Assessment report for biopharmaceutical medicinal product

Registration Form for VaxigripTetra

2th expert meeting, held on the 23th August, 2017

Thai Food and Drug Administration

Name of product	VaxigripTetra
Active Substance (s)	Influenza virus (inactivated, split) of the following strains A/California/7/2009 (H1N1) A/Texas/50/2012 (H3N2) B/Massachusetts/ 2012/2 B/Brisbane/60/2008
Pharmaceutical form	Suspension for injection in pre-filled syringe
Strength	15 mcg haemagglutinin/strain per 0.5 ml (1 dos)
Route(s) of administration	Intramuscular or Subcutaneous
Therapeutic indication(s)	**Indications as stated in the Patient Information leaflet (PIL):** ป้องกันโรคไข้หวัดใหญ่ในผู้ใหญ่และเด็กอายุตั้งแต่ 6 เดือนขึ้นไป **Indications as stated in the Summary of Product Characteristic (SmPC):** VaxigripTetra 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.
Submitted number and date of submission	2C 15038/60 (NB) 17 July2017
E-identifier Number	e5900038

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List of Abbreviations

CPP	Critical process parameter
CQA	Critical quality attributes
DP	Drug product
DS	Drug substance
ELLA assay	Enzyme Linked Lectin Assay

GMTs	Geometric Mean Titer
GMTQIV/GMTTIV (GMTRs)	Ratio of Geometric Mean Titer
HAI	Haemagglutination Inhibition
ICH	International Committee on Harmonization
IPCs	In Process Controls
Ph. Eur.	European Pharmacopoeia
QIV	Quadrivalent inactivated influenza vaccine
SN	Seroneutralization
SRID	Single Radial Immunodiffusion (SRID) Assay
TIV	Trivalent inactivated influenza vaccine
TIV1	Trivalent inactivated influenza vaccine for B/Massachusetts
TIV2	Trivalent inactivated influenza vaccine for B/Brisbane
USP	United States Pharmacopoeia (US

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Registration Form for VaxigripTetra

Submitted number 2C 15038/60 (NB)

E-identifier e5900038

(Manufacturing site: Sanofi Pasteur S.A., France)

Submitted date: 17th July, 2017

Part 1: Introduction and summary review

Influenza is an infectious disease caused by an influenza virus.[1] Three types of influenza viruses affect people, called Type A, Type B, and Type C. The greatest risk of catching influenza is during the cold months, between October and March. Usually, the virus is spread through the air from coughs or sneezes. This is believed to occur mostly over relatively short distances. It can also be spread by touching surfaces contaminated by the virus and then touching the mouth or eyes.[2] A person may be infectious to others both before and during the time they are showing symptoms. The infection may be confirmed by testing the throat, sputum, or nose for the virus. Symptoms can be mild to severe.[1] The most common symptoms include: a high fever, runny nose, sore throat, muscle pains, headache, coughing, and feeling tired. These symptoms typically begin two days after exposure to the virus and most last less than a week. Complications of influenza may include viral pneumonia, secondary bacterial pneumonia, sinus infections, and worsening of previous health problems such as asthma or heart failure.[2,3]

Influenza is a disease that can spread rapidly and is caused by different types of strains that can change every year. So 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.[4]

Frequent hand washing reduces the risk of viral spread. Wearing a surgical mask is also useful. Yearly vaccinations against influenza are recommended by the World Health Organization (WHO) for those at high risk. Antiviral drugs such as the neuraminidase inhibitor oseltamivir, among others, have been used to treat influenza. Their benefits in those who are otherwise healthy do not appear to be greater than their risks. No benefit has been found in those with other health problems.[1,2]

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

The mechanism of action of the influenza vaccine consists of the induction of immune responses against the viral antigen components contained in the formulation. VaxigripTetra induces humoral antibodies against the haemagglutinins within 2 to 3 weeks. These antibodies neutralise influenza viruses. Specific levels of haemagglutination-inhibition (HAI) antibody titre post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the HAI antibody titres have been used as a measure of vaccine activity. In some human challenge studies, HAI antibody titres of ≥1 :40 have been associated with protection from influenza illness in up to 50% of subjects.[3]

Six phase III studies (GQM11, GQM02, GQM05, GQM09, GQM01, and GQM04) were conducted to evaluate the safety and efficacy of the VaxigripTetra in 18 to 60-year-old adults, the elderly > 60 years, and in paediatric subjects from 6 to 35 month, 3 to 17 years of age. The efficacy of the VaxigripTetra (QIV) is inferred from its immunogenicity based on comparative immunogenicity evaluation with Sanofi Pasteur's Vaxigrip (TIV) which is licensed in the European Union since 2001. The target population is adequately reflected in the clinical trials. Two trials GQM01 and GQM04 were conducted with VaxigripTetra batches from an initial Drug substance manufacturing process with a slightly higher than expected HA content for B strains (mainly in B/Florida). These trials are considered supportive. Four others trials (GQM02, GQM09, GQM05, GQM11) were conducted with VaxigripTetra batches from a final commercial DS manufacturing process for which the HA content is in accordance with European Pharmacopoeia requirements for all strains. These trials are considered pivotal.

The efficacy of the VaxigripTetra (QIV) is inferred from the demonstration of non-inferior immune response of the VaxigripTetra (QIV) compared with the Vaxigrip (TIV) manufactured by Sanofi Pasteur. Assessment of the immunogenicity of influenza vaccines is primarily based on detection of serum antibodies directed against the viral HA antigen. The findings based on HAI assay results were further supported by the neutralizing antibody response data (assessed using the SN assay) and the anti-NA antibody response data (assessed using the ELLA). It is generally accepted that anti-HA antibodies strongly correlate with protection against influenza. However, an absolute protective titre threshold has not yet been established. There was no evidence that the addition of a second B strain interferes with the immune response to the other strains included in the vaccine.

No significant safety concerns have been identified in the previous years, it can be expected that the safety profile of the VaxigripTetra (QIV) is comparable to that of the comparator Vaxigrip (TIV). After administration of the VaxigripTetra a higher rate of solicited ARs were observed in children and adults compared with elderly ones. This is the case for many vaccines. Overall, no new safety signal was seen in the submitted clinical database. Only one SAE/AESI was considered to be vaccine related. A 3-year-old female subject without relevant medical history developed severe thrombocytopenia 9 days following vaccination 1 with VaxigripTetra. She recovered within 38 days after the onset. Thrombocytopenia following vaccination is a very rare event already known from the Vaxigrip and other vaccines (e.g. measles-mumps-rubella). The adverse drug reaction of thrombocytopenia is included into the SmPC. The event of thrombocytopenia is adequately reflected in the RMP.

VaxigripTetra is indicated for active immunization of adults and children from 6 months of age and older for the prevention of influenza disease caused by the 2 influenza-A virus subtypes and the 2 influenza-B virus types contained in the vaccine. The manufacture, formulation and controls for VaxigripTetra were established based on Sanofi Pasteur's experience of the current Vaxigrip licensed in the European Union. VaxigripTetra has been investigated in a comprehensive clinical trial program. The increasing antigen amount due to the additional B strain does not have any clinically relevant impact on the safety of the vaccine. The recommendations and contraindications that currently apply to Sanofi`s Vaxigrip should be adopted for the VaxigripTetra. The safety profile of VaxigripTetra is considered positive. Thus, VaxigripTetra is concluded to have at least the same benefit-risk ratio for individuals from 6 months onwards compared to other inactivated influenza vaccines licensed in the EU. Most likely benefits will be higher (while the potential risks remain the same) due to the second Influenza B strain.

Part 2 Summary of the dossier

➢ 2.1 Type of marketing authorisation application

- **Product type:** New biological entity
- **Application type:** Standalone application

- **Review method:** Abbreviated assessment: un-redacted evaluation report from stringent NRAs from France and review the quality part by the external expert from Institute of biologics, Department of Medical Science

➢ **2.2 Administrative data**

2.2.1 Product

Name of Product: Invented name	VaxigripTetra
Active Substance(s)	Influenza virus (inactivated, split) of the following strains A/California/7/2009 (H1N1) A/Texas/50/2012 (H3N2) B/Massachusetts/ 2012/2 B/Brisbane/60/2008
Strength	15 mcg haemagglutinin/strain per 0.5 ml (1 dose)
Therapeutic Class	influenza vaccine, inactivated, split virus or surface antigen ACT code: J07BB02
Pharmaceutical form	Suspension for injection in pre-filled syringe
Route of administration	Intramuscular or subcutaneous
Drug Characteristics	Colorless opalescent liquid
Packaging	0.5 ml of suspension in pre-filled syringe (type I glass) with attached needle or without needle, equipped with a plunger stopper, box of 1, 10, 20

2.2.2 Source

1. **Name and address of the applicant for importation**

   Sanofi Pasteur LTD, Bangkok, Thailand.

2. **Name and address of the manufacturer(s) of the dosage form**

Sanofi Pasteur S.A., Val de Reuil, France republic.

3. **Name and address of the filling**

   The same as stated in the name and address of the manufacturer(s) of the dosage form.

4. **Name and address of the final product release**

   The same as stated in the name and address of the manufacturer(s) of the dosage form.

Evaluation result on source

All the stated manufacturers hold GMP certificates from France which complied with the standard of GMP/PICS to ensure the good quality standard as manufacturing sites for pharmaceutical substances. The GMP documents are already submitted in module 1 via e-CTD system.

Part 3 Analytical (Physico-Chemical, Biological And Microbiological Documentation)

3.1 Drug substance (DS)

3.1.1 Manufacture

The name and address of manufacturers for Drug Substance (DS) is Sanofi Pasteur – Val de Reuil (VDR), France.

A master and a working seed were prepared for each of the virus strains, received from the WHO collaborating centres. The manufacturing process for the monovalent bulk is similar to the well-known manufacturing process for the monovalent bulks of the company's trivalent vaccine Vaxigrip. The only change implemented at the drug substance level is at the final dilution step. The change became necessary in order to increase the concentration of the antigen in the monovalent bulk, to allow formulation of the final vaccine. The manufacturing process can be divided into four main parts:

1. Propagation of the working seed in fertilized hen's eggs, harvesting of infected allantoic fluid followed by clarification, filtration and concentration.
2. Purification of the virus particles by ultracentrifugation using a sucrose gradient
3. Splitting of the virus particles with octoxynol-9
4. Inactivation of the viral suspension using formaldehyde, Finally, a sterile filtration is conducted and the DS is stored until formulation.

