VaxigripTetra®, seasonal influenza vaccine, tetravalent
Solution for Injection in a prefilled syringe
MA no. 66427

Active substance
Influenza virus (inactivated, split) to the following strains:
A/<Official strain> (H1N1) like strain (<actual strain>)
A/<Official strain> (H3N2) like strain (<actual strain>)
B/<Official strain> like strain (<actual strain>) (Victoria lineage)
B/<Official strain> like strain (<actual strain>) (Yamagata lineage)

Risk-Management Plan Summary
V 5.0, dated 15 March 2017

Marketing Authorization Holder
Sanofi-Aventis (Suisse) SA
1214 Vernier/GE
Switzerland

Disclaimer: The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.
The RMP summary of VaxigripTetra is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation /Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of VaxigripTetra in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Sanofi-Aventis (Suisse) SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of VaxigripTetra.

Document Name	Document Number
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Title	
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	Approver Name	Date (Universal Time)	Reason for Signature
Approval	KHROMAVA Alena Sr Director, Gobal Head Pharmaco (sanofi pasteur)	13 Jul 2017 16:10:46	I am approving this document
Approval	MALLETT MOORE Tamala Head Safety Evaluation Group (sanofi pasteur)	14 Jul 2017 15:17:10	I am approving this document
Approval	BELLE Susanne QPPV (sanofi pasteur)	18 Jul 2017 08:17:18	I am approving this document
Approval	CHABANON Anne-Laure GSO (sanofi)	18 Jul 2017 08:33:08	I am approving this document as an author

Part VI: Summary of activities in the risk management plan by product

Active substance	Influenza virus (inactivated, split) to the following strains: - A/<Official strain> (H1N1) like strain (<actual strain>) - A/<Official strain> (H3N2) like strain (<actual strain>) - B/<Official strain> like strain (<actual strain>) (Victoria lineage) - B/<Official strain> like strain (<actual strain>) (Yamagata lineage)
Product(s) concerned (brand name(s))	Quadrivalent Influenza Vaccine (split virion, inactivated) (VaxigripTetra®) / Vaxigrip Tetra / Quadrivalent influenza vaccine (split virion, inactivated)
MAH/MAA name	Sanofi Pasteur SA Sanofi Pasteur Europe

Data lock point for this module 15/Mar/2017

Version number of RMP when this module was last updated 5.0

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List of Tables

List of Abbreviations

AE	Adverse Event
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
EMA	European Medicines Agency
EPSS	Enhanced Passive Safety Surveillance
GBS	Guillain-Barré Syndrome
GIHSN	Global Influenza Hospital Surveillance Network
HIV	Human Immunodeficiency Virus
ICSR	Individual Case Safety Report
IM	Intramuscular
IMI	Innovative Medicines Initiative
IVE	Influenza Vaccine Effectiveness
JIVES	Joint Influenza Vaccine Effectiveness Surveillance
MAH	Marketing Authorization Holder
NH	Northern Hemisphere
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
QIV	Quadrivalent Influenza Vaccine
RMP	Pharmacovigilance Risk Management Plan
SH	Southern Hemisphere
SmPC	Summary of Product Characteristics
SRC	Safety Report Card
TIV	Trivalent Influenza Vaccine
Vaxigrip®	Sanofi Pasteur Intramuscular Trivalent Influenza vaccine (Split virion inactivated) thiomersal free and thiomsersal lower content
VaxigripTetra®	Sanofi Pasteur Intramuscular Quadrivalent Influenza vaccine (Split virion inactivated) thiomersal free and thiomsersal lower content
WHO	World health Organisation

1 Elements of summary tables in the EPAR

1.1 Summary table of safety concerns

Table 1: Summary table of safety concerns

Important identified risks	None
Important potential risks	Adverse events of special interest: · Anaphylactic reaction · Convulsions (including febrile) · Guillain-Barré Syndrome · Encephalitis/myelitis · Neuritis (including Bell's palsy) · Vasculitis · Thrombocytopenia
Missing information	Very rare unanticipated AEs that could not be identified during the clinical development At the time of this RMP version, QIV has not been studied in: · Pregnant or lactating women · Immuno-compromised patients Vaccine effectiveness

1.2 Table of on-going and planned additional PV studies/activities in the Pharmacovigilance Plan

At the time of the preparation of this RMP, no additional Pharmacovigilance studies/activities were deemed necessary.

