1. Name of the medicinal product

Vaxigrip Tetra, 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/2570/2019 (H1N1)pdm09 - like strain (A/Victoria/2570/2019, IVR-215) ……...15 micrograms HA**
A/Darwin/9/2021 (H3N2) - like strain (A/Darwin/9/2021, IVR-228)…….....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**
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 2022/2023 season.
For the full list of excipients, see Section 6.1.
Vaxigrip Tetra may contain traces of eggs, such as ovalbumin, and of neomycin, formaldehyde and octoxinol-9, which are used during the manufacturing process (see Section 4.3).

3. Pharmaceutical form

Suspension for injection in pre-filled syringe.
The vaccine, after shaking gently, is a colourless opalescent liquid.

4. Clinical particulars

4.1 Therapeutic indications

Vaxigrip Tetra (Quadrivalent Influenza Vaccine (split virion, inactivated) is indicated for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine for:
- active immunisation of adults, including pregnant women, and children from 6 months of age and older,
- passive protection of infant(s) from birth to less than 6 months of age following vaccination of pregnant women (see Sections 4.4, 4.6 and 5.1).

The use of Quadrivalent Influenza Vaccine (split virion, inactivated) 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 Vaxigrip Tetra administration (active immunisation) have not been established. No data are available.

Regarding passive protection: one 0.5mL dose given to pregnant women may protect infants from birth to less than 6 months of age; however, not all these infants will be protected (see section 5.1).

Method of administration
The vaccine should be given by intramuscular or subcutaneous injection.
The preferred sites for intramuscular injection are the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in children 6 months through 35 months of age, or the deltoid muscle in children from 36 months of age and adults.
Precautions to be taken before handling or administering 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.
Vaxigrip Tetra 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.
Vaxigrip Tetra is intended to provide protection against those strains of influenza virus from which the vaccine is prepared.
As with any vaccine, vaccination with Vaxigrip Tetra may not protect all vaccinees.
Regarding passive protection, not all infants less than 6 months of age born to women vaccinated during pregnancy will be protected (see section 5.1).
Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.
Interference with serological testing
See Section 4.5.
Vaxigrip Tetra (split virion, inactivated) contains potassium and sodium
This medicine contains less than 1 mmol potassium (39 mg) and less than 1 mmol sodium (23 mg) per dose, that is to say 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 Vaxigrip Tetra.
Vaxigrip Tetra can be given at the same time as other vaccines, based on clinical experience with Inactivated Influenza Vaccine (Split Virion) BP. Separate injection sites and separate syringes 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 reactions 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, hospitalization, and death: pregnant women should receive an influenza vaccine.
Vaxigrip Tetra 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 Vaxigrip Tetra and Inactivated Influenza Vaccine (Split Virion) BP (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 Quadrivalent Influenza Vaccine (split virion, inactivated) and Inactivated Influenza Vaccine (Split Virion) BP were administered in pregnant women during the second or third trimester (230 exposed pregnancies and 231 live births for Quadrivalent Influenza Vaccine (split virion, inactivated) and 116 exposed pregnancies and 119 live births for Inactivated Influenza Vaccine (Split Virion) BP).
Data from four clinical studies with the trivalent inactivated influenza vaccine (Inactivated Influenza Vaccine (Split Virion) BP thiomersal-free formulation) 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 Inactivated Influenza Vaccine (Split Virion) BP 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 Inactivated Influenza Vaccine (Split Virion) BP 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 Vaxigrip Tetra did not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development or early post-natal development.

Breastfeeding

Vaxigrip Tetra may be used during breastfeeding.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety of Vaxigrip Tetra 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 Vaxigrip Tetra and 884 children from 3 to 8 years of age received one or two doses of Vaxigrip Tetra depending on their influenza vaccination history and 1,614 children from 6 to 35 months of age received two doses (0.5 mL) of Vaxigrip Tetra.
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%),
- In 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 to 35 months of age: headache (11.9%) and myalgia (11.6%).

Overall, 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 Vaxigrip Tetra 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 reported following commercial use of Vaxigrip Tetra based on spontaneous reporting. Because these reactions are reported voluntarily from populations of uncertain size, it is not possible to reliably estimate their frequency.
Within each frequency grouping the adverse reactions are presented in the order of decreasing seriousness.