Evaluation result

Manufacturing process is considered appropriate. The stated manufacturers hold GMP certificates from France to ensure the good quality standard as manufacturing sites and manufacturing process for biological substances.

3.1.2 Control of drug material

Steps that control the quality of drug substance including starting materials; fertilized eggs and viral strains.

Control of Critical Steps and Intermediates

Critical Steps

The manufacturer provided enough critical steps and considered appropriate.

Intermediates

is no intermediate in the DS manufacturing process.

Control of drug substance:

The manufacturer provided list of drug substances controlled according to European Pharmacopoeia and some from in house method. All of listing was considered appropriate.

Process Validation and Evaluation

Validation data are provided for the purification, splitting and inactivation steps, considered as critical and considered appropriate.

Analytical procedures

The analytical procedures (principle, equipment, standards/solution, procedure, measurement/evaluation) are concisely described and the validation reports provided: identification of Haemagglutinin antigen and Neuraminidase, enzymatic activity test for Neuramindase, sterility, residual infectious influenza virus, and Octocynol-9, the chemical used for disruption.

Batch analysis.

The batch analysis results demonstrated that the monovalent bulk production is fairly consistent as regards the HA content and met all release criteria.

Evaluation result

Drug material of VaxigripTetra meets the quality standard of drug material to ensure the quality in terms of the control of raw and starting materials, the control of critical steps

and intermediates, also the control of process validation and batch analysis. Therefore the quality of drug material is acceptable and pass the standard criteria.

3.1.3 Container closure system

Container closure system was 45-L stainless steel containers or 50-L a polypropylene as alternative. The container closure system meets the quality standards and complied with Ph. Eur. and/or USP.

Evaluation result

The container closure system is acceptable and meets the standard criteria.

3.1.4 Stability

The DS stored in 45-L stainless steel containers or, as alternative, in a 50-L polypropylene container. The batches included in the studies were manufactured at industrial scale. Real-time stability studies at real-time (+5°C ± 3°C for 24 months) and under accelerated conditions (+25°C ± 2°C for 30 Days) have been performed. All specifications were met and support the proposed shelf life for the DS of 24 months at +5°C ± 3°C.

Evaluation result

The stability of drug substance is acceptable and meets the standard criteria.

- **3.2 Drug product**

The Drug product is generated by aseptic blending of four inactivated monovalent influenza split virus DS bulks, 2x influenza B with phosphate buffered saline (PBS) solution and subsequent filling (after on-line sterilization filtration) into single-dose containers. Apart from PBS no other (or novel) excipients or materials from animal or human origin are utilized for DP formulation.

3.2.1 Manufacture

The Drug Product (DP) is manufactured and controlled in accordance with Good Manufacturing Practices (GMP) at Sanofi Pasteur S.A., Val de Reuil, France republic.

DP manufacture process for “VaxigripTetra” is identical to the applicant´s trivalent seasonal inactivated influenza vaccine (TIV) “Vaxigrip”. The development of the manufacturing process and the control elements (CQA, CPP, IPC) implemented to assure

consistency of “VaxigripTetra” production have been based on experiences and knowledge from the TIV process. The DP manufacturing process has been proper validated for all manufacturing sites involved, which are the same established sites that are also used for the licensed TIV “Vaxigrip”.

In a comprehensive serious of investigations that include full assay validation as well as “spiking” and “degradation” were studied.

The manufacturing process for the VaxigripTetra drug product has been developed based on the Vaxigrip drug product manufacturing process and consists of the following steps:

1. Formulation of the final bulk;

2. Transfer of the final bulk into SP network for filling (when filling takes place outside the formulation site);

3. Filling (including stoppering) and inspections of the final containers;

4. Transfer of the final containers into SP network for labeling and packaging (when labeling and packaging take place outside the filling site);

5. Labeling and packaging of the VaxigripTetra final product.

The process uses the same starting materials, equipment and facilities as Vaxigrip. The development of the manufacturing process is limited to the production scale-up and to technical adjustments during the formulation process.

Evaluation result:

Manufacturing process is considered appropriate. The stated manufacturers hold GMP certificates from France to ensure the good quality standard as manufacturing sites for sterile product and biological medicinal product.

3.2.2 Qualitative and quantitative particulars of the constituents

Table **Formulation**

Component(S)	Reference	Quantity (per dose) (0.5 ml (1 dose))
Active Ingredients		
Strains NH2012015/4		

Influenza virus (inactivated, split) of the following strains*		
A/California/7/2009 (H1N1) pdm09 – like strain (A/California/7/2009, NYMC X-179A)	Ph. Eur. 0158, current edition "Influenza vaccine (split virion, inactived)"	15 micrograms HA**antigen
A/Texas/50/2012 (H3N2) – like strain (A/Texas/50/2012, NYMC X-223A)		15 micrograms HA** antigen
B/Massachusetts/2/2012 (Yamagata lineage)		15 micrograms HA** antigen
B/Brisbane/60/2008 (Victoria lineage)		15 micrograms HA** antigen
Excipient		
PBS Solution +	Internal standard	q.s. 0.5 ml

* propagated in fertilised hens' eggs from healthy chicken flocks

**haemagglutinin

+ composition of PBS solution:

- Sodium chloride
- Potassium chloride
- Disodium phosphate dihydrate
- Potassium dihydrogen phosphate
- Water For Injections (WFI)

Evaluation result:

The formulation is considered appropriate. The ingredients in the stated batch formula meet the quality standard in terms of the drug product inspections.

3.2.2 Control of drug product

Control of excipients:

The excipients used in the manufacture of the Finished Product are referenced in the Ph. Eur. All of the listed excipients are used to prepare the Phosphate Buffered Saline (PBS) solution.

Controls of Critical Steps and Intermediates

Critical Steps and Controls

The critical steps of DP manufacturing process were described and considered to be appropriate.

Intermediate

There is no intermediate in the DP manufacturing process.

Control of Drug Product

Specification(s) and Justification of Specification(s)

Release specifications of the Quadrivalent Influenza Vaccine (QIV) Drug Product (DP) stages are based on:

• Ph. Eur. 0153, current edition, "Vaccine for human use";

• Ph. Eur. 0158, current edition, "Influenza vaccine (split virion, inactivated)";

• ICH Q6B "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" September 1999;

• WHO TRS 927, 2005, Recommendations for the Production and Control of Influenza Vaccines (Inactivated);

• The experience gained during pharmaceutical and clinical development.

The release specifications for QIV Final Bulk Product (FBP) and Filled product (FP) are based on internal standard (Ph. Eur., ICH guidelines, etc.) with a justification for each test, method reference and acceptance criteria.

Analytical Procedures and Validation of Analytical Procedures

Analytical procedures is in line with the Ph. Eur. Controls of final bulk product (bacterial and fungal sterility, appearance, pH value, extractable volume, HA Antigen content and identification by SRD, bacterial endotoxins). Methods are either in line with Ph. Eur. or have been adequately described and validated.

Batch analysis

The batch analysis data confirm that FBP and FP of consistent and expected quality within the limits set by specifications can be manufactured by the implemented process.

Evaluation result

Drug product of VaxigripTetra meets the standard criteria. The analytical procedures and validation of analytical procedures are appropriate.

3.2.3 Container closure system

In principle, the Container closure system for the tetravalent vaccine is identical to that used for the applicant´s licensed TIV and the materials used are in accord with respective Ph. Eur. requirements. The FP is filled into type I glass single-dose syringes provided with or without needle. Alternative bromobutyl stopper plungers are proper for the tetravalent vaccine, which are licensed also for TIV. Compatibility studies have been conducted for all plunger stopper materials.

Evaluation result

Container closure system meets the quality standards of Europe.

3.2.4 Stability

VaxigripTetra shows the acceptable stability according to ICH Guidelines. Therefore, the stability of drug product is acceptable and meets the standard criteria. The only requirement is "Store in a refrigerator (2°C - 8°C), Do not freeze, Keep the syringe in the outer carton in order to protect from light and Keep out of the sight and reach of children" should be stated clearly on label. The shelf-life of this product when stored at 2-8°C is 12 months.

Evaluation result

The proposed shelf-life of 12 months for the VaxigripTetra final product by storage at 2 to 8°C could be granted.

Assessor's conclusions on Quality

VaxigripTetra use the same method of synthesis to prepare Vaxigrip drug substance which is licensed in the European Union since 2001. All the stated manufacturers hold GMP certificates from France to ensure the good quality standard as manufacturing sites for pharmaceutical substances. Manufacturers and manufacturing process of drug substance and drug product of VaxigripTetra is acceptable and pass the standard criteria to ensure the quality in terms of the control of starting materials, the control of critical steps and intermediates, the control of validation process, the control of closure system, and also the control of stability of drug substance and drug product.

Part 4: Non-clinical documentation

➢ 4.1 Pharmacology

A primary pharmacodynamic study was experimented in mice and demonstrated a clear dose-response within a range from 1/27 human dose to full human dose administered subcutaneously. After a single vaccination, sustained HI responses against two A strains were detected with mean HI titers ranging from 14 to 376 for the A/California/7/2009 (H1N1) and from 13 to 243 for the A/Texas/50/2012 (H3N2) strain. After the second immunization, HI titers to two A strains were further increased and meanwhile HI responses against two B strains were also detected with positive antigen dose effect evidenced. These data provide a rationale for including the additional B strain in vaccine.

A safety pharmacology study was performed in rabbits. A single dose and repeated dose (3 injections 2 weeks apart) intramuscular administrations of a filled product of VaxigripTetra did not cause overt adverse effect on cardiovascular and respiratory functions, and body temperature. Data are supported by those of a repeat-dose toxicity study and consistent with clinical trial data suggestive of no overt adverse effect of VaxigripTetra candidate on the vital function.

➢ 4.2 Pharmacokinetics

Pharmacokinetics studies were not performed as these are not considered applicable to vaccines and is in accordance to the EMA "Note for guidance on preclinical pharmacological and toxicological testing of vaccines" and WHO guidelines on nonclinical evaluation of vaccines.