To comply with the Interim Guidance on enhanced safety surveillance for seasonal influenza vaccines (EMA/PRAC/222346/2014) (1), and according to PRAC recommendation to MAHs (EMA/PRAC/775434/2014 (2) and EMA/PRAC/209591/2015 (3) a passive enhanced safety surveillance (EPSS) is to be set up for influenza vaccines. This EPSS will allow near real-time detection of early signals of potentially clinically significant changes of the safety profile compared to previous seasonal composition. It will be performed every year unless there is no strain change compared to the previous influenza season or if relevant product-specific safety data

are available from prior use of the vaccine in the Southern Hemisphere (SH). In such situations and in the absence of any identified signals following confirmed use of the product, the MAH may not perform an EPSS for the given season. This strategy is applicable from the 2015-2016 influenza season onwards and will be discussed with the Competent Authorities as soon as the information on the strains targeted by the vaccine and/or the SH safety data are available and anyway before submitting the annual strain change procedure.

The Primary Objective of the EPSS is to estimate reporting rates of suspected adverse reactions (ARs) occurring within 7 days after routine vaccination with QIV IM during the influenza season. Results from the Northern Hemisphere (NH) 2017/18 EPSS will be used as reference for the comparison with data from the following flu seasons.

EPSS relies on enhanced routine PV and coverage data collection using

- Enhanced (facilitated) AR reporting:
  - by increasing awareness and informing vaccinated people through trained Health Care Professionals on the importance of reporting suspected AR following vaccination,
  - by distributing Safety Report Card (SRC) that will allow the patient to report suspected ARs; at least 1000 cards will be distributed.
- Near real time data collection of age and brand specific influenza vaccination coverage from the same population of vaccine recipients.
- Near real time analysis to estimate reporting rates of suspected AR for QIV IM within 7 days after routine vaccination during the influenza season

The criteria below will be used to trigger the submission of an Expedited Safety Summary Report of the EPSS:

- Impact on patient safety/ public health / benefit-risk balance
- Health Authority (HA) communication need
- Media attention/reputation risk

Expedited Safety Summary report will be prepared and submitted to the Competent Authority only if such a signal is detected during the EPSS.

As part of routine safety surveillance, medical review of spontaneous Individual Case Safety Reports (ICSRs) is performed on a weekly basis in order to detect new signals. Assessment of the detected signals is usually conducted using qualitative methods. Similarly, weekly review of reports from the EPSS is also conducted with the goal of detecting early signals in near real-time. This is done using both qualitative and quantitative assessments. Quantitative methods include weekly descriptive analysis of suspected ARs. If there is an unusual number of cases or an increase in seriousness/severity of a suspected AR, or if there is any reason to suspect that patient safety/public health/benefit-risk balance is affected, then additional quantitative methods such as observed-to-expected (O/E) analyses may be used to complement routine signal detection methods.
Competent Authorities will be informed as per applicable standards and regulation. As per EMA requirement, any new information (from routine safety surveillance or EPSS) that may affect the risk-benefit balance of the product will be communicated promptly to the Competent Authorities

of the Member States in which the product is authorized and to the Agency via email (P-PVemerging-safety-issue@ema.europa.eu).

TIV IM data from EPSS during the same flu season will also be considered as supportive data for QIV.

