VaxigripTetra NH™

Quadrivalent influenza vaccine (split virion, inactivated)

Suspension for injection in pre-filled syringe

SANOFI

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/Michigan/45/2015 (H1N1)pdm09 - like strain (A/Michigan/45/2015, NYMC X-275) ..... 15 micrograms HA**

A/Hong Kong/4801/2014 (H3N2) - like strain (A/Hong Kong/4801/2014, NYMC X-263B) ..... 15 micrograms HA**

B/Brisbane/60/2008 - like strain (B/Brisbane/60/2008, 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 2017/2018 season.

For the full list of excipients, see section List of excipients

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

PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.

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

CLINICAL PARTICULARS

Therapeutic indications

VaxigripTetra NH is indicated for active immunisation of adults and children from 6 months of age and older for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine, particularly in subjects showing a high risk of associated complications.

The use of VaxigripTetra NH should be based on official recommendations.

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.

- Children less than 6 months of age: the safety and efficacy of VaxigripTetra NH have not been established. No data are available.

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 Special precautions for disposal & other handling.

Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section List of Excipients 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.

Special warnings and precautions for use

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 NH should under no circumstances be administered intravascularly.

As with other vaccines administered intramuscularly, the vaccine should be administered with caution to subjects with thrombocytopaenia 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 NH is intended to provide protection against those strains of influenza virus from which the vaccine is prepared.

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

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

Interference with serological testing

See section Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with VaxigripTetra NH.

VaxigripTetra NH 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.

Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of VaxigripTetra NH in pregnant women. One animal study with VaxigripTetra NH did not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development or early post-natal development.

Breastfeeding

There are no data on the use of VaxigripTetra NH in breastfeeding women.

Fertility

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

Effects on ability to drive and use machines

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

Undesirable effects

a. Summary of the safety profile

The safety of VaxigripTetra NH 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 NH, 884 children from 3 to 8 years of age received one or two doses of VaxigripTetra NH depending on their influenza vaccination history and 1614 children from 6 to 35 months of age received two doses (0.5 ml) of VaxigripTetra NH.

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.

b. Tabulated summary of adverse reactions

The data below summarize the frequencies of the adverse reactions that were recorded following vaccination with VaxigripTetra NH during clinical trials.

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).

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.

ADVERSE REACTIONS	FREQUENCY
Blood and lymphatic system disorders	
Lymphadenopathy (1)	Uncommon
Immune system disorders	
Hypersensitivity (1), allergic reactions such as erythema, urticaria (1), pruritus (2), pruritus generalised (1), dermatitis allergic (1), angioedema (1)	Rare
Nervous system disorders	
Headache	Very common
Dizziness (3)	Uncommon
Somnolence, paraesthesia	Rare
Vascular disorders	
Hot flush (4)	Uncommon
Respiratory, thoracic and mediastinal disorders	
Dyspnoea (1)	Rare
Gastrointestinal disorders	
Diarrhoea, nausea (5)	Uncommon
Skin and subcutaneous system disorders	
Hyperhidrosis	Rare
Musculoskeletal and connective tissue disorders	
Myalgia	Very common
Arthralgia (1)	Rare
General disorders and administration site conditions	
Malaise (6) Injection site pain	Very common
Shivering, fever (2) Injection site erythema, injection site swelling, injection site induration	Common

ADVERSE REACTIONS	FREQUENCY
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 NH and from 884 children from 3 to 8 years of age who received one or two doses of VaxigripTetra NH depending on their influenza vaccination history.

ADVERSE REACTIONS	FREQUENCY
Blood and lymphatic system disorders	
Thrombocytopaenia [1]	Uncommon
Psychiatric disorders	
Moaning [2], restlessness [2]	Uncommon
Nervous system disorders	
Headache	Very common
Dizziness [2]	Uncommon
Gastrointestinal disorders	
Diarrhoea, vomiting [2], abdominal pain upper [2]	Uncommon
Musculoskeletal and connective tissue disorders	
Myalgia	Very common
Arthralgia [2]	Uncommon
General Disorders and administration site conditions	
Malaise, shivering [3] Injection site pain, injection site swelling, injection site erythema [3], injection site induration [3]	Very common
Fever Injection site ecchymosis	Common
Fatigue [2] Injection site warmth [2], injection site pruritus [4]	Uncommon

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

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

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

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

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

c. Potential adverse events

There are no safety data from post-marketing experience with VaxigripTetra NH.

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

- ***Immune system disorders***

Severe allergic reactions: shock
Allergic reactions: rash, generalised erythema

- ***Nervous system disorders***

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

- ***Vascular disorders***

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

d. Other special populations

The safety profile of VaxigripTetra NH 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.

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.

Overdose

Not documented for VaxigripTetra NH. 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: influenza vaccine, ATC code: J07BB02.

Mechanism of action

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

VaxigripTetra NH 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 NH 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 NH

Paediatric population

- Children from 6 to 35 months of age:

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 NH (N=2,722), or placebo (N=2,717) 28 days apart to assess VaxigripTetra NH 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 NH Efficacy against laboratory-confirmed influenza illness in children from 6 to 35 months of age

	VaxigripTetra NH (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 NH 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 NH were 59.2% (95% CI: 44.4; 70.4) less likely to experience a medically attended influenza illness than subjects receiving placebo.

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

- fever > 39.5°C for subjects aged < 24 months or ≥ 39.0°C for subjects aged ≥ 24 months,
- and/or at least one significant ILI symptom which prevents daily activity (cough, nasal congestion, rhinorrhoea, pharyngitis, otitis, vomiting, diarrhoea),

- and/or one of the following events: acute otitis media, acute lower respiratory infection (pneumonia, bronchiolitis, bronchitis, croup), inpatient hospitalisation.

- Children from 3 to 8 years of age:

Based on immune responses observed in children from 3 to 8 years of age, the efficacy of VaxigripTetra NH 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 NH" below).

Immunogenicity of VaxigripTetra NH

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 NH 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 NH 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 NH.

VaxigripTetra NH 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 NH.

Immunogenicity results are presented in the tables below:

Table 2: 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)

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 NH, 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 NH depending on their previous influenza vaccination history.

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

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

Immunogenicity results are presented in the table below:

Table 3: 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 NH).

Pharmacokinetic properties

Not applicable.

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.

PHARMACEUTICAL PARTICULARS

List of excipients

Buffer Solution:

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

Incompatibilities

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

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.

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.

Packaging Presentation
Box, 1 prefilled syringe 0,5 ml
Reg No. DKIXXXX

HARUS DENGAN RESEP DOKTER

Registered by
PT Aventis Pharma, Jakarta-Indonesia

Manufactured by
Sanofi Pasteur, 27100 Val de Reuil, France

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