)**		
	A (H1N1)*	751 (605; 932)	576 (492; 675)	
	A (H3N2)*	324 (232; 452)	305 (246; 379)	
	B1 (Victoria)*	608 (479; 772)	444 (372; 530)	
	B2 (Yamagata)*	-	921 (772; 1099)	
		Transplacental transfer: BL03B/BL03M ** **GMT (95% CI)**		
	A (H1N1)*	1.83 (1.64; 2.04)	1.89 (1.72; 2.08)	
	A (H3N2)*	1.75 (1.55; 1.97)	1.71 (1.56; 1.87)	
	B1 (Victoria)*	1.64 (1.46; 1.85)	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 QIV or TIV, delivered at least 2 weeks after injection and with available cord blood and mother blood at the time of delivery. GMT: Geometric Mean Titer; 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 TIV composition; B2: B/Phuket/3073/2013-like virus (B/Yamagata lineage): this strain was not included in the TIV composition. ** If a mother have X babies, her titers values is counted X times				

At delivery, the higher level of antibodies in the cord sample compared to the maternal sample is consistent with transplacental antibody transfer from mother to the newborn following vaccination of women with Vaxigrip or Vaxigrip Tetra 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).

- *Paediatric population*

• Children from 9 to 17 years of age

In a total of 55 children from 9 to 17 years of age who received one dose of Vaxigrip and 429 who received one dose of Vaxigrip Tetra, the immune response against the strains contained in the vaccine was similar to the immune response induced in adults 18 to 60 years of age.

• Children from 3 years to 8 years of age

In one clinical study, the immune response was described in children from 3 to 8 years of age who received either one or two 0.5-mL doses of Vaxigrip or Vaxigrip Tetra, depending on their previous influenza vaccination history.

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

The immunogenicity results by HAI method 28 days after receipt of the last injection are presented in Table 9.

• Children from 6 months to 35 months of age

In one clinical trial, the immune response was described in children from 6 to 35 months of age who received two 0.5-mL doses of Vaxigrip or Vaxigrip Tetra.

The immunogenicity results by HAI method, 28 days after receipt of the last injection are presented in Table 9.

Table 9:Immunogenicity results in children from 6 months to 35 months of age and from 3 to 8 years of age, 28 days after the last injection of Vaxigrip or Vaxigrip Tetra

	Children 6-35 months of age			**Children 3-8 years of age**		
Antigen Strain	**Alternative TIV [a] (B Victoria) N=172**	**Licensed TIV [b] [c] (B Yamagata) N=178**	**QIV N=341**	**Alternative TIV [a] (B Victoria) N=176**	**Licensed TIV [b] (B Yamagata) N=168**	**QIV N=863**
	GMT (95% CI)					
A (H1N1) [d]	637 (500; 812)	628 (504; 781)	641 (547; 752)	1141 (1006; 1295)		971 (896; 1052)
A (H3N2) [d]	1021 (824; 1266)	994 (807; 1224)	1071 (925; 1241)	1746 (1551; 1964)		1568 (1451; 1695)
B (Victoria) [e]	835 (691; 1008)	-	623 (550; 706)	1120 (921; 1361)	-	1050 (956; 1154)
B (Yamagata) [f] *[g]*	-	1009 (850; 1198)	1010 (885; 1153)	-	1211 (1003; 1462)	1173 (1078; 1276)
	SC % [h] (95% CI)					
A (H1N1) [d]	87.2 (81.3; 91.8)	90.4 (85.1; 94.3)	90.3 (86.7; 93.2)	65.7 (60.4; 70.7)		65.7 (62.4; 68.9)
A (H3N2) [d]	88.4 (82.6; 92.8)	87.6 (81.9; 92.1)	90.3 (86.7; 93.2)	67.7 (62.5; 72.6)		64.8 (61.5; 68.0)
B (Victoria) [e]	99.4 (96.8; 100.0)	-	98.8 (97.0; 99.7)	90.3 (85.0; 94.3)	-	84.8 (82.3; 87.2)
B (Yamagata) [f] *[g]*	-	99.4 (96.9; 100.0)	96.8 (94.3; 98.4)	-	89.9 (84.3; 94.0)	88.5 (86.2; 90.6)
	GMTR [i] (95% CI)					
A (H1N1) [d]	35.3 (27.4; 45.5)	40.6 (32.6; 50.5)	36.6 (30.8; 43.6)	7.65 (6.54; 8.95)		6.86 (6.24; 7.53)
A (H3N2) [d]	44.1 (33.1; 58.7)	37.1 (28.3; 48.6)	42.6 (35.1; 51.7)	7.61 (6.69; 9.05)		7.49 (6.72; 8.35)
B (Victoria) [e]	114 (94.4; 138)	-	100 (88.9; 114)	17.8 (14.5; 22.0)	-	17.1 (15.5; 18.8)
B (Yamagata) [f] *[g]*	-	111 (91.3; 135)	93.9 (79.5; 111)	-	30.4 (23.8; 38.4)	25.3 (22.8; 28.2)

N=number of subjects with available data for the considered endpoint
GMT: Geometric Mean Titer; CI: Confidence Interval

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

2. 2014-2015 licensed TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 (Yamagata lineage)
3. Dose of 0.5 mL in children 6-35 months of age
4. For children -3-8 years of age: pooled TIV group includes participants vaccinated with either alternative TIV or licensed TIV, N=344
5. N=169 for TIV (B Yamagata) group in children 3-8 years of age
6. N=862 for QIV group in children 3-8 years of age
7. For alternative TIV (B Victoria) group: N=171 for children 6-35 months of age; N=175 for children 3-8 years of age
8. SC: Seroconversion or significant increase: for subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥40 (1/dil) and for subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titer
9. GMTR: Geometric mean of individual titer ratios (post-/pre-vaccination titers)

These immunogenicity data provide supportive information in addition to efficacy data available in children from 6 to 35 months of age (see Section Efficacy).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Data in animals generated with Vaxigrip Tetra (60 µg of total amount HA/dose) can be extrapolated to Vaxigrip (45 µg of total amount HA/dose): these data revealed no unexpected findings and no target organ toxicity.

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.
Vaxigrip remains stable for 72 hours up to 25°C ±2°C. This is not a recommended storage condition, but it is intended to guide healthcare professionals in case of temporary temperature excursion only.

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 bromobutyl) – pack size of 1 or 10.

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

- Pack size of 1 or 10 pre-filled syringe(s) without needle(s)
- Pack size of 1 or 10 pre-filled syringe(s) with separate needle(s) (stainless steel)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use.

Shake before use. Inspect visually prior to administration.

The vaccine should not be used if foreign particles are present in the suspension.

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
Gentilly
94250
France

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