Table 2: On-going and planned additional PV studies/activities in the Pharmacovigilance Plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
GQM14	Immunogenicity and Safety of Quadrivalent Influenza Vaccine (VaxigripTetra®) in Pregnant Women	Missing information in Pregnant women	Planned	End of 2018

1.3 Summary of post-authorization efficacy developmental plan

Table 3: Summary of post-authorization efficacy development plan

Study	Objectives	Efficacy concerns addressed	Status	Date for submission of final report
GQM05: Efficacy and Immunogenicity Study of Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Healthy Children Aged 6 to 35 Months (randomized, double-blind placebo-controlled trial)	Evaluate efficacy against placebo, immunogenicity and safety profile	Missing efficacy information in children	Completed	Summary report to be submitted by end of July 2017 to all EU countries where study was conducted Final Report submitted Q3 2017 to all EU countries
Supportive program: Foundation for Influenza Epidemiology Global Influenza Surveillance Network - hospital-based, prospective, multi-country and multi-season, case-control study (non-Sanofi Pasteur specific	Document strain circulation by season, burden of severe influenza (leading to hospitalization) and provide information on vaccine effectiveness against	Need for continuous evidence on effectiveness of influenza vaccine	Ongoing for licensed influenza vaccines	Yearly in Periodic Safety Reports upon results publication

Study	Objectives	Efficacy concerns addressed	Status	Date for submission of final report
data)*	hospitalizations associated with influenza infection pending sufficient vaccine coverage rate in the EU countries participating.			
Supportive program: IMI Project DRIVE initiative: A public private partnership between EFPIA: Sanofi Pasteur Abbott, Seqirus, GSK & Public Consortium of 11 partners led by FISABIO (Spain)	Operational research project focusing on brand vaccine effectiveness data collection	Focus on brand vaccine effectiveness data collection	Duration 5 years – First season NH 2017/2018	Results submission to be defined/under assessment

*This program was not implemented specifically for QIV but for licensed influenza vaccines in general; it is considered as supportive.

1.4 Summary table of Risk Minimization Measures

Table 4: Summary table of Risk Minimization Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Adverse event of special interest: Anaphylactic reaction	Text in SmPC: Section 4.3 Contraindication: *"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 octoxynol-9."* Section 4.4 Special warnings and precaution of 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."* Listed in Section 4.8b: Hypersensitivity, allergic reactions such as erythema, urticaria, pruritus, pruritus generalised, dermatitis allergic, angioedema, Listed Section 4.8c: Potential adverse events: "…the following adverse reactions have been reported with Vaxigrip® during clinical trials or from post-marketing experience and may occur in people receiving VaxigripTetra®: Severe allergic reactions: shock, Allergic reaction: rash, generalized erythema..."	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Adverse events of special interest:, convulsions (including febrile), Guillain-Barré Syndrome, encephalitis/myelitis, neuritis (including Bell's palsy), vasculitis, and thrombocytopenia	Text in SmPC: Listed in Section 4.8b: Thrombocytopenia, Listed in Section 4.8c: Potential adverse events: "…the following adverse reactions have been reported with Vaxigrip® during clinical trials or from post-marketing experience and may occur in people receiving VaxigripTetra®: Guillain-Barre syndrome (GBS), neuritis, neuralgia, convulsions, encephalomyelitis, and vasculitis, such as Henoch-Schonlein purpura, with transient renal involvement in certain cases."	None

2 Elements for a public summary

2.1 What is Influenza?

Influenza, also called flu, is an extremely common and contagious disease caused by a virus - *Myxovirus influenzae*. Uncomplicated infection is usually accompanied by the abrupt onset of fever (sometimes as high as 39°C to 40°C), and by some or all of the following: fatigue, headache, cough, muscle and joint pain, chills and runny nose.