➢ 4.3 Toxicology

➢ Repeat-Dose Toxicity

A pivotal GLP-compliant local tolerance and repeat-dose toxicity study were performed in rabbits using the human dose under intramuscular route. Following up to three intramuscular injections at two-week intervals, no adverse systemic effects were observed. No premature deaths occurred during the study and there were no adverse clinical signs. Body weight, food consumption and body temperature were unaffected by QIV and no QIV-related ophthalmologic findings were observed. There were no QIV-related effects on haematology, coagulation or clinical chemistry parameters. There were no organ weight changes attributed to the administration of the QIV. QIV-related changes were limited to

minimal and transient macroscopic and microscopic findings consistent with local reaction at the injection site. At the end of the recovery period, data showed a partial recovery of the local inflammation seen at the injected muscle.

- **Reproductive and Developmental Toxicity**

In a pivotal GLP-compliant developmental and reproductive toxicity study were conducted to evaluate the effects of QIV on the embryo-fetal and early post-natal developments in rabbits after five intramuscular injections of one human dose QIV prior to mating (2 doses) and during gestation (3 doses). There was no indication of maternal systemic toxicity induced during the gestation and lactation periods with no unscheduled deaths and no adverse clinical signs. There was no effect on the mating performance and female fertility. There was no indication of a teratogenic potential and no effect on pre and post natal development.

- **Other Toxicity**

The safety pharmacology study was conducted to evaluate the effects of QIV on the cardiovascular (blood pressure, heart rate and electrocardiogram (ECG) parameters), respiratory (breathing rate) functions and body temperature in conscious and unrestrained telemetered rabbits over a 24h-period following one to three intramuscular injections of one human dose of QIV at two-week intervals. No premature deaths occurred during the study and there were no adverse clinical signs. Clinical observations were limited to transient erythema and/or edema indicative of a slight local reactogenicity. Blood pressure, heart rate, ECG and breathing rate parameters as well as body temperature were unaffected by the QIV treatment following each injection

Evaluation result

The immunogenicity profile of the QIV vaccine candidate was investigated in a mouse study comparing the immunogenicity induced by three QIV batches to that induced by two TIV vaccines (commercial and alternative). The functional HI responses measured with the three QIVs were similar to those induced by the two TIVs except for the B strain not included in the TIV vaccine for which superiority of the QIV vaccines over the related TIV vaccine was observed. Nonclinical safety testing of QIV did not raise any safety concerns and under the testing conditions, the vaccine was well-tolerated and was not teratogenic. The results are in accordance with those observed in clinical trials.

Part 5: Clinical Study Reports

The overall goal of the clinical development plan of the QIV was to show that the addition of a second B strain does not impact the safety of the vaccine and does not interfere with the immune response against the other strains in the vaccine. Another objective of the clinical development plan was to demonstrate vaccine efficacy of the QIV compared with Placebo in infants, toddlers, and children aged from 6 to 35 months who had not previously been vaccinated against influenza.

The QIV manufacture, formulation and controls were established based on Sanofi Pasteur's experience of the current TIV licensed in the European Union (EU); the QIV contains the same HA content per strain. The QIV clinical development plan is based on studies comparing safety and immunogenicity of the QIV versus the TIV in the different claimed population sub-groups. Indeed, in accordance with European Medicines Agency (EMA) draft guidelines on influenza vaccines, the efficacy of new seasonal inactivated influenza vaccines in subjects aged from 3 years is inferred from their immunogenicity based on comparative immunogenicity studies with an EU authorized inactivated vaccine. Consequently, the efficacy of the QIV is inferred from the demonstration of non-inferior immune response of the QIV compared with the TIV manufactured by Sanofi Pasteur France and licensed in EU.

The manufacturing process for QIV is largely based on the process for TIV and the main difference between the 2 vaccines is the addition of a fourth strain. Although the antigen content of the QIV (60 µg HA per 0.5 mL) is higher than the TIV (45 µg HA per 0.5 mL), based on earlier observations with quadrivalent vaccines, the safety profile of the QIV is expected to be comparable to TIV. Therefore, evaluation of the safety of the QIV in a Phase I study and dose selection in a Phase II study were not considered necessary and the clinical development plan for the QIV started directly with Phase III studies to evaluate the safety and immunogenicity of the QIV in comparison with the TIV.

Six Phase III studies, i.e., Studies GQM11, GQM02, GQM05, GQM09, GQM01, and GQM04 were conducted to evaluate the safety and efficacy of the QIV in adults and children from 6 months of age and older. Of the 6 Phase III clinical studies that support the present application for the QIV, studies GQM11, GQM02, GQM09 and GQM05 were considered as the main/pivotal studies for characterization of the immunogenicity and safety of the candidate vaccine QIV. GQM11 (enrolled adults and elderly) and GQM02 (enrolled children aged 3 to 8 years) included two comparator groups, one receiving the trivalent influenza vaccine

containing the strains recommended for the ongoing season, and one a second trivalent vaccine that contained a strain of the B lineage not included in the seasonal vaccine. The third pivotal study GQM09 enrolled children aged 9 to 17 years to evaluate data regarding safety and immunogenicity in this age group. Vaccine efficacy was also evaluated in children aged 6 to 35 months in Study GQM05.

Two supportive Phase III studies GQM01 and GQM04 evaluated the candidate vaccine in adults, elderly and children from 9 years of age. GQM04 included a control group that received the seasonally recommended trivalent influenza vaccine, whereas GQM01 included control groups with trivalent influenza vaccine containing B strains of either the recommended or the B lineage not included in the seasonal influenza vaccine. Both studies were conducted with QIV batches from an initial Drug substance manufacturing process with a slightly higher than expected HA content for B strains (mainly in B/Florida)

The supporting data for VaxigripTetra is indicated for active immunization 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, are shown in Table 5

Table 12 Clinical trials of VaxigripTetra

No	Author/ Year	Study place	Design	Subjects/	Intervention	Outcome
1	Study GQM 11 trail, 17 September 2014 - 23 October 2015[5]	Multicentre (Poland, France, Germany, Belgium)	Phase III; randomized; double-blind (QIV and TIV2 groups) or single-blind (up to D21 TIV1 group); active-controlled;	Adult (18 - 60 years) and Elderly (> 60 years) Subjects	n = 2219 18 - 60 years (n = 1111) - QIV: 833 - TIV1: 140 - TIV2: 138 > 60 years (n = 1108) - QIV: 833 - TIV1: 138 - TIV2: 137 Random allocation to receive one IM or deep SC injection of either 1 of 3 lots of QIV or TIV1 or TIV2 (licensed TIV for the 2014-2015 season).	Primary outcome • Equivalence (lot-to-lot consistency) of 3 different QIV lots Lot-to-lot consistency of the 3 QIV lots could be demonstrated, as the equivalence criteria were met. For each pair of lots and for each of the 4 strains, the 2-sided 95% CIs lay between 1/1.5 (0.667) and 1.5. • Non-inferiority of the antibody response1) induced by QIV (pooled lots) vs TIV for each vaccine strain. The lower limit of the two-sided 95% CI of the ratios GMTQIV/GMTTIV post-vaccination was above the pre-specified limit of 0.667 for each of the 4 strains. Secondary outcome • Superiority of the immune response (HAI assay) to each B strain in the QIV compared with the TIV not containing the corresponding B strain. The lower limit of the 2-sided 95% CI for GMTQIV/GMTTIV > 1 for each of the 4 strains. • A certain level of cross-reactivity has been observed between the two B lineages, resulting in somewhat increased post-TIV vaccination GMTs against the B strain not contained in the TIV administered. However, the immune response induced by the QIV was distinctly higher. • Descriptive analysis of the immunogenicity of QIV in each age group as assessed by HAI assay. • Seroconversion rates > 90% for all 4 strains in 18 to 60-year-old QIV recipients. • For both, QIV and TIV, GMTs, GMTRs and seroconversion /significant titre increase rates were lower in subjects > 60 years. • With regard to the B strains, QIV elicited a response

						comparable to that in the TIV group for the shared B strain, but distinctly higher for the alternate strain not contained in the respective trivalent formulation. • In the TIV groups, the proportion of subjects with anti-HA cross-reactivity against the alternate B strain was higher for the TIV1 (B Victoria) group than for the TIV2 (B Yamagata) group. • Comparative description of the safety profile of QIV vs TIV. - Similar proportions of participants vaccinated with QIV and TIV reported solicited injection-site reactions, solicited systemic reactions, and vaccine-related adverse events. - Solicited injection-site reactions were higher in adult than early <u>Adult</u> - Solicited systemic reactions were reported by 42.5% of QIV and 40.6% in TIV group. Headache and myalgia was the most frequently reported solicited reaction (26.7% for QIV, 26.3% for TIV) ,followed by myalgia)18.5% (and shivering)6.1%(. Fever was report by 0.4% of subjects. - Unsolicited non serious AEs were reported by 22.3% of QIV and 19.1% in TIV The most frequently reported unsolicited AEs were infection and infestation (11.0% for QIV, 10.4% for TIV) and respiratory ,thoracic and mediastinal disorders (4.6% for QIV, 2.2% for TIV). Most of the unsolicited non serious AEs reported within 21 days after vaccination were of Grade 1, 2. <u>Early</u> - Solicited systemic reactions were reported by 24.45% of QIV and 23.9% in TIV group. Headache was the most frequently reported solicited reaction (15.2%) ,followed by myalgia)12.8% (and shivering)4.0%(. Fever was report by 0.4% of subjects. - Unsolicited non serious AEs were reported by 13.2% of QIV and 16.3% in TIV The most frequently reported unsolicited AEs were infection and infestation (4.3% for QIV, 6.2% for TIV) and musculoskeletal and connective tissue disorders (2.5% for QIV, 2.5% for TIV). Most of the unsolicited non serious AEs reported within 21 days after vaccination were of Grade 1, 2. <u>Observational</u> • Description of the immune response by virus seroneutralization (SN) in a randomized subset of subjects in each age group. • At baseline, neutralizing antibody titres > 10 (1/dil) against all

