Unit: Technical Assessment Unit

Public assessment report for biological products

VaxigripTetra

Administrative information:

Trade name of the medicinal product:	VaxigripTetra.
INN (or common name) of the active substance(s):	Influenza virus (inactivated, split) of the following strains: A/Michigan/45/2015 (H1N1) pdm09 - like strain (A/Michigan/45/2015, NYMC X-275) 15 mcg haemagglutinin A/Singapore/INFIMH-16-0019/2016 (H3N2) - like strain (A/Singapore/INFIMH-16-0019/2016, IVR-186) 15 mcg haemagglutinin B/Colorado/06/2017 - like strain (B/Maryland/15/2016, NYMC BX-69A) 15 mcg haemagglutinin B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, wild type) 15 mcg haemagglutinin
Manufacturer of the finished product	Sanofi Pasteur Parc Industriel d'Incarville 27100 Val de Reuil France.
Marketing Authorization holder	Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly. - FRANCE;
Applied Indication(s):	Active immunization of adults, including pregnant women, and children from 6 months of age and older, passive protection of infant(s) from birth to less than 6 months of age following vaccination of pregnant women.
Pharmaceutical form(s) and strength(s):	Suspension for injection.
Route of administration	Intramuscular or subcutaneous injection.
Type of registration (EMA/FDA – Local)	Imported.

List of abbreviations

I.M.	Intramuscular
S.C.	Subcutaneous

TIV	Trivalent Inactivated Influenza Vaccine
QIV	Quadrivalent Inactivated Influenza Vaccine
WHO	World Health Organization
HA	Haemagglutinin
NA	Neuraminidase
Ph. Eur	European pharmacopeia
MA	Marketing Authorization
MBV	Monovalent Bulk vaccine
CVV	Candidate Vaccine Virus
ERL	Essential Regulatory Laboratories
DS	Drug substance
WFI	water for Injections
DP	Drug Product
PBS	Phosphate Buffered Saline
FBP	Final Bulk Product
FP	Filled Product
DART	Developmental and Reproductive Toxicology
ECG	Electrocardiogram
EDA	Egyptian Drug Authority
EMA	European Medicines Agency
HA	haemagglutinin
HD	Human dose
PSUR	Periodic Safety Update Report
SC	subcutaneous

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1. **General introduction about the product including brief description of the AI, its mode of action and indications**

Influenza is a highly contagious acute respiratory disease caused by influenza A and B viruses, which continually undergo antigenic changes in their surface proteins, hemagglutinin (HA) and neuraminidase (NA). Seasonal influenza epidemics are driven mainly by influenza A (H1N1 and H3N2) and two influenza B lineages, Victoria and Yamagata. To monitor circulating strains and guide vaccine composition, the World Health Organization (WHO) annually recommends influenza vaccine strains for each hemisphere. Consequently, Sanofi Pasteur developed a quadrivalent influenza vaccine (QIV) containing two influenza A strains and one strain from each B to enhance protection against seasonal influenza. The vaccine was developed based on established trivalent influenza vaccine technology and in accordance with relevant European regulatory and pharmacopeial requirements.

The Quadrivalent Influenza Vaccine provides active immunization of adults and children from 6 months of age and older against four influenza virus strains (two A subtypes and two B types) contained in the vaccine. The Quadrivalent Influenza Vaccine induces humoral antibodies against the haemagglutinins within 2 to 3 weeks. These antibodies neutralize influenza viruses.

The safety and efficacy of the Quadrivalent Influenza Vaccine in children less than 6 months have not been established.

2. **Quality aspects:**

2.2.1 Introduction

- As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient)

- **General information**

  The A/H1N1, A/H3N2 and B strains are provided by World Health Organization (WHO) Collaborative Centers and selected in accordance with the annual recommendation (based on antigen variations).

- **Manufacture, process controls and characterization:**

  Address 1: SANOFI PASTEUR - MARCY L'ETOILE (MLE) 1541 avenue Marcel Mérieux 69280 MARCY L'ETOILE France

  Address 2: SANOFI PASTEUR – VAL DE REUIL (VDR) Parc Industriel d'Incarville Voie De L'Institut
  P.O. Box 101 27100 VAL DE REUIL France

- **Description of Manufacturing Process and Process Controls.**

The Drug Substance (DS) is an aqueous suspension of inactivated, split viral particles that are propagated in embryonated eggs. The Candidate Vaccine Virus (CVV), used to prepare the DS, are selected based on the annual recommendations made by the World Health Organization

(WHO) and are supplied by WHO Collaborative Centers, Essential Regulatory Laboratories (ERL) or CVV reassorting labs.
Quadrivalent Influenza Vaccine (QIV) is composed of a mixture of two A strains (H1N1 and H3N2) and two B strains.

- **Control of Materials.**
  A list and specifications of raw materials used in the production of seeds & Monovalent bulk are provided in the MA file.