Flu occurs in people of all ages, even healthy people. Flu is not usually a harmful disease but it can cause severe illness especially in the elderly, pregnant women, young children aged less than 2 years, and people with certain chronic diseases such as asthma, chronic bronchitis or heart disease, whatever their age, because these groups of people are at greater risk of complications such as pneumonia, life-threatening conditions and even death. However, even in healthy people, influenza may cause considerable illness, for example when a new influenza virus emerges that is highly infective. In addition, the negative impact of the disease is high when taking into consideration sick leave, family disturbances, loss of productivity, and health care costs.

2.2 Summary of treatment benefits

Annual influenza vaccination is the most effective method for preventing seasonal flu and its complications. Antiviral drugs and treatments for the flu symptoms such as painkillers and fever medications may also be used to treat flu once you are sick (ask your doctor for advice).

Because the two types of influenza virus (type A virus and type B virus) responsible for flu can change from year to year, the composition of the vaccine has also to be updated every year. This is why every year experts from, or collaborating with, the World Health Organization (WHO)

meet and propose recommendations for the influenza virus strains to be used in the composition of the next season's vaccine.

Historically influenza vaccines have been trivalent, which means that they contain three (tri-) different inactivated influenza viruses to provide protection against flu: two influenza A virus subtypes and one influenza B virus. Vaxigrip® is such a trivalent vaccine.
Since 2001, two different lineages (families) of type B viruses have appeared and co-circulated. Therefore in order to increase protection against flu due to the type B viruses, Sanofi Pasteur has developed a quadrivalent influenza vaccine which contains four (quadri-) different inactivated influenza viruses: two influenza A virus subtypes and both influenza B lineages (families). QIV is such a quadrivalent vaccine.

2.3 Unknowns relating to treatment benefits

The clinical vaccine efficacy of two-0.5 mL doses of QIV was assessed in a randomized, placebo-controlled clinical efficacy study (GQM05) conducted in more than 5,500 children 6-35 months of age, who had never received influenza vaccine. Data showed QIV prevents 52.03% of influenza illness laboratory-confirmed by RT-PCR and/or viral culture caused by any strain A and/or B and 69.33% of laboratory-confirmed influenza illness caused by vaccine similar strains

However, to assess the protective effect of influenza vaccines in routine use in general populations and those populations considered specifically at risk to suffer from influenza-related illness, Sanofi Pasteur has fostered the development of a Global Influenza Hospital Surveillance Network in several countries worldwide (Spain, China, Turkey, Brazil, the Czech Republic and the Russian Federation). This program aims to document the burden of severe influenza (leading to hospitalization) and to estimate the protective effects of influenza vaccine (vaccine effectiveness against severe influenza. Sanofi Pasteur is also involved in a collaborative European operational research project between several vaccine manufacturers focusing on generating brand-specific effectiveness data in Europe.

As with all vaccines, VaxigripTetra® may not fully protect all persons who are vaccinated.

2.4 Summary of safety concerns

No important risks were identified for VaxigripTetra® during clinical trials.

Table 5: Important identified risks

Risk	What is known	Preventability
Not applicable	Not applicable	Not applicable

Vaxigrip® (the trivalent formulation) has been in use for more than 16 years and more than 1.5 billion doses of this vaccine have been distributed worldwide. During this post-authorization use, some adverse events were observed and are considered as important identified or potential risks for Vaxigrip®. Given the similarity between TIV and QIV, these adverse events can potentially occur with the VaxigripTetra®, they are considered as important potential risks for this vaccine.