						4 strains in the QIV and the majority had pre-vaccination titres > 40 • More than 90% had neutralizing antibody titres > 40 and the great majority had titres > 80 (more than 90% against A/H1N1 and the B strains, and 82% or 77.3% against A/H3N2, respectively). • For each of the 4 strains, a majority of subjects in both age groups had a ≥ 2-fold rise of antibody titres, and in the 18 to 60-year-old group, a majority had a > 4-fold increase for A/H1N1 and the B strains. • GMTs and GMTRs were higher in the younger age category. • Anti-HA persistence 6 & 12 months after QIV vaccination in a randomized subset of subjects in each age group. -The 6-month and 12-month post-vaccination GMTs remained above baseline GMTs. -At least 92.6% of adult subjects in the pooled QIV Group and 90.9% in the pooled TIV, TIV1 and TIV2 Groups remained seroprotected 6 months after vaccination. -At least 91.4% of adult subjects in the pooled QIV Group and 89.7% in the pooled TIV group (pooled TIV for A strains, TIV1 or TIV2 according to the B strain) remained seroprotected 12 months after vaccination. -At least 76.2% of elderly subjects in the pooled QIV Group and 85.3% in the pooled TIV, TIV1 and TIV2 Groups remained seroprotected 6 months after vaccination and at least 75.0% of elderly subjects in the pooled QIV Group and 80.3% in the pooled TIV, TIV1 and TIV2 Groups remained seroprotected 12 months after vaccination. - At month 12 the majority of subjects in both age groups were still seroprotected in the QIV and the TIV groups. - Seroprotection rates were generally comparable between the two vaccine groups.
2.	Study GQM 02 trial, 2013 12 September 2013 - 25 June 2014[6]	Multi-centre (Poland, Finland; Mexico; Taiwan)	Phase III; randomized; double-blind; active-controlled	Children 3 - 8 years <u>Primed</u>: Children received 1 injection if they had received a full schedule of influenza vaccination (i.e., 2 injections in the same year) in any of the years preceding the study <u>Unprimed</u>: Children had not been given a full	n = 1242 Children 3 - 8 years - QIV: 887 - TIV1: 181 - TIV2: 174	<u>Primary outcome</u> • Non-inferiority of the antibody response1) induced by QIV vs TIV1 and TIV2 for each vaccine strain. - The lower limit of the two-sided 95% CI of the ratios GMTQIV/GMTTIV was above the pre-specified limit of 0.667 for each of the 4 strains. - The trend was the same in primed and unprimed children as observed in the overall population <u>Secondary</u> • Superiority of the antibody response1) to each B strain in QIV compared with TIV

				schedule of 2 injections in any year preceding the study, they received 2 injections 28 days apart The proportions of primed and unprimed subjects in the QIV and TIV groups were similar.		not containing the corresponding B strain. - The lower limit of the 2-sided 95% CI for the ratio GMT(QIV) to GMT(TIV not containing the B lineage strain tested) was > 1. - The trend was the same in primed and unprimed subjects as in the overall population. - Addition of the second B strain provides a benefit in terms of immune response to influenza B strains compared with any response due to cross-reactivity. - Both vaccines elicited a strong HAI antibody response against the shared strains, with comparable GMTRs, seroconversion rates and significant titre increase rates. - Pre-vaccination GMTs for the shared strains were comparable between the QIV and TIV group, but higher in primed children. - Post-vaccination GMTs, GMTRs, seroconversion rates and significant titre increase rates were higher in unprimed children. ● Descriptive analysis of QIV immunogenicity as assessed by Neutralizing antibody response (SN assay). - The majority (> 70%) of children in the QIV group had detectable (SN > 10) pre-vaccination neutralizing antibodies against the 4 strains, with higher proportions and GMTs in primed children. - Pre-vaccination GMTs were higher for the two influenza A strains, particularly for A/H1N1, than for the two B strains both in primed and unprimed subjects. - Post-vaccination GMTs, GMTRs and fold-increase rates were distinctly higher in unprimed subjects. - As for HAI antibody titres, a higher increase in SN titres was observed in the QIV group for the alternate B strain not contained in the TIV comparator. ● Comparative description of the safety profiles of QIV and TIV. - Similar proportions of participants vaccinated with QIV and TIV reported solicited injection-site reactions, solicited systemic reactions, and vaccine-related adversenevents. - A single vaccine-related serious adverse event, Thrombocytopenia with QIV - Solicited injection-site reactions were reported by 62.4% of participants in both groups - Solicited systemic reactions were reported by 48.9% of QIV and 45.5% in TIV group.

						At the site of injection, pain was the most frequently reported solicited reaction (56.5% for QIV, 55.4% for TIV) The most common solicited systemic reactions were malaise (30.7% for QIV, 28.2% for TIV), myalgia (28.5% for QIV, 26.8% for TIV), and headache (25.7% for QIV, 19.2% for TIV). - Unsolicited AEs were reported by 41.5% of QIV and 35.6% in TIV The most frequently reported unsolicited AEs were nasopharyngitis (7.1% for QIV, 6.2% for TIV) and upper respiratory tract infection (3.8% for QIV, 4.2% for TIV). Grade 3 non-serious AEs were reported by 2.0% in the QIV group and 2.5% in TIV <u>Observational</u> • Description Descriptive analysis of Anti-NA antibody response (ELLA) - Pre-vaccination, the majority of subjects in the QIV group (71.4%) had detectable anti-NA antibodies (i.e., titre ≥ 10), and more than half (55.7%) had titres ≥ 80. - These proportions increased to 85.7% (titre > 10) and 62.9% (titre > 80) post-vaccination (D28 for primed children; D56 for unprimed children). - More than two thirds (68.6%) had a ≥ 2-fold rise in titres, and 37.1% showed a ≥ 4-fold titre increase.
3.	Study GQM 05, 2017, 12 March 2014 - 27 July 2016 [8]	Multi-centre (Dominican Republic, France, Germany, Greece, Honduras, Italy, Philippines, South Africa, Spain, Turkey)	Phase III; randomized, observer-blind (except for trivalent influenza vaccine [TIV] groups which will be open-label), placebo-controlled *healthy children aged 6 to 35 months who have never been vaccinated against influenza in the past	6 - 35 Months	n = 5806 - QIV: 2721 - Placebo: 2715 - TIV1: 183 - TIV2: 186	<u>Primary outcome</u> - Among these, 24 subjects (0.96%) in the QIV group and 76 subjects (3.05%) in the Placebo group had influenza illness due to a virus strain similar to those in the vaccine. - The clinical efficacy of 2 doses of 0.5 mL of QIV in previously unvaccinated subjects aged 6 to 35 months for the prevention of laboratory-confirmed influenza illness was demonstrated for both primary endpoints as the 97% lower bound of the CIs for the corresponding VE were > 20%. <u>Secondary outcome</u> -The efficacy of QIV against influenza illness in the PPE was similar irrespective of the method of laboratory confirmation used: 50.98% for PCR and/or culture, 51.40% for PCR alone, and 57.44% for culture alone. The same trend of stability across methods was observed when considering cases due to strains similar to those contained in the vaccine. - Severe laboratory-confirmed influenza illnessa caused by any influenza strains occurred in 42 subjects (1.6%) in the QIV group and 97 subjects (3.7%) subjects in the Placebo group in the FASE and the relative risk of 43.42% indicated an efficacy of 56.58% (95% CI: 37.03; 70.52). When considering virus strains similar to the vaccine, 11 subjects (0.4%) in the QIV

						group and 39 subjects (1.5%) in the Placebo group reported severe laboratory-confirmed influenza illness, and the relative risk of 28.28% indicated an efficacy of 71.72% Observational outcome -Efficacy against influenza illness caused by viral strains similar to those contained in the vaccine was 68.40% and the efficacy against strains not similar to those contained in the vaccine was 48.72% - A total of 99 subjects (3.98%) in the QIV group (PPE) experienced AEs defined as ILI symptoms within 15 days after the onset of the ILI in subjects with a laboratory-confirmed influenza. The relative risk was 45.87% (95% CI: 35.79; 58.45) for any ILI symptom and 16.68% (95% CI: 5.05; 43.42) for other AEs. The rates of AOM within 15 days after the onset of the ILI were low in the QIV group (5 subjects, 0.20%) and the Placebo group (16 subjects, 0.64%) among subjects with a laboratory-confirmed influenza. The rates of ALRI within 15 days after the onset of the ILI were also low in both the QIV group (5 subjects, 0.20%) and the Placebo group (23 subjects, 0.92%). The relative risk for AOM associated with laboratory-confirmed influenza illness was 31.28% (95% CI: 8.96; 89.34) and for ALRI it was 21.76% (95% CI: 6.46; 58.51), which suggested that in subjects who received QIV, vaccination reduced the risk for AOM associated with influenza by approximately 69%, and the risk for ALRI associated with influenza by 78%. The rates of pneumonia associated with laboratory-confirmed ILI were low in the QIV group (7 subjects, 0.27%) and Placebo group (14 subjects, 0.54%), with a relative risk of 50.14% (95% CI: 17.13; 132.74), which suggested that in subjects who received QIV, vaccination reduced the risk of pneumonia associated with influenza by 50%. - A total of 59 subjects (2.3%) in the QIV group used health care resources within 15 days after the onset of a laboratory-confirmed ILI. The proportion was higher in the Placebo group, with 145 subjects (5.6%). The difference was more marked when cases due to vaccine-similar strains

						were considered, with 9 subjects (0.3%) in the QIV group and 38 subjects (1.5%) in the Placebo group. The relative risk of 40.80% (95% CI: 29.62; 55.59) suggests that subjects receiving QIV were 59.2% less likely to experience a medically attended influenza illness than subjects receiving Placebo. <u>Exploratory Analysis</u> -Efficacy results based on strain identification with ferret antisera HAI testing were overall concordant with those obtained with sequencing. <u>Immunogenicity Results</u> - Non-inferiority on immune response was demonstrated in the PPI for 3 of the vaccine strains as the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups (QIV/TIV) was > 0.667 for each of the 3 strains. - The QIV demonstrated superior immunogenicity compared to the TIV for the additional B strains. The superiority of the immune response to the QIV compared to the TIV that does not contain the B lineage tested was demonstrated as the lower limit of the 2-sided 95% CI of GMTQIV/GMTTIV was > 1. - One injection of QIV induced a higher immune response in children aged 6 to 35 months who initially received 2 injections of QIV than one dose given to previously unvaccinated children. -In children aged 6 to 35 months, the baseline GMTs against the A/H1N1 and A/H3N2 strain and post-vaccination GMTs increased with increasing age. For the B/Victoria and B/Yamagata strains, the baseline GMTs were similar across age groups. Post-vaccination GMTs tended to increase with increasing age. -Immune response induced by QIV in children aged 3 to 8 years is at least as good as those observed in children aged 6 to 35 months.