Adult 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 Vaxigrip Tetra and from 884 children from 3 to 8 years of age who received one or two doses of Vaxigrip Tetra 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 Vaxigrip Tetra.
- 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 Vaxigrip Tetra was similar after the first and the second injections with a trend of lower incidence of adverse reactions after the second injection compared to the first one in children from 6 to 35 months.

Adverse events

The following adverse events were reported following commercial use of Inactivated Influenza Vaccine (Split Virion) BP. A causal relationship with Vaxigrip Tetra 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 Vaxigrip Tetra observed in a limited number of subjects with co-morbidities enrolled in the clinical studies does not differ from the one observed in the overall population. In addition, studies conducted with Vaxigrip in renal transplant patients, and asthmatic patients showed no major differences in terms of safety profile of Vaxigrip in these populations.
- Pregnant women
In clinical studies conducted in pregnant women in South Africa and Mali with Inactivated Influenza Vaccine (Split Virion) BP (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 conducted with Inactivated Influenza Vaccine (Split Virion) BP. In the South Africa study, local reactions were more frequent in the Inactivated Influenza Vaccine (Split Virion) BP group than in the placebo group in both HIV-negative and HIV-positive cohorts. There were no other significant differences in solicited reactions between Inactivated Influenza Vaccine (Split Virion) BP and placebo groups in both cohorts.
In one clinical study conducted in pregnant women in Finland with Vaxigrip Tetra (see sections 4.6 and 5.1), frequencies of local and systemic solicited reactions reported within 7 days following administration of Vaxigrip Tetra were consistent with those reported for the non-pregnant adult population during clinical studies conducted with Vaxigrip Tetra 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.
Any suspected adverse events should be reported to the Ministry of Health (www.health.gov.il) according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

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

5. Pharmacological properties
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02.
Mechanism of action
Vaxigrip Tetra provides active immunisation against four influenza virus strains (two A subtypes and two B types) contained in the vaccine.

Vaxigrip Tetra induces humoral antibodies against the haemagglutinins within 2 to 3 weeks. These antibodies neutralise influenza viruses.
Specific levels of haemagglutination-inhibition (HAI) antibody 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 revaccination with Vaxigrip Tetra has not been studied. However, based on clinical experience with the trivalent vaccine, annual influenza vaccination is recommended given the duration of immunity provided by the vaccine and because circulating strains of influenza virus change from year to year.
Efficacy of Vaxigrip Tetra
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 Vaxigrip Tetra (N=2,722), or placebo (N=2,717) 28 days apart to assess Vaxigrip Tetra efficacy for the prevention of laboratory-confirmed influenza illness caused by any strain A and/or B and caused by vaccine similar strains (as determined by sequencing).
Laboratory-confirmed influenza illness was defined as influenza like-illness (ILI) [occurrence of fever ≥ 38°C (that lasts at least 24 hours) concurrently with at least one of the following symptoms: cough, nasal congestion, rhinorrhoea, pharyngitis, otitis, vomiting, or diarrhoea] laboratory-confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) and/or viral culture.

Table 1: Influenza Attack Rates and Vaxigrip Tetra Efficacy against laboratory-confirmed influenza illness in children from 6 to 35 months of age

	Vaxigrip Tetra (N=2,584)		**Placebo (N=2,591)**		**Efficacy**
	n	**Influenza Attack Rate (%)**	**n**	**Influenza Attack Rate (%)**	**% (2-sided 95% CI)**
Laboratory-confirmed influenza illness caused by:					
- Any influenza A or B type	122	4.72	255	9.84	52.03 (40.24; 61.66)
- Viral strains similar to those contained in the vaccine	26	1.01	85	3.28	69.33 (51.93; 81.03)

N: Number of children 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 observed in children 3 to 8 years of age, the efficacy of Vaxigrip Tetra in this population is expected to be at least similar to the efficacy observed in children from 6 to 35 months (see “Children from 6 to 35 months of age” above and “Immunogenicity of Vaxigrip Tetra“ below).
- Infants less than 6 months of age born to vaccinated pregnant women (passive protection):
Infants less than 6 months of age are at high risk of influenza, resulting in high rates of hospitalisation; however influenza vaccines are not indicated for active immunisation in this age group.
Efficacy in infants of women who received a single 0.5 mL dose of Vaxigrip Tetra during the second or third trimester of pregnancy has not been studied; however, efficacy in infants of women who received a single 0.5 mL dose of the trivalent inactivated influenza vaccine (Inactivated Influenza Vaccine (Split Virion) BP) during the second or third trimester has been demonstrated in clinical trials and can be extrapolated to Vaxigrip Tetra.
Efficacy of the trivalent inactivated influenza vaccine (Inactivated Influenza Vaccine (Split Virion) BP) 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 Inactivated Influenza Vaccine (Split Virion) BP (trivalent influenza thiomersal-free vaccine) and approximately 5,000 pregnant women received placebo or control vaccine (quadrivalent meningococcal conjugate vaccine) during the second or third trimester of pregnancy. Vaccine efficacy against laboratory confirmed influenza in pregnant women was evaluated as a secondary endpoint in all three studies.
The studies conducted in Mali and South Africa demonstrated the efficacy of Inactivated Influenza Vaccine (Split Virion) BP 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 Inactivated Influenza Vaccine (Split Virion) BP for the prevention of influenza in pregnant women following vaccination during these trimesters of pregnancy was not demonstrated.

