

SAP / ID. number : PI-PIL VAXIGRIP TETRA NH 2023-2024 / XXXXXX		Film code : SP/XXXXXX	Printing Colour
Country : INDONESIA	Min. point size of text : 6 pt Type of text : Ocean Sans Pro Family Dimensions : 192 x 400 mm Type of prefold : 3x Horizontal - 2x Vertical Dimension after folded : 24 - 100 mm (± 2 mm)		 Pantone Black
Version number : 2			
Date : 02.05.2023			
Material : HVS 60 g/m²			
Pharmacode : XXXXX			
Prepared by : Rahmat Hafid			Technical Information  outline

- Sakit kepala: hanya terlihat pada anak-anak berusia dari 24 bulan.
- Mengantuk, tangisan yang tidak biasa: hanya terlihat pada anak-anak berusia kurang dari 24 bulan.
Umum (dapat mempengaruhi sampai 1 dari 10 orang):
- Menggigil: hanya terlihat pada anak-anak berusia 24 bulan dan lebih tua.
- Reaksi di tempat suntikan: engeras (indurasi), pembengkakan, memar (*ecchymosis*).
Jarang (dapat mempengaruhi sampai 1 dari 100 orang):
- Diare, hipersensitivitas.
Jarang (dapat mempengaruhi sampai 1 dari 1.000 orang):
- Penyakit seperti flu, reaksi di tempat suntikan: ruam, pruritus (gatal).
Pada anak-anak dari usia 6 bulan hingga 8 tahun yang menerima 2 dosis, mendapat efek samping serupa setelah dosis pertama dan kedua. Efek samping yang lebih sedikit dapat terjadi setelah dosis kedua pada anak-anak dari usia 6 sampai 35 bulan.

Efek samping umumnya terjadi dalam 3 hari pertama setelah vaksinasi dan hilang dengan sendirinya dalam 1 hingga 3 hari setelah mulai terjadi efek samping. Intensitas efek samping yang diamati ringan.
Efek samping umumnya lebih jarang terjadi pada lansia dibandingkan pada orang dewasa dan anak-anak.
Efek samping berikut telah dilaporkan setelah pemberian Vaxigrip. Efek samping ini dapat terjadi dengan VaxigripTetra NH:
- Nyeri terletak pada jalur saraf (neuralgia), kejang (kejang), gangguan neurologis yang dapat menyebabkan kaku leher, kebingungan, mati rasa, nyeri dan kelemahan anggota badan, kehilangan keseimbangan, kehilangan refleks, kelumpuhan sebagian atau seluruh tubuh (*encephalomyelitis*, neuritis, sindrom *G Guillain-Barre*).
- Peradangan pembuluh darah (*vasculitis*) yang dapat menyebabkan ruam kulit dan dalam kasus yang sangat jarang terjadi pada masalah ginjal sementara.
- Trombositopenia transien, limfadenopati, parestesia dalam kelompok usia selain yang dijelaskan di atas untuk efek samping ini.

Pelaporan efek samping
Jika Anda atau anak Anda mendapatkan efek samping, bicarakanlah dengan dokter, apoteker atau perawat Anda. Termasuk kemungkinan efek samping yang tidak tercantum dalam brosur ini.
Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Bagaimana cara menyimpan VaxigripTetra NH
Jauhkan vaksin ini dari pandangan dan jangkauan anak-anak.
Jangan gunakan vaksin ini setelah tanggal kedaluwarsa yang tercantum pada label dan karton setelah EXP. Tanggal kedaluwarsa mengacu pada hari terakhir bulan itu.
Simpan dalam lemari pendingin (2°C – 8°C). Jangan dibekukan. Simpan alat suntik di karton luar, untuk melindungi dari cahaya.
Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakanlah pada apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi dari kemasan dan informasi lainnya
Apa isi dari VaxigripTetra NH
- Zat aktifnya adalah: Virus influenza (tidak aktif, terbagi) dari organisme berikut *:
A/Victoria/4897/2022 (H1N1)pdm09-like virus (A/Victoria/4897/2022, IVR-238)15 mikrogram HA**
A/Darwin/9/2021 (H3N2)-like virus (A/Darwin/9/2021, IVR-228)15 mikrogram HA**
B/Australia/1359417/2021-like virus (B/Michigan/01/2021, wild type)15 mikrogram HA**
B/Phuket/3073/2013 - like virus (B/Phuket/3073/2013, wild type)15 mikrogram HA**
.....15 mikrogram HA**