4	Study GQM 09, 2013 18 October 2013 - 10 December 2013[7]	Mono-centre (Taiwan)	Phase III; open-label; no control arm	Children and Adolescents 9 - 17 years	n = 100 Children 9 - 17 years	• Descriptive analysis of QIV immunogenicity (HAI assay) - The QIV elicited a HAI antibody response against all 4 strains, with a particularly sharp rise in GMT, higher GMTRs and higher significant titre increase rates for the B strains. - Post-vaccination titres > 40 against all 4 strains, and more than 90% had titres > 100 against each of the 4 strains. - Post-vaccination titres in this 9 to 17-year-old study population appear similar to those observed in adults in study GQM11 (as also observed in study GQM04). - Non-inferiority of the QIV compared to TIV was demonstrated in children and adolescents aged 9 to 17 years. • Description of the QIV safety profile - Injection-site pain (56%), myalgia (45%), and malaise (15%) were the most frequently reported solicited reactions, and most solicited reactions were mild or moderate. No treatment-related AEs, immediate unsolicited AEs, unsolicited non-serious injection-site AEs, grade 3 unsolicited AEs, or serious AEs were reported.
5.	Study GQM01, 2012, 2 1 October 2011 - 11 June 2012[9]	Multi-centre (France, Germany)	Phase III; randomized; double-blind (QIV and TIV1); open-label (TIV2); active-controlled	≥ 18 years	n = 1568 <u>18 - 60 years (n = 783)</u> - QIV: 559 - TIV1: 113 - TIV2: 111 <u>> 60 years (n = 785)</u> - QIV: 558 - TIV1: 113 - TIV2: 114	• Non-inferiority for all 4 strains was achieved, as the lower limit of the age-stratified two-sided 95% CI of the ratio of GMTs post-vaccination between the QIV and TIV groups was > 1/1.5 (0.667) for each strain. Therefore, QIV is as immunogenic as TIV for each of the 3 shared influenza strains overall in adults and the elderly. • The superiority tests demonstrate that the post-vaccination immune response (as measured by HAI) to QIV compared with the TIV containing the non-corresponding B strains is higher, as the lower limit of the two-sided 95% CI of the ratio of GMTs between groups was > 1 for the 2 B strains and in each age group. Therefore, the data show that QIV may provide superior immune response against influenza B than TIV for both age groups.
6.	Study GQM04, 2012, 19 March 2012 - 7 November 2012[10]	Multi-centre (Australia, Philippines)	Phase III; randomized; double-blind (QIV lots); open-label (QIV or TIV receipt); active-controlled	9 – 17 years 18 – 60 years	n = 2090 <u>9 - 17 years (n = 385)</u> - QIV: 330 - TIV: 55 <u>18 - 60 years (n = 1705)</u> - QIV: 1649 - TIV: 56	• QIV demonstrated superior immunogenicity compared to the TIV for the additional B strain. • One dose of 0.5 mL of QIV induced a strong immune response in all age groups aged 9 years and above. • The immunogenicity results (based on the HAI method) for the child/adolescent subjects aged 9 to 17 years were comparable to those of the adult group. Child/adolescent subjects achieved seroconversion and / or a significant increase at

						a rate similar to or higher than adults, and GMTRs were higher than those of adults.

QIV = Quadrivalent inactivated influenza vaccine

TIV = Trivalent inactivated influenza vaccine

TIV1 = Trivalent inactivated influenza vaccine for B/Massachusetts

TIV2 = Trivalent inactivated influenza vaccine for B/Brisbane

GMTs = Geometric Mean Titer

GMTQIV/GMTTIV (GMTRs) = Ratio of Geometric Mean Titer

SN = Seroneutralization

HAI = Haemagglutination Inhibition

ELLA assay = Enzyme Linked Lectin Assay

Evaluation result:

Six phase III studies (GQM11, GQM02, GQM09, GQM05, GQM01 and GQM04) were conducted to evaluate the safety and efficacy of the QIV. The target population is adequately reflected in the clinical trials. There is sufficient information to support the efficacy and safety. Assessor's overall conclusions on clinical efficacy

- In all age groups studied (6-35 month, 8-3 years; 17-9 years; 60-18 years; > 60 years), the QIV induced an immune response against all 4 strains contained in the formulation.
- The immune response induced by QIV was shown to be non-inferior to that induced by the TIV for the shared influenza strains (as shown in all age groups).
- Immunogenic superiority of the QIV compared to the TIV for the additional B strain not contained in the trivalent comparator formulation was also demonstrated in these age categories.
- The immune response in individuals with underlying chronic illness [Defined as at risk for influenza-related complications. The most frequent underlying medical conditions were vascular disorders (most frequently hypertension), metabolism and nutrition disorders (most frequently type 2 diabetes mellitus, obesity, hypercholesterinaemia), respiratory disorders (most frequently asthma), and cardiac disorders (most frequently coronary artery disease)] was similar to the immune response in the overall study population.
- There was no evidence that the addition of a second B strain interferes with the immune response to the other strains included in the vaccine. Based on the data provided, it is concluded that addition of the second B strain provides a benefit in terms of broader immune response to influenza
- The findings based on HAI assay results were further supported by the neutralizing antibody response data (assessed using the SN assay) and the anti-NA antibody response data (assessed using the ELLA).
- The analysis of the immunogenicity 6and 12months after vaccination showed that the QIV induced an immune response that lasted in a majority of subjects for 12 months. The immune response in the QIV vaccine group through month 12was generally comparable to the immune response in the TIV vaccine groups through month .12

- After a review of the available data VaxigripTetra appears to be safe in each vaccine population. The safety profile of the QIV is deemed to be comparable to that of the TIV.
- Solicited adverse reactions (ARs) and unsolicited adverse events are not severe.
- Serious adverse events (SAEs) was generally low in all age groups. SAEs were reported by a maximum of 1.6% subjects in the QIV and 1.1% of subjects in the TIV group. Only one of SAEs was considered to be vaccine related. A 3-year-old female subject without relevant medical history developed severe thrombocytopenia 9 days following vaccination 1 with QIV. This event led to discontinuation. Of note, the child was followed up. She recovered within 38 days after the onset. The adverse drug reaction of thrombocytopenia is included into the SmPC in section 4.8. The event of thrombocytopenia is adequately reflected in the RMP.

The aggregate analysis of unredacted assessment report from France FDA including detailed analysis based on the context and requirements of Thai FDA and ASEAN finds the clarify information of important issues such as data on safety and quality part more over concerns in each critical performance as 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. Therefore, overall concluded information in clinical, VaxigripTetra is accepted in evidence to protect against infection by Influenza viruses.

Part 6: Risk Management Plan

Risk Management Plan (RMP) are contain with

1. Summary of the safety concerns

2 .Pharmacovigilance plan including:

- Safety concerns and overview of planned pharmacovigilance actions
- Additional pharmacovigilance activities to assess effectiveness of risk minimization measures

3. Risk minimization measures

For more information please see in **Appendix 1**

Label evaluation result (secondary packaging)

Label

The label submitted by Sanofi Pasteur LTD can be categorized as label on unit carton and label on container. This label follows the standard of Thai FDA 2009, appendix 3 on the label and SmPC for the registration of marketing authorization in Thailand. Label is appropriate and acceptable according to the standard of Thai FDA 2009 that follows the guidelines of ASEAN Harmonization.

1. Unit Carton

No.	Title	Check list	Acceptable
1	Trade name	✓	✓
2	Dosage form	✓	✓
3	Name of the active ingredient(s)	✓	✓
4	Strength	✓	✓
5	Lot number	✓	✓
6	Manufacturing date	✓	✓
7	Expire date	✓	✓
8	Route of administration	✓	✓
9	Storage condition	✓	✓
10	Registration number for marketing authorization	✓	✓
11	Name and address of the distributor	✓	✓
12	Name and address of the manufacturer	✓	✓
13	Special notice	✓	✓
14	Recommend dose for vitamins and minerals	n/a	n/a
15	Warnings	✓	✓
16	Pack size	✓	✓

✓ The title is stated on lable/ acceptable

n/a not related to the topic evaluated

Patient Information Leaflet evaluation result

Patient information leaflet or PIL of VaxigripTetra that has the content and format aligned with the Guideline for Leaflet Development of Thai FDA (the guideline was announced on the 3rd of July, 2013 and edited in April 2017), appendix 1. This PIL content and format is acceptable with condition to perform user testing within 12 months after approval.

SmPC evaluation result

SmPC for specialties of VaxigripTetra that is submitted for registration for marketing authorization, contains the information is aligned with the one that is approved by EMA.

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Overall Benefit/risk assessment

Refer to unredacted assessment report from France and found that all concerns have been clearly explained and support by studies, appropriate justifications and data in accordance with ICH guidelines and ASEAN guideline. The evaluation result has been presented to the experts meeting held on the 23rd August, 2017, which conclude that quality safety and efficacy of VaxigripTetra is acceptable.

In conclusion, the overall benefit risk of VaxigripTetra is positive 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 under the following conditions:

"Submit the update data and follow the Risk Management Plan as submitted via eCTD module1.8.2 and the important concerns are

(1) This product is classified as special controlled drug and can only be distributed to be used in hospitals and the sentence that has meaning about "hospitals and the sentence use only" should be stated on label.

(2) Monitor the ADRs follows the submitted SMP protocol

(3) Submit the patient information leaflet which passed the user testing within 12 months after the marketing authorization approval"

Details of the RMP see appendix 1.