- **Controls of Critical Steps and Intermediates.**
  A flow diagram includes the in-process control measures. All manufacturing steps are considered as critical for the Drug Substance (DS) quality are described in the MA file.
- **Process Validation**
  The Process validation is performed to demonstrate that critical processes, operated within established parameters, can perform effectively and reproducibly.
- **Manufacturing Process Development.**
  - **Characterization.**
    The characterization tests from Seed Lots to Drug Product (DP) performed on Quadrivalent Influenza Vaccine (QIV). The tests focus on the global characterization of the Drug Substance (DS) (protein profile and particle size) and on the characterization of the active moieties of the viruses, i.e. the Haemagglutinin (HA) and Neuraminidase (NA) antigens are in accordance with the Guideline on Influenza Vaccines - Quality module (EMA/CHMP/BWP/310834/2012).
  - **Specification**
    The release specification for MVB is presented in the MA file.
    SOPs were provided with the MA file.

  - **Batch analysis.**
    QIV and TIV DS have exactly the same manufacturing process and the same Quality Control testing; moreover, batches are produced in the same manufacturing buildings.
  - **Reference Standards or Materials.**
    For the testing of the potency of the influenza vaccine virus strains in both Monovalent Bulk Vaccine and the Final Lot official reference standard antigens and antisera are used.
  - **Container closure system**
    Stainless-steel vessels, Plastic Carboys or Single Use Bag System can be used for the storage of the Drug Substance (DS).
  - **Stability of drug substance**
    Based on available stability data
    - ✓ **Approved Shelf Life:** 24 months
    - ✓ **Approved Storage Conditions:** 2-8°C

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  The Quadrivalent Influenza Vaccine (QIV), vaccine (split virion, inactivated), is a sterile suspension of influenza virus, containing 15 µg per dose of Haemagglutinin (HA) antigen of two A strains (H1N1 and H3N2) and of two B strains (Victoria lineage and Yamagata lineage). It is a colorless opalescent liquid presented in a pre-filled syringe that contains one dose of 0.5 mL.

- **Pharmaceutical Development including brief description on**

  - **Components of drug product.**

  QIV is a sterile suspension of a mixture of two influenza virus strains type A (H1N1 sub-type and H3N2 sub-type) and two influenza virus strains type B (Yamagata and Victoria lineages) formulated with Phosphate Buffered Saline (PBS) solution, which is the current excipient of Sanofi Pasteur for its seasonal trivalent influenza vaccine for intramuscular use (TIV).

  - Formulation Development

  The QIV is a mixture of two strains of influenza virus type A (H1N1 and H3N2) and two strains of influenza virus type B (Victoria lineage and Yamagata lineage) formulated with Phosphate Buffered Saline (PBS) solution.

  - Manufacturing Process Development.

  The manufacturing process of QIV was developed based on the manufacturing process of TIV. As the manufacturing of QIV required the addition of a fourth strain, the manufacturing process development was therefore focused on formulation and filling steps.

  - Microbiological Attributes.

  The Trivalent Influenza Vaccine (TIV) is a sterile product and is free from preservative. Product sterility and container closure integrity are performed on the Filled Product (FP) during stability studies.

  - Compatibility.

  The Quadrivalent Influenza Vaccine is a ready-to-use formulation; therefore, there is no dilution of the Filled Product.

- **Manufacture of the drug product:**
  Sanofi Pasteur Parc Industriel d'Incarville 27100 Val de Reuil France.

Process validation and / or evaluation:
The overall validation of QIV process manufacture consists of validation of the critical steps of the FBP (blending step) and FP process manufacture (aseptic filling), to ensure adequate quality assurance of the DP.

Product specification:
Release specifications of the Quadrivalent Influenza Vaccine (QIV) Drug Product (DP) are provided in the MA file.

- **Reference Standards or Materials.**
  The reference standards that are official reference standards or reference standards calibrated against official reference standards, and chemical reference standards are described for each test.
- **Container closure system.**
  A single dose glass syringe with attached needle, a needle shield and closed with a plunger Stopper or without needle and a tip cap.

- **Stability of the drug product.**
  Based on available stability data,
  Approved Shelf Life: 12 months
  Approved Storage Conditions: 2-8°C

3. Non –clinical aspect:
Pharmacology: The immunogenicity of the QIV vaccine candidate administered via the SC route was evaluated in BALB/c ByJ mice, comparing three QIV batches (3-fold escalating doses from 1/27 human dose [HD] to 1 HD, corresponding to 0.55-15 µg HA per strain per dose) against two TIV vaccines (commercial and alternative). Functional hemagglutination (HA) responses to the three QIVs were comparable to those induced by the TIVs, except for the B strain not covered by the TIV vaccines, where the QIVs demonstrated superiority.