Table 6: Important potential risks

Risk	What is known
· Allergic reactions leading to medical emergency with a failure of the circulatory system to maintain adequate blood flow to the different organs (shock) in rare cases · Pain situated on the nerve route (neuralgia); fits/seizures (convulsions) associated with fever; and nervous system disorders that may results in neck stiffness, confusion, numbness, limb pain and weakness, loss of balance, loss of reflexes, or paralysis of all or part of the body (encephalomyelitis, neuritis, Guillain-Barré syndrome) · Blood vessel inflammation (vasculitis) that could cause a skin rash and in very rare cases, temporary renal problems	Observed following the more than 16-year use of Vaxigrip® corresponding to more than 1.5 billion doses distributed worldwide but were not seen in the clinical trials for VaxigripTetra® involving 8705 subjects, considered as important potential risks.
· Temporary reduction in the number of certain types of particles in the blood called platelets; a low number of these can result in excessive bruising or bleeding (transient thrombocytopenia	Observed following the more than 16-year use of Vaxigrip® corresponding to more than 1.5 billion doses distributed worldwide, considered as important potential risks. One case of transient thrombocytopenia related to VaxigripTetra® was observed during clinical trials.

During the development of VaxigripTetra®, some populations were not studied, and therefore are considered as missing information at this stage of development.

Table 7: Missing information

Risk	What is known
Pregnant or lactating women	Experience gathered from worldwide inactivated trivalent influenza vaccine use indicate that the vaccine is safe in pregnant or lactating women Results from animal studies with Vaxigrip Tetra® did not indicate direct or indirect harmful effects
Patients with lowered immunity either due to their medical history or to concomitant medication	Information on the use of inactivated trivalent influenza vaccines in patients with lowered immunity is limited A clinical study with Vaxigrip® in recipients with renal transplant and receiving medication lowering their immunity showed that vaccination (inactivated influenza vaccine) was safe and well tolerated. Other studies with inactivated trivalent influenza vaccines from other manufacturers showed that the vaccine was safe in patients with lowered immunity such as HIV positive patients. As with other vaccines, it is anticipated that patients with lowered immunity could have a reduced response to VaxigripTetra®.
Vaccine effectiveness	Once the vaccine is marketed, the GIHSN may provide information on the influenza vaccine effectiveness in several countries worldwide (Spain, China, Turkey, Brazil, the Czech Republic and the Russian Federation) pending sufficient vaccine coverage. In addition, the Joint vaccine European manufacturers initiative is under preparation (First season NH2017/2018)

3 Summary of additional risk minimization measures by safety concern

Since the manufacturing process of VaxigripTetra® was developed on the basis of the one used for Vaxigrip®, the more than 16-years of data from more than 1.5 billion doses distributed worldwide with Vaxigrip® are considered as supportive data when anticipating the safety profile of VaxigripTetra®.

Based on the data available for both VaxigripTetra® and Vaxigrip®, routine pharmacovigilance activities and routine risk minimization activities are considered sufficient, no additional risk minimization measure is deemed necessary for VaxigripTetra®".

4 Planned post authorization development plan

4.1 List of studies in post-authorization development plan

Table 8: List of studies in post authorization development plan

Study	Objectives	Efficacy concerns addressed	Status	Date for submission of final report
GQM05: Efficacy and Immunogenicity Study of Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Healthy Children Aged 6 to 35 Months (randomized, double-blind placebo-controlled trial)	Evaluate efficacy against placebo, immunogenicity and safety profile	Missing efficacy information in children	Completed	Summary report to be submitted by end of July 2017 to all EU countries where study was conducted Final Report submitted Q3 2017 to all EU countries
Supportive program: Foundation for Influenza Epidemiology Global Influenza Surveillance Network - hospital-based, prospective, multi-country and multi-season, case-control study (non-Sanofi Pasteur specific data)*	Document strain circulation by season, burden of severe influenza (leading to hospitalization) and provide information on vaccine effectiveness against hospitalizations associated with influenza infection pending sufficient vaccine coverage rate in the EU countries participating.	Need for continuous evidence on effectiveness of influenza vaccine	Ongoing for licensed influenza vaccines	Yearly in Periodic Safety Reports upon results publication
Supportive program: IMI Project DRIVE initiative: A public private partnership between EFPIA: Sanofi Pasteur Abbott, Seqirus, GSK & Public Consortium of 11 partners led by FISABIO (Spain)	Operational research project focusing on brand vaccine effectiveness data collection	Focus on brand vaccine effectiveness data collection	Duration 5 years – First season NH 2017/2018	Results submission to be defined/under assessment

*This program was not implemented specifically for Vaxigrip® Tetra but for licensed influenza vaccines in general; it is considered as supportive.