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Appendix

Appendix 1

1. Summary of the Safety Concerns

Summary of Safety Concerns	
Important potential risks	• Anaphylactic reaction • Convulsions (including febrile) • Guillain-Barre syndrome • Neuritis (including Bell's palsy) • Encephalitis/myelitis • Vasculitis • Thrombocytopenia
Missing information	• Pregnant or lactating women • Immuno-compromised patients

2. Pharmacovigilance Plan

2.1 Safety concerns and overview of planned pharmacovigilance actions

Table 1: Potential risk: Adverse Events of Special Interest

Areas requiring confirmation or further investigation	Proposed routine and additional PV activities	Objectives
Adverse events of special interest: • Anaphylactic reaction • Convulsions (including febrile) • Guillain-Barre Syndrome • Encephalitis /myelitis • Neuritis (including Bell's palsy) • Vasculitis • Thrombocytopenia	Routine Pharmacovigilance including signal detection and evaluation	Detect and characterize these events Obtain qualitative and quantitative data, reporting rate trend Update the SmPC in a timely manner if these potential risks are confirmed

Table 3: Missing information: Very rare adverse events

Areas requiring confirmation or further investigation	**Proposed routine and additional PV activities**	**Objectives**
Very rare AEs that could not be identified during the clinical development	Routine Pharmacovigilance including signal detection and evaluation	-Detect and characterize these adverse events -Obtain qualitative and quantitative data, reporting rate trend -Update the SmPC in a timely manner if this potential risk is confirmed

Table 3: Missing information: Pregnant or lactating women

Areas requiring confirmation or further investigation	**Proposed routine and additional PV activities**	**Objectives**
Data in pregnant or lactating women	Routine Pharmacovigilance including a specific pregnancy follow-up questionnaire (already put in place in routine for all vaccines)	Obtain safety data in pregnant or lactating women, and newborns

Table 4: Missing information: lmmuno-compromised patients

Areas requiring confirmation or further investigation	**Proposed routine and additional PV activities**	**Objectives**
Data in immuno-compromised patients	Routine Phannacovigilance including targeted follow-up questionnaire to document patient medical history	Obtain safety data in immuno- compromised patients

Table 5: Missing information: Vaccine efficacy/effectiveness

Areas requiring confirmation or further investigation	**Proposed routine and additional PV activities**	**Objectives**
Data on QIV vaccine efficacy/effectiveness	Routine Phannacovigilance including post-marketing surveillance data on vaccination failures Non-product specific vaccine effectiveness data will be obtained through the Global Hospital based Influenza Surveillance Network in the European countries participating. Joint European manufacturers approach together with EMA and ECDC is under discussion through an IMI 2 project to evaluate the feasibility of a brand specific approach to measure the vaccine effectiveness	Obtain data on influenza vaccine efficacy in people for which influenza vaccination is recommended

2.2 Additional pharmacovigilance activities to assess effectiveness of risk minimization measures

Based on the available information from clinical studies GQMO1, GQM04, GQM05, GQM09, GQM02, GQM01, and on supportive data from VaxigripTetra ® and on TIV literature data, it is considered that no further risk minimization activities are deemed necessary at this point. No additional pharmacovigilance activities to assess effectiveness of risk minimization measures are ongoing or planned.

Table 6: Risk minimization measure

Component measured	Activity(ies)	Rationale
Not applicable	Not applicable	Not applicable

3. Risk management Plan (RMP) of VaxigripTetra

Risk	Management (Routine)
Important potential risks	
Adverse events of special interest	
Anaphylactic reaction	- Careful assessment of patient's history of allergy, particularly to the components of the vaccine. - Vaccinations are performed by health care professionals and immediate surveillance of the subject is recommended after the injection as per routine vaccination practice - Surveillance and monitoring of patients at risk. - Text in SmPC: Section 4.3 Contraindication, section 4.4 Special warnings and precaution of use and section 4.8 Undesirable effects
Convulsions (including febrile)	- Use of antipyretics according to local medical practice could be recommended in patients at risk for febrile convulsions who present with fever after vaccination. - Surveillance and monitoring of patients at risk. - Routine Pharmacovigilance including signal detection and evaluation - Text in SmPC, Section 4.8: Undesirable effects
Guillain-Barre syndrome	- Unpredictable AE - Surveillance and monitoring of patients at risk. - Routine Pharmacovigilance including signal detection and evaluation - Text in SmPC, Section 4.8: Undesirable effects
Neuritis (including Bell's palsy)	- Unpredictable AE - Surveillance and monitoring of patients at risk. - Routine Pharmacovigilance including signal detection and evaluation

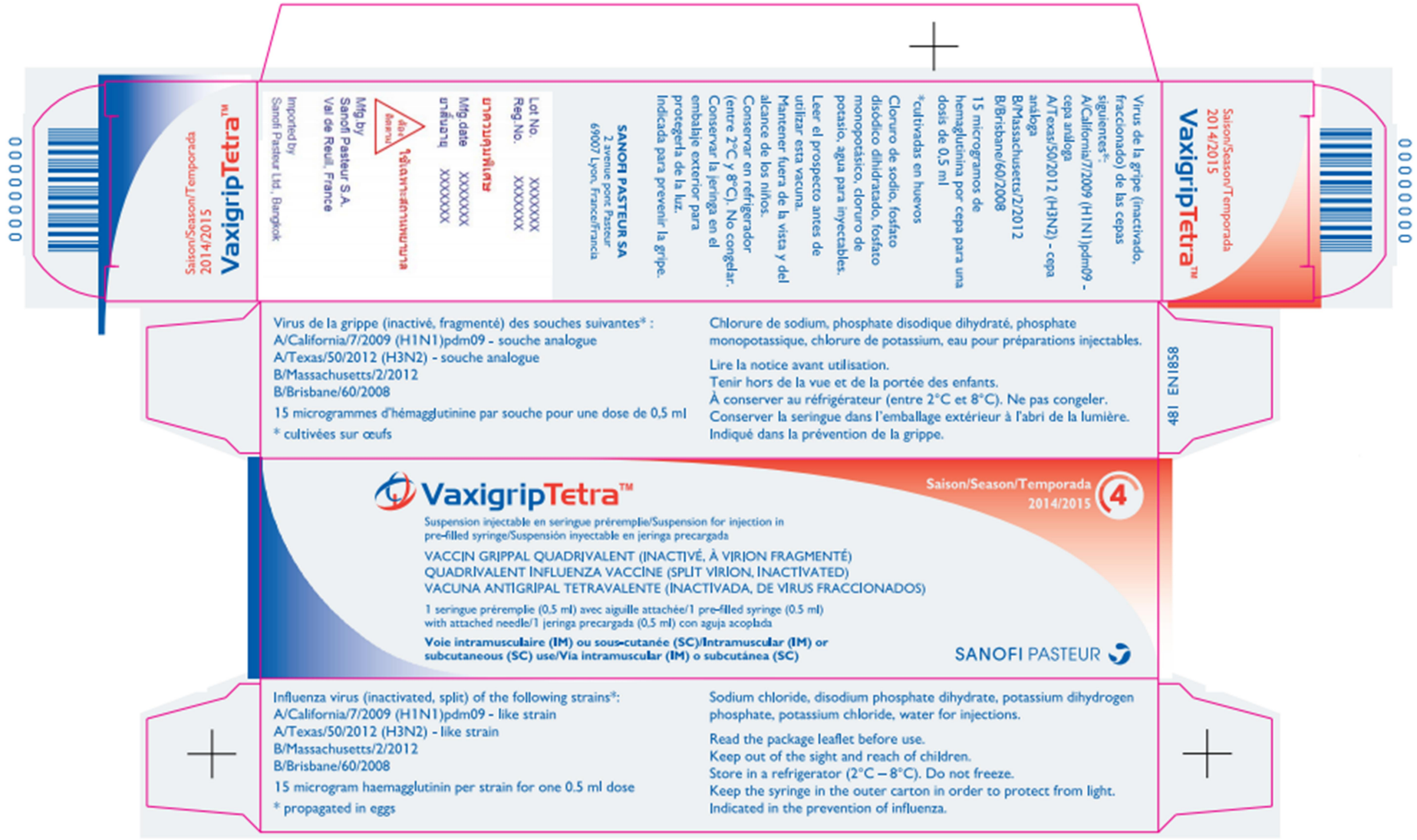
	- Text in SmPC, Section 4.8: Undesirable effects
Encephalitis/myelitis	- Unpredictable AE - Surveillance and monitoring of patients at risk. - Routine Pharmacovigilance including signal detection and evaluation - Text in SmPC, Section 4.8: Undesirable effects
Vasculitis	- Unpredictable AE - Surveillance and monitoring of patients at risk. - Routine Pharmacovigilance including signal detection and evaluation - Text in SmPC, Section 4.8: Undesirable effects
Thrombocytopenia	- Unpredictable AE - Surveillance and monitoring of patients at risk. - Routine Pharmacovigilance including signal detection and evaluation - Text in SmPC, Section 4.8: Undesirable effects
Missing information	
Pregnant or lactating women	- For ethical reasons pregnant women are currently excluded from clinical trials. Therefore, no clinical study in pregnant women was performed with the QIV. - The increasing data collected from post marketing experience with inactivated influenza vaccines (e.g. registries and spontaneous reports) and from women inadvertently vaccinated during pregnancy . - Routine Pharmacovigilance including a specific pregnancy follow-up questionnaire (already put in place in routine for all vaccines)
Immuno-compromised patients	-Routine Phannacovigilance including targeted follow-up questionnaire to document patient medical history
Vaccine efficacy/effectiveness	- Routine Phannacovigilance including post-marketing surveillance data on vaccination failures