Toxicology: Nonclinical safety of QIV was assessed through a repeat-dose toxicity study, a developmental and reproductive toxicity (DART) study, and a safety pharmacology study, all conducted in New Zealand White rabbits with QIV administered at one human dose via the IM route. No adverse systemic effects were observed across toxicology, cardiovascular, and respiratory endpoints; QIV-related findings were limited to minimal, transient local inflammation at the injection site in the repeat-dose and safety pharmacology studies.
The DART study showed no maternal toxicity and no adverse effects on mating performance, fertility, embryo-fetal development (including teratogenicity), or early

postnatal development. In addition, the immune response to vaccine-specific antibodies was demonstrated in dams before mating. It was also demonstrated a robust exposure of fetuses but lower in pups to vaccine-specific maternal antibodies.

In Conclusion, the immunogenicity and nonclinical safety data demonstrate that single and repeated administration of QIV (15 µg HA per strain) was immunogenic, well tolerated, and associated only with expected, low-grade local reactogenicity typical of vaccine administration.

4.Clinical aspect:

➢ **Clinical overview:**

The Quadrivalent Influenza Vaccine provides active immunization against four influenza virus strains (two A subtypes and two B types) contained in the vaccine. The Quadrivalent Influenza Vaccine induces humoral antibodies against the haemagglutinins within 2 to 3 weeks. These antibodies neutralize influenza viruses. Since 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.

The clinical development program for Quadrivalent Influenza Vaccine consisted of:

Five Phase III clinical studies conducted:

- Two studies were conducted in adults (**GQM11 and GQM01**).
- Two studies were conducted in children/adolescents (**GQM09 and GQM04**).
- One study was conducted in children (**GQM02**).

➢ **Clinical Efficacy:**

Study GQM11:

The immunogenicity at Day 21 assessed by SN method showed similar results were obtained in QIV and TIV Groups on common strains, except in adults, for the A/H3N2 strain where post-vaccination parameters were estimated slightly lower in the QIV groups compared to the TIV groups and for the B/ Massachusetts strain where GMTR was estimated slightly higher in the QIV groups compared to the TIV groups.

Study GQM02:

The distribution of titers against each of the 4 strains was overall similar in primed and unprimed subjects, although with slightly higher percentages in each titer range for unprimed subjects.

Finally, in adult and elderly subjects, the 3 QIV lots were shown to be as immunogenic as the licensed TIV influenza vaccine and with a similar safety profile to TIV. In addition, the 3 QIV lots provided superior immunogenicity against influenza B strains of both lineages simultaneously compared to TIV. QIV also induced an immune response that lasted for 12 months. In addition, in children aged 3 to 8 years, primed after one dose of QIV and unprimed after 2 doses of QIV 28 days apart, the QIV has been shown to be as immunogenic as licensed influenza vaccine.

➢ **Clinical Safety:**

Across clinical studies, vaxigrip demonstrated an acceptable safety profile:

- Incidences of unsolicited AE was low most commonly is nasopharyngitis in children.
- No death related to vaxigrip treatment.
- **pain** is common injection site reaction.
- Most frequently reported systemic reactions including increased **headache**, **malaise, shivering and fever** are commonly reported.

Finally, Vaxigrip was generally well-tolerated and had a manageable safety profile in children, adolescent, adults and elderly.

➢ **Clinical Immunogenicity:**

-Vaxigrip induces strong and protective immune responses against all 4 strains (two A subtypes and two B types) contained in the vaccine. Non-inferiority of the immune response of the QIV compared to the TIV was demonstrated for all strains in adults and the elderly aged > 18 years, and in children aged 3 to 8 years.

-The addition of the second B strain did not impact the immune response to other strains included in the vaccine.

-The immunogenicity of the QIV after 1 or 2 injections administered to children aged 3 to 8 years showed that a satisfactory immune response is obtained in subjects with previous influenza vaccination who mainly received 1 injection and in subjects without previous influenza vaccination who mainly received 2 injections, with a trend towards slightly higher immune response in subjects without previous influenza vaccination who received 2 injections.

Finally, the formation of antibodies and neutralizing antibodies did not meaningfully affect PD, or efficacy.

- **Benefit-Risk:**

Based on the totality of submitted evidence, the overall benefit-risk balance of vaxigrip is considered favorable when used in active immunization of adults and children from 3 years 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.

- **Overall conclusion:**

The submitted clinical data support the efficacy, immunogenicity, and safety of Vaxigrip Quadrivalent Influenza Vaccine for the prevention of seasonal influenza in adults and children aged 3 years and older.
The vaccine demonstrated non-inferior immune responses to the licensed trivalent influenza vaccine for the shared influenza strains and provided additional protection against the second influenza B lineage. The safety profile was consistent with the established safety profile of inactivated influenza vaccines, with no new safety concerns identified. Overall, the available evidence supports a favorable benefit-risk balance for the approved indication.

5. **General Conclusion and Recommendations if any:**
Based on the review of CTD modules and other supplementary documents, the product is approved.