4.2 Studies which are a condition of the marketing authorization

Not applicable.

5 Summary of changes to the Risk Management Plan over time

Table 9: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
5.0	25 April 2017	Identified risks: None Potential risks: Adverse events of special interest: • Anaphylactic reaction • Convulsions (including febrile) • Guillain-Barré Syndrome • Encephalitis/myelitis • Neuritis (including Bell's palsy) • Vasculitis • Thrombocytopenia Missing information: Very rare unanticipated AEs that could not be identified during the clinical development At the time of this RMP version, QIV has not been studied in: • Pregnant or lactating women • Immuno-compromised patients Vaccine effectiveness	Not applicable
4.0	16 March 2016	Identified risks: None Potential risks: Adverse events of special interest: • Anaphylactic reaction • Convulsions (including febrile) • Guillain-Barré Syndrome • Encephalitis/myelitis • Neuritis (including Bell's palsy) • Vasculitis • Thrombocytopenia Missing information: Off-label use in children below 3 years of age Very rare unanticipated AEs that could not be identified during the clinical development	Not applicable

Version	Date	Safety Concerns	Comment
		At the time of this RMP version, QIV has not been studied in: • Children below 3 years of age • Pregnant or lactating women • Immuno-compromised patients Vaccine efficacy/effectiveness	
3.0	31 July 2015	Identified risks: None	Not applicable
		Potential risks: Adverse events of special interest: · Anaphylactic reaction · Convulsions (including febrile) · Guillain-Barré Syndrome · Encephalitis/myelitis · Neuritis (including Bell's palsy · Vasculitis · Thrombocytopenia Off-label use in children below 3 years of age	
		Missing information: Very rare unanticipated AEs that could not be identified during the clinical development At the time of this RMP version, QIV has not been studied in: · Children below 3 years of age · Pregnant or lactating women · Immuno-compromised patients Vaccine efficacy/effectiveness	
2.0	25 October 2013	Identified risks: None	Not applicable
		Potential risks: Adverse events of special interest: · Thrombocytopenia · Anaphylaxis · Guillain-Barré Syndrome · Convulsions (including febrile) · Neuritis (including Bell's palsy) · Encephalitis / myelitis · Vasculitis Off-label use in children below 9 years of age	

Version	Date	Safety Concerns	Comment
		Missing information: Very rare unanticipated AEs that could not be identified during the clinical development At the time of this RMP version, QIV has not been studied in: · Children below 9 years of age · Pregnant or lactating women · Immuno-compromised patients · Patients with co-morbidities, sub-populations with genetic polymorphisms or patients of different ethnic origins Vaccine efficacy/effectiveness	
1.0	31 January 2012 (Previous marketing authorization application withdrawn by the Applicant)	Identified risks: None Potential risks: Adverse events of special interest: · Thrombocytopenia · Anaphylaxis · Guillain-Barré Syndrome · Convulsions (including febrile) · Neuritis (including Bell's palsy) · Encephalitis / myelitis · Vasculitis Missing information: Very rare unanticipated AEs that could not be identified during the clinical development At the time of this RMP version, QIV has not been studied in: · Pregnant or lactating women · Immuno-compromised patients · Patients with co-morbidities, sub-populations with genetic polymorphisms or patients of different ethnic origins Vaccine efficacy/effectiveness	Not applicable

References List

1 Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU, 10 April 2014, EMA/PRAC/222346/2014

2 Letter 12th of December 2014 from EMA/Emil Cochino

3 Pharmacovigilance Risk Assessment Committee (PRAC), Minutes of the meeting on 09-12.