* diperbarikan dalam telur ayam yang dibuahi dari unggas ayam yang sehat
** haemagglutinin

Vaksin ini sesuai dengan rekomendasi WHO (*World Health Organization*/Organisasi Kesehatan Dunia) (Belahan Bumi Utara) dan keputusan EU untuk musim 2023/2024.
- Bahan lain adalah: larutan penyangga yang mengandung natrium klorida, kalium klorida, disodium fosfat dihidrat, kalium dihidrogen fosfat, dan air untuk injeksi.
Beberapa komponen seperti telur (ovalbumin, protein ayam), neomisin, formaldehida atau oktoksinol-9 mungkin ada dalam jumlah yang sangat kecil (lihat Bagian 2).

Seperti apa VaxigripTetra NH dan isi kemasannya
Vaksin, setelah dikocok dengan perlahan, adalah cairan *opaque*sent tak berwarna.
Bentuk sediaan adalah suspensi untuk injeksi dengan kemasan sebagai berikut :

Kemasan : Dus, 1 <i>pre-filled syringe</i> @ 0.5 mL No. Registrasi: DK12059703543A1	Harus Dengan Resep Dokter
Didaftarkan oleh : PT Aventis Pharma Jakarta, Indonesia	
Diproduksi oleh : Sanofi Pasteur, Val-de- Reuil, France	
Dirilisikan oleh : Sanofi Pasteur, Lyon, France	

circulating strains of influenza virus change from year to year.

Efficacy of VaxigripTetra NH
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 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

	Vaxigrip Tetra NH (N=2,584)		Placebo (N=2,591)		Efficacy % (2-sided 95% CI)
	n	Influenza attack rate (%)	n	Influenza attack rate (%)	
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 hospitalization.

• 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 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).

• Pregnant women
There are no clinical efficacy data describing use of VaxigripTetra NH in pregnant women. However,data are available on Vaxigrip (TIV) and cited below, and can be extrapolated to VaxigripTetra NH.

In the randomised, controlled, phase IV, clinical studies conducted in Mali, Nepal, and South Africa, approximately 5,000 pregnant women received Vaxigrip (TIV) 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 (during pregnancy and for approximately 6 months post-delivery), following vaccination during these trimesters of pregnancy.
In the study conducted in Nepal, the efficacy of Vaxigrip (TIV) 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)
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 influenza illness
CI: Confidence Interval

• Infants younger than 6 months of age born to vaccinated pregnant women (passive protection)
Infants younger than 6 months of age are at high risk of influenza, resulting in high rates of hospitalization; however, influenza vaccines are not indicated for use in this age group.
There are no clinical efficacy data in infants born to women vaccinated with VaxigripTetra NH during pregnancy; however, efficacy in infants younger than 6 months of age whose mothers received a single 0.5-mL dose of Vaxigrip (TIV) during the second or third trimester has been demonstrated in clinical trials in Nepal, Mali and South Africa and can be extrapolated to VaxigripTetra NH. Efficacy of Vaxigrip (TIV) in infants younger than 6 months of age whose mothers were vaccinated during the first trimester has not been studied in these trials. Nevertheless, influenza vaccination during the first trimester should not be postponed (see Section Fertility, pregnancy and lactation).

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)
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 of protection in infants born to vaccinated mothers over 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 25.3% (95% CI, -47.9 to 67.8) for infants >8 to 16 weeks of age and 30.4% (95% CI, -154.9 to 82.8) for infants >16 to 24 weeks of age.