Appendix 2

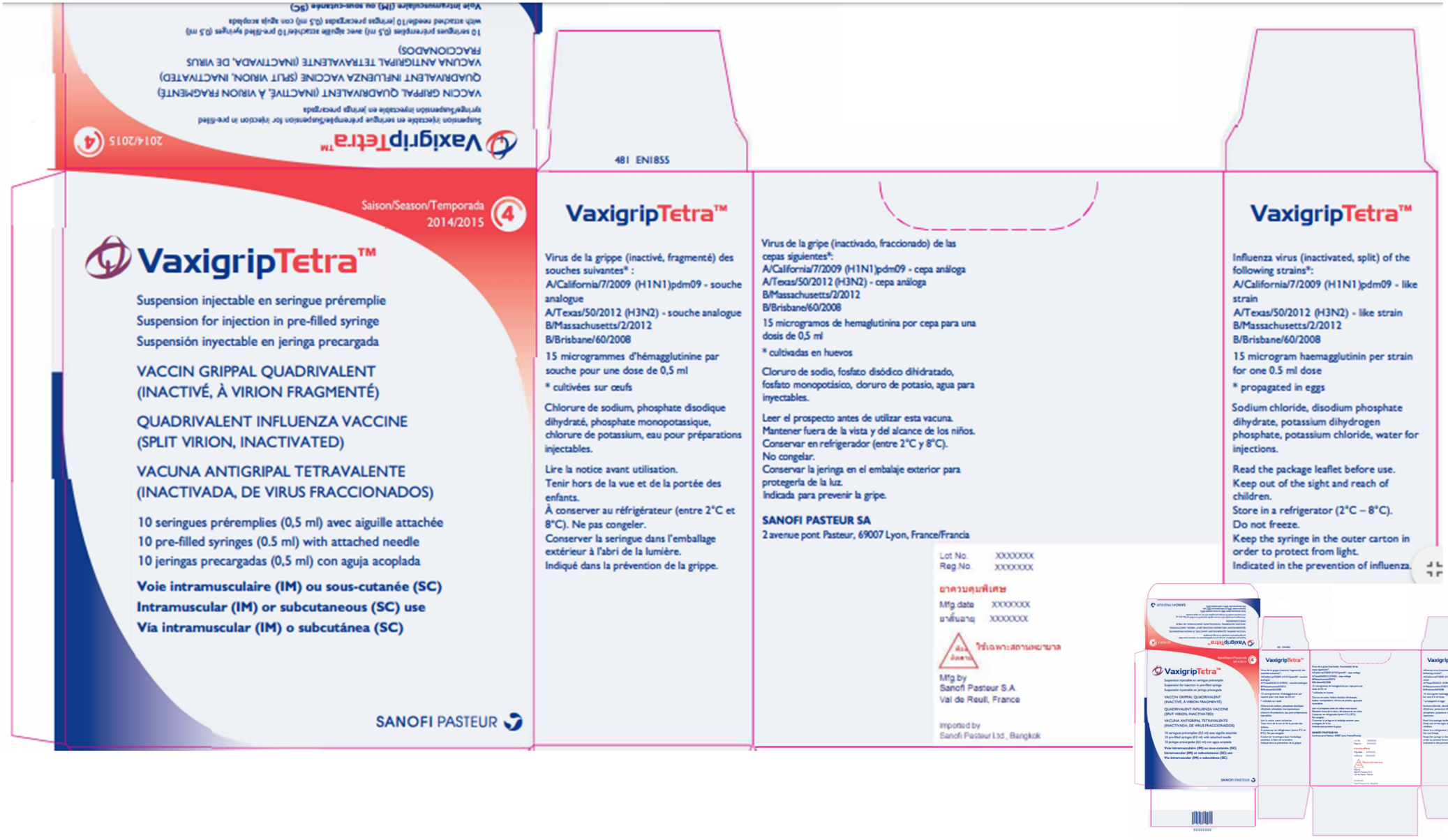
Label

Unit carton of 1 pre-filled syringe (0.5 ml, Compact box)

Unit carton of 1 pre-filled syringe (0.5 ml, Normal box)

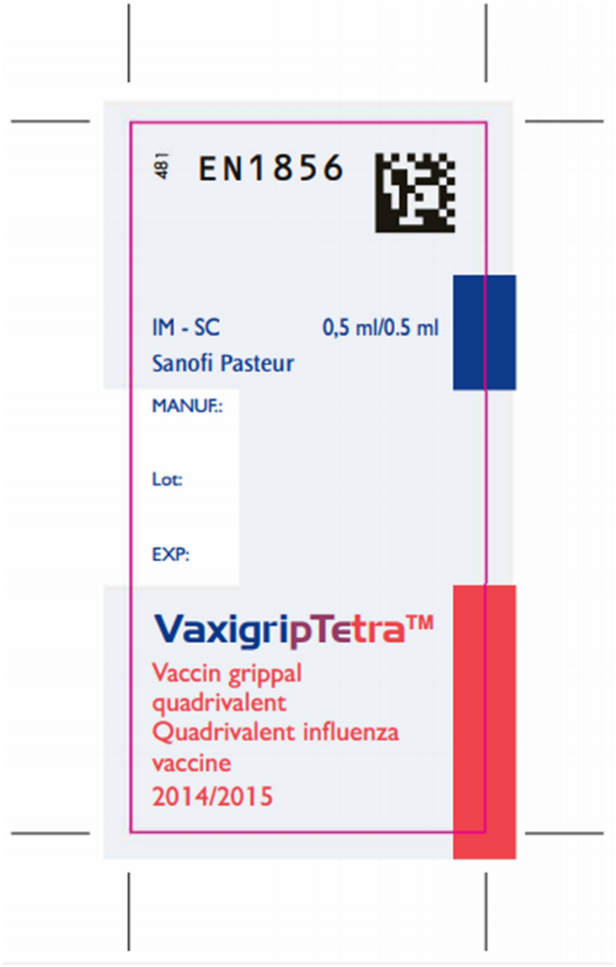


Unit carton of 10 pre-filled syringe (0.5 ml)

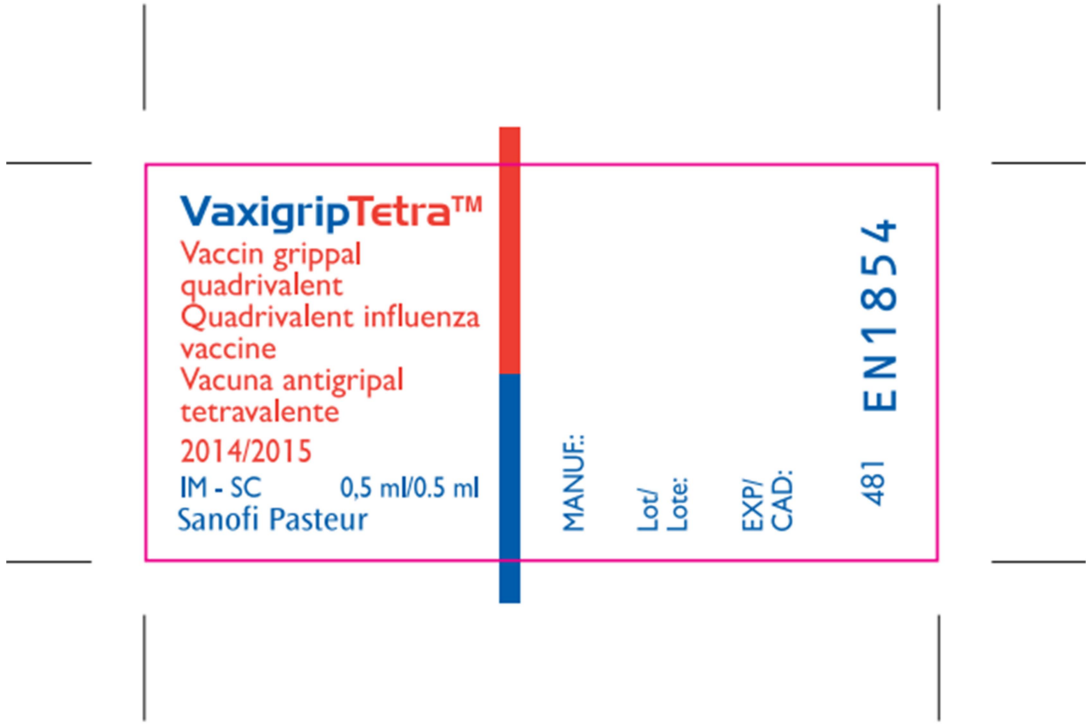


Unit carton of 20 pre-filled syringe (0.5 ml)

Inner label (0.5 ml, Compact box)



Inner label (0.5 ml, Normal box)



วัคซีนไข้หวัดใหญ่ชนิด 4 สายพันธุ์

0.5 มิลลิลิตร

ชนิดฉีดเข้ากล้ามเนื้อหรือใต้ผิวหนัง

(วาซิกริปเตตร้า)

1. ยานี้คืออะไร

- ยานี้มีชื่อสามัญว่าวัคซีนไข้หวัดใหญ่ชนิด 4 สายพันธุ์ (quadrivalent influenza vaccine, split virion, inactivated) เป็นยาในกลุ่มวัคซีน
- ยานี้ใช้เพื่อ ป้องกันโรคไข้หวัดใหญ่

2. ข้อควรรู้ก่อนใช้ยา

2.1 <u>ห้ามใช้</u>ยานี้เมื่อไร

- เคยแพ้ยานี้หรือส่วนประกอบของยานี้ เช่น ไข่ เนื้อไก่ ยานีโอมัยซิน ฟอร์มาลดีไฮด์ หรือออคโตซินอล-9
- หากมีไข้สูงหรือไข้สูงปานกลาง หรือเกิดเจ็บป่วยเฉียบพลัน ควรเลื่อนการฉีดวัคซีนนี้ออกไปจนกว่าจะหายเป็นปกติ

2.2 ข้อควรระวังเมื่อใช้ยานี้

- ผู้ที่มีภาวะเกล็ดเลือดต่ำหรือเป็นโรคเกี่ยวกับความบกพร่องในการหยุดเลือดควรระมัดระวังการใช้ เนื่องจากการฉีดวัคซีนอาจจะทำให้เลือดออกได้
- อาจเกิดอาการวูบหรือเป็นลม ก่อนหรือหลังการฉีดวัคซีน เนื่องจากกลัวการฉีดยา ควรแจ้งแพทย์หากท่านเคยมีประวัติดังกล่าวมาก่อน
- ผู้ป่วยที่มีภาวะภูมิคุ้มกันบกพร่องอาจทำให้ประสิทธิภาพของวัคซีนลดลงได้

3. วิธีใช้ยา

3.1 ขนาดและวิธีใช้ ควรมารับวัคซีนตามคำแนะนำของแพทย์หรือเภสัชกร

- ผู้ใหญ่: 0.5 มิลลิลิตร ฉีดครั้งเดียว
- เด็กอายุ 6-17 ปี: 0.5 มิลลิลิตร ฉีดครั้งเดียว
- เด็กอายุต่ำกว่า 9 ปี ที่ไม่เคยได้รับวัคซีนไข้หวัดใหญ่มาก่อน: ต้องได้รับการฉีดครั้งที่ 2 ในระยะเวลาอย่างน้อย 4 สัปดาห์หลังการได้รับการฉีดครั้งแรก
- สามารถรับวัคซีนนี้ในเวลาเดียวกับวัคซีนอื่นได้ โดยแยกฉีดที่ขาหรือแขน เข็มละข้าง
- เช่นเดียวกับวัคซีนทุกชนิด วัคซีนนี้อาจไม่ได้ให้ผลป้องกันได้อย่างเต็มที่กับทุกคนที่ได้รับวัคซีน
- วัคซีนนี้จะมีผลป้องกันโรคไข้หวัดใหญ่หลังจากได้รับวัคซีนไปแล้ว 2-3 สัปดาห์
- วัคซีนป้องกันไข้หวัดใหญ่ ไม่มีผลในการป้องกันไข้หวัดธรรมดา