Table 2: Influenza Attack Rates and Inactivated Influenza Vaccine (Split Virion) BP Efficacy against Laboratory-confirmed influenza in pregnant women

	Influenza Attack Rate (Any influenza A or B type) % (n/N)		Inactivated Influenza Vaccine (Split Virion) BP 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 infuenza
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 Inactivated Influenza Vaccine (Split Virion) BP (trivalent influenza thiomersal free vaccine) and 4532 of 4868 (93%) infants born to pregnant women who received a placebo or control vaccine (quadrivalent meningococcal conjugate vaccine) (see table 3) during the second or third trimester of pregnancy, were followed up until approximately 6 months of age.
The studies confirmed the efficacy of Inactivated Influenza Vaccine (Split Virion) BP 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; Inactivated Influenza Vaccine (Split Virion) BP efficacy in infants born to mothers vaccinated during the first trimester could therefore not be evaluated.

Table 3: Influenza Attack Rates and Inactivated Influenza Vaccine (Split Virion) BP Efficacy against Laboratory-confirmed influenza in infants following vaccination in pregnant women

	Influenza Attack Rate (Any influenza A or B type) % (n/N)		Inactivated Influenza Vaccine (Split Virion) BP 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 the trivalent inactivated influenza vaccine 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.

Immunogenicity of Vaxigrip Tetra

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 assessed Vaxigrip Tetra 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 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 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.

Vaxigrip Tetra induced a significant immune response to 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 Vaxigrip Tetra.

Immunogenicity results are presented in the table below:

Table 4: Immunogenicity results in adults aged from 18 to 60 years 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)	1,715 (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 ≥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

A total of 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 Tetra are presented in table 5.

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

Antigen Strain	QIV 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)

	≥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 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 ≥four-fold increase from pre- to post-vaccination titer
(b) 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) 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 vaxigrip Tetra, at delivery

Antigen Strain	**QIV 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 QIV, 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 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 Quadrivalent Influenza Vaccine (split virion, inactivated) 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 Inactivated Influenza Vaccine (Split Virion) BP in studies conducted in Mali, Nepal, and South Africa (see subsection Efficacy of Quadrivalent Influenza Vaccine (split virion, inactivated)).

Paediatric population
- Children from 9 to 17 years of age:
In a total of 429 children from 9 to 17 years of age who received one dose of Vaxigrip Tetra, the immune response against the 4 strains contained in the vaccine was similar to the immune response induced in adults 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 Vaxigrip Tetra depending on their previous influenza vaccination history. Children who received a one- or two-dose schedule of Vaxigrip Tetra presented a similar immune response following the last dose of the respective schedule.
In addition to the Vaxigrip Tetra efficacy, the immunogenicity of two 0.5 mL-dose of Vaxigrip Tetra was assessed 28 days after receipt of the last injection of Vaxigrip Tetra by HAI method in 341 children 6 to 35 months of age.
Immunogenicity results are presented in the table below:

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

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; 1,052)
A (H3N2)	1,071 (925; 1,241)	1,568 (1,451; 1,695)
B (Victoria)	623 (550; 706)	1,050 (956; 1,154)
B (Yamagata) [(a)]	1,010 (885; 1,153)	1,173 (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 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 ≥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 Vaxigrip Tetra).

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

The expiry date of the product is indicated on the packaging material.

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) – pack size of 1, 10 or 20.
0.5 mL of suspension in pre-filled syringe (type I glass) without needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) – pack size of 1, 10 or 20.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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8. Registration holder

MEDICI MEDICAL LTD. 3 Hamachshev St. Netanya 4250713, Israel

9. Marketing authorisation number

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