In the trial conducted in Mali, there is also a trend of higher efficacy of the trivalent inactivated influenza vaccine in infants during the first 4 months after birth (70.2% [95% CI, 35.7 to 87.6]), with lower efficacy within the fifth month of surveillance (60.7% [95% CI, 33.8 to 77.5]) and a marked fall within the sixth month (37.3% [95% CI, 7.6 to 57.8]).

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

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 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 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.
One clinical study performed in pregnant women described the immune response of VaxigripTetra NH versus Vaxigrip (TIV) 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 of ratio cord blood/maternal blood, at delivery.
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 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 Titer; 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 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 $\geq$ four-fold increase from pre- to post-vaccination titer
(d) GMTR: Geometric mean of individual titer ratios (post-/pre-vaccination titers)

Pregnant women and transplacental transfer
In a randomised, controlled clinical study conducted in Finland, a total of 230 pregnant women received VaxigripTetra NH and 116 pregnant women received Vaxigrip (TIV) 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 NH or Vaxigrip (TIV) are presented in table 5.

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 5.

At delivery, the level of antibodies in the cord sample compared to the mother sample

was almost doubled for the A/H1N1 strain and increased between 1.5 and 1.7 times for the A/H3N2, B/Brisbane, and B/Phuket strains, supporting that there is transplacental antibody transfer from mother to the newborn, following vaccination of women with VaxigripTetra NH or Vaxigrip (TIV) 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 (TIV) in studies conducted in Mali, Nepal, and South Africa.

Table 5: Immunogenicity results by HAI method in pregnant women, 21 days post-vaccination with Vaxigrip Tetra NH and at delivery

Antigen strain	Pregnant woman GMT (95% CI)	At Delivery N* =178 BL03M ^(c) GMT (95% CI)
	GMT (95% CI)	
A (H1N1) *	525 (466; 592)	304 (265 ; 349)
A (H3N2) *	341 (286; 407)	178 (146 ; 218)
B1 (Victoria) *	568 (496; 651)	290 (247 ; 341)
B2 (Yamagata) *	993 (870; 1134)	547 (463 ; 646)
	≥4-fold-rise n (%) ^(a)	GMT (95% CI)
A (H1N1) *	38.0 (31.5; 44.8)	576 (492 ; 675)
A (H3N2) *	59.3 (52.4; 65.9)	305 (246 ; 379)
B1 (Victoria) *	61.1 (54.3; 67.7)	444 (372 ; 530)
B2 (Yamagata) *	59.7 (52.9; 66.3)	921 (772 ; 1099)
	GMTR (95% CI)^(b)	Transplacental transfer: BL03B/BL03M^(c) GMT (95% CI)
A (H1N1) *	3.81 (3.11; 4.66)	1.89 (1.72 ; 2.08)
A (H3N2) *	8.63 (6.85; 10.9)	1.71 (1.56 ; 1.87)
B1 (Victoria) *	8.48 (6.81; 10.6)	1.53 (1.37 ; 1.71)
B2 (Yamagata) *	6.26 (5.12; 7.65)	1.69 (1.54 ; 1.85)

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

*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)

GMT: Geometric Mean Titer; CI: Confidence Interval

(a) 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 $\ge$ four-fold increase from pre- to post-vaccination titer
(b) GMTR: Geometric mean of individual titer ratios (post-/pre-vaccination titers)
(c) BL03M: Blood sample of mother at delivery
(d) BL03B: Cord blood sample at delivery
(e) If a mother has X babies, her titers values is counted X times

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 6: 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 (1078; 1276)
	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 Titer; 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 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 $\ge$ four-fold increase from pre- to post- vaccination titer
(c) GMTR: Geometric mean of individual titer ratios (post-/pre-vaccination titers)
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 pre-filled syringe @ 0.5 mL
Reg No. DK12059703543A1

HARUS DENGAN RESEP DOKTER
Registered by
PT Aventis Pharma, Jakarta-Indonesia

Manufactured by:
Sanofi Pasteur, Val-de- Reuil, France

Released by:
Sanofi Pasteur, Lyon, France