3.2 หากลืมมารับวัคซีนควรทำอย่างไร

- ให้มาพบแพทย์เพื่อปรึกษาถึงความเหมาะสมในการได้รับวัคซีน

3.3 ถ้ารับยานี้เกินขนาดที่แนะนำควรทำอย่างไร

- ควรเฝ้าติดตามอาการที่เกิดขึ้น หากมีอาการรุนแรงให้รีบไปพบแพทย์

4. ข้อควรปฏิบัติหลังจากฉีดยา

- ควรเฝ้าติดตามอาการที่เกิดขึ้นภายหลังการได้รับวัคซีน หากพบอาการผิดปกติ ควรรีบแจ้งบุคลากรทางการแพทย์ที่เกี่ยวข้อง
- หากท่านต้องตรวจเลือดหลังจากฉีดวัคซีนนี้ไม่กี่วัน ให้แจ้งแพทย์ว่าท่านเพิ่งได้รับวัคซีนนี้ เพราะวัคซีนนี้อาจทำให้เกิดผลบวกลวงกับการตรวจเลือดบางชนิด

5. อันตรายที่อาจเกิดจากยา

5.1 อาการที่ต้อง<u>ไปพบแพทย์ทันที</u>

- บวมที่ใบหน้า เปลือกตา ริมฝีปาก ลมพิษ
- หน้ามืด เป็นลม แน่นหน้าอก หายใจลำบาก
- ผื่นแดง ตุ่มพอง ผิวหนังหลุดลอก มีจ้ำตามผิวหนังหรือเลือดออกผิดปกติ

5.2อาการที่<u>ไม่จำเป็นต้องไปพบแพทย์ทันที</u> แต่ถ้ามีอาการรุนแรงให้รีบไปพบแพทย์

- ปวดศีรษะ
- ปวดกล้ามเนื้อ
- รู้สึกไม่สบาย
- ปวดบริเวณที่ฉีด
- มีไข้
- มีอาการแดง บวม และผิวหนังแข็งกระด้างบริเวณที่ฉีด
- เกิดจ้ำเลือดบริเวณที่ฉีด

6. ควรเก็บยานี้อย่างไร

- เก็บไว้ในภาชนะบรรจุเดิมตามที่ได้รับมา
- เก็บที่อุณหภูมิไม่เกิน 2-8 องศาเซลเซียส
- ห้ามแช่แข็ง
- ยานี้จะเก็บที่สถานพยาบาล ท่านจะไม่ได้รับยานี้กลับบ้าน

ผู้ผลิต Sanofi Pasteur S.A., Val de Reuil, France republic.
ผู้นำเข้า บริษัท ซาโนฟี่ ปาสเตอร์ จำกัด
เอกสารนี้ปรับปรุงครั้งล่าสุดเมื่อ 23 สิงหาคม 2560

เอกสารนี้เป็นข้อมูลโดยย่อ หากมีข้อสงสัย ให้ปรึกษาแพทย์หรือเภสัชกร

Summary of Product Characteristic (SmPC)

▼**This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See Section 4.8 for how to report adverse reactions.**

1. NAME OF THE MEDICINAL PRODUCT

VaxigripTetra, suspension for injection in pre-filled syringe

Quadrivalent influenza vaccine (split virion, inactivated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/California/7/2009 (H1N1)pdm09 - like strain (A/California/7/2009, NYMC X-179A).....15 micrograms HA**

A/Texas/50/2012 (H3N2) - like strain (A/Texas/50/2012, NYMC X-223A).....15 micrograms HA**

B/Massachusetts/2/2012 (Yamagata lineage).....15 micrograms HA**

B/Brisbane/60/2008 (Victoria lineage).....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 2014/2015 season.

For the full list of excipients, see Section 6.1.

VaxigripTetra may contain traces of eggs, such as ovalbumin, and of neomycin, formaldehyde and octoxinol-9, which are used during the manufacturing process (see Section 4.3).

3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VaxigripTetra is indicated for 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.

The use of VaxigripTetra should be based on official recommendations.

4.2 Posology and method of administration

Posology

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

Adults: one dose of 0.5 ml.

Paediatric population

- Children from 6 months to 17 years of age: one dose of 0.5 ml.
  For children less than 9 years of age who have not previously been vaccinated, a second dose of 0.5 ml should be given after an interval of at least 4 weeks.
- Children less than 6 months of age: the safety and efficacy of VaxigripTetra have not been established. No data are available.

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

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

VaxigripTetra should under no circumstances be administered intravascularly.

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

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

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

Interference with serological testing

See Section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with VaxigripTetra.

VaxigripTetra can be given at the same time as other vaccines, based on clinical experience with Vaxigrip. Separate injection sites and separate 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

Inactivated influenza vaccines can be used in all stages of pregnancy. Larger datasets on safety are available for the second and third trimester, compared with the first trimester; however, data from

worldwide use of inactivated influenza vaccines do not indicate any adverse foetal and maternal outcomes attributable to the vaccine.

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

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

Breastfeeding

VaxigripTetra may be used during breastfeeding.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

The safety of VaxigripTetra was assessed in six clinical trials in which 3,040 adults from 18 to 60 years of age, 1,392 elderly over 60 years of age and 429 children from 9 to 17 years of age received one dose of VaxigripTetra and 884 children from 3 to 8 years of age received one or two doses of VaxigripTetra depending on their influenza vaccination history and 1,614 children from 6 to 35 months of age received two doses (0.5 ml) of VaxigripTetra.

Most reactions usually occurred within the first 3 days following vaccination, resolved spontaneously within 1 to 3 days after onset. The intensity of these reactions was mild.
The most frequently reported adverse reaction after vaccination, in all populations including the whole group of children from 6 to 35 months of age, was injection site pain (between 52.8% and 56.5% in children from 3 to 17 years of age and in adults, 26.8% in children from 6 to 35 months of age and 25.8% in elderly). In subpopulation of children less than 24 months of age, irritability (32.3%) was the most frequently reported adverse reaction.

In subpopulation children from 24 to 35 months of age, malaise (26.8%) is the most frequently reported adverse reaction.

The other most frequently reported adverse reactions after vaccination were:

- In adults: headache (27.8%), myalgia (23%) and malaise (19.2%),

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

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.

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	

ADVERSE REACTIONS	FREQUENCY
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
Fatigue Injection site ecchymosis, injection site pruritus, injection site warmth	Uncommon
Asthenia, flu-like illness Injection site discomfort [1]	Rare

[1] In adults [2] Uncommon in elderly [3] Rare in adults [4] In elderly

[5] Rare in elderly [6] Common in elderly

Paediatric population

The safety profile presented below is based on data from 429 children from 9 to 17 years of age who received one dose of VaxigripTetra and from 884 children from 3 to 8 years of age who received one or two doses of VaxigripTetra depending on their influenza vaccination history.

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 who received two doses of VaxigripTetra.

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 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.

c. Potential adverse events

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

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.

- *Immune system disorders*

Severe allergic reactions: shock

Allergic reactions: rash, generalized 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 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.

4.9 Overdose

Not documented for VaxigripTetra. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02.

Mechanism of action

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

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

Specific levels of haemagglutination-inhibition (HAI) antibody 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 VaxigripTetra has not been studied. However, based on clinical experience with the trivalent vaccine, annual influenza vaccination is recommended given the duration of immunity provided by the vaccine and because circulating strains of influenza virus change from year to year.

Efficacy of VaxigripTetra

Paediatric population

- Children aged from 6 to 35 months:

A randomized placebo controlled study was conducted in 4 regions (Africa, Asia, Latina America and Europe) over 4 influenza seasons, in more than 5,400 children from 6 to 35 months of age who received two doses (0.5 ml) of VaxigripTetra (N=2,722), or placebo (N=2,717) 28 days apart to assess VaxigripTetra efficacy for the prevention of influenza illness laboratory-confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) and/or viral culture caused by strain A and/or B and caused by vaccine similar strains (as determined by sequencing).

ILI was defined as 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.

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

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

N: Number of children analysed (full set)

n: number of subjects fulfilling the item listed

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

Based on immune responses observed in children 3 to 8 years of age, the efficacy of VaxigripTetra in this population is expected to be at least similar to the efficacy observed in children from 6 to 35 months (see “Children from 6 to 35 months of age ” above and “Immunogenicity of VaxigripTetra“ below).

Immunogenicity of VaxigripTetra

Clinical studies performed in adults from 18 to 60 years of age, in elderly over 60 years of age, in children from 3 to 8 years of age and from 6 to 35 months of age assessed VaxigripTetra 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 for HAI Geometric mean antibody titer (GMT) at Day 21. Another clinical study performed in children from 9 to 17 years of age described the immune response of VaxigripTetra.

VaxigripTetra 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 VaxigripTetra.

Immunogenicity results are presented in the table below:

Table 2: 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; GMTR: Geometric Mean Titer Ratio; CI: Confidence Interval; SC: Seroconversion; SI: Significant Increase

(a) N=833 for 18-60 years of age group

(b) N=832 for over 60 years of age group

(c) 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) Geometric mean of individual ratios (post-/pre-vaccination titers)

Paediatric population

- Children from 9 to 17 years of age:

In a total of 429 children from 9 to 17 years of age who received one dose of VaxigripTetra, the immune response against the 4 strains contained in the vaccine was similar to the immune response induced in adults from 18 to 60 years of age.

- Children from 6 months to 8 years of age:

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

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

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

Immunogenicity results are presented in the table below:

Table 3: Immunogenicity results in children aged from 6 months to 8 years

Antigen Strain	6-35 month 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; GMTR: Geometric Mean Titer Ratio; CI: Confidence Interval; SC: Seroconversion; SI: Significant Increase

(a) N=862 for for 3-8 years of age group

(b) 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) Geometric mean of individual 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).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Buffer Solution:

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

6.2 Incompatibilities

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

6.3 Shelf life

1 year

6.4 Special precautions for storage

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

6.5 Nature and contents of container

0.5 ml of suspension in pre-filled syringe (type I glass) with attached needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) – 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. MARKETING AUTHORISATION HOLDER

Sanofi Pasteur Ltd., Bangkok

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 August 2016

10. DATE OF REVISION OF THE TEXT

26 October 2017