Unit: Technical Assessment Unit

Public assessment report for biological products

(Verorab)

Administrative information:

Trade name of the medicinal product:	Verorab
INN (or common name) of the active substance(s):	After reconstitution, each 1 dose 0.5 ml contains: Inactivated rabies virus (wister rabies virus strain PMW1 38-1503-3M) ≥ 2.5 IU
Manufacturer of the finished product	Sanofi Winthrop Industrie, 1541, Avenue Marcel Merieux- Marcy l'etoile-69280-France.
Marketing Authorization holder	Sanofi Winthrop Industrie, 82 Avenue Raspail, 94250 Gentilly-France
Applied Indication(s):	Pre-exposure and post-exposure rabies prophylaxis in all age groups
Pharmaceutical form(s) and strength(s):	Powder and solvent in PFS
Route of administration	Intramuscular and intradermal injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

Abbreviation	
GMT	Geometric Mean Titer
TT	Tetanus Toxoid
Td	Tetanus and Reduced Diphtheria Toxoid
DTP	Diphtheria, Tetanus, and Pertussis Vaccine
U/ml	Units per Milliliter
hr	Hour

Abbreviation

min	Minute
p	Probability Value
EMA	European Medicine Agency
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HDCV	Human Diploid Cell Vaccine
HRIG	Human Rabies Immunoglobulin
HTRIG	Heat Treated Rabies Immune Globulin
IV	Intravenous
PVRV	Purified Vero Rabies Vaccine
SC	Subcutaneous
WHO	World Health Organization

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1. **General introduction about the product including brief description of the AI, its mode of action and indications.**
   Verorab is a sterile stable freeze-dried product of purified and inactivated rabies virus from Wistar strain PM/WI38 1503-3M. It is cultured on Vero cell, inactivated with Beta-propiolactone and purified by ultracentrifugation. One dose of vaccine contains 3.25 international units (IU) of rabies antigen (in vitro potency measured using G protein content by ELISA method) (corresponds to ≥ 2.5 IU by NIH test). The vaccine is administrated by intramuscular and intradermal routes.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned in the general introduction

2.2.2 Drug Substance (Active ingredient)

- **General information**

Nomenclature:

- International Nonproprietary Name (INN): Rabies vaccine for human use prepared in cell cultures
- Compendial Name(s): "Rabies vaccine for human use prepared in cell cultures" Ph. Eur. 0216, current edition
- World Health Organization Name (WHO TRS 941, Annex 2): Rabies Vaccine for Human Use
- Trade name: VERORAB®.

General properties:

The Purified Vero Rabies vaccine virus seed lots are derived from the same Pitman Moore Master Seed Lot. A Vero cell suspension is produced by subsequent amplification steps from a Vero working cell bank. The Vero cell suspension is infected with the virus working seed lot for replication of the rabies virus in the Vero cells. For each production batch of the Drug Substance, one to six harvests are pooled. Prior to pooling, each individual harvest is inactivated with Beta-propiolactone and purified by ultracentrifugation. The biological property of the Drug Substance is mainly linked to the G protein antigen which originates from the rabies strain.

Manufacture, process controls and characterization:

Manufacturer :

Sanofi Winthrop Industrie, 1541, Avenue Marcel Merieux- Marcy l'etoile-69280-France. (Manufacture of Seed lots and Cell banks)

Sanofi Winthrop Industrie- Parc Industriel d'Incarville - Voie de l'Institut-P.O Box101 – Val de Reuil 27100- France. (Manufacture from Cell culture to DS)

Description of Manufacturing Process and Process Controls.

The manufacture of Concentrated Bulk is divided into 4 major manufacturing process stages:

• Production and concentration of the individual harvests,
• Inactivation of the concentrated individual harvests,
• Concentration and purification of the Inactivated individual harvests and
• Preparation of the drug substance (i.e. the Concentrated Bulk).

The steps of each process are described in details.

* IPCs for the intermediates of the DS include tests with specified acceptance criteria and tests to monitor the process. All IPCs applied are in compliance with the international pharmacopeias, and with WHO guidelines.
* IPCs during the production process are well defined in the process schemes

- **Control of Materials**

-Sufficient information on seed bank system used in the DS manufacturing process has been submitted.

-Materials used in the manufacture of DS are tested internally and accepted on the basis of relevant pharmacopeia testing methods & Supplier's Certificate of Analysis with reference to internal specifications.

- IPCs applied during production of pre master, master, working seed bank and its validation are included in details.

- **Controls of Critical Steps and Intermediates**

Process parameter and the Critical quality attribute for the manufacturing process stages had been identified. Information on the quality control of the intermediate had been submitted with description of the acceptance criteria of tests and process parameter.

- **Process Validation**

-The DS manufacturing process has been validated adequately. All process parameters were maintained and all CQA were achieved.

- Tests results of critical quality attribute and results for critical parameter attribute in each stage of DS manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and show production process consistency.

- **Control of Drug substance:**
  - **Specification**

The release specification for the concentrated bulk comprises tests for bacterial and fungal sterility test and G protein content test. The specification has been prepared in line with the requirements of pharmacopeia.

  - **Analytical Procedures.**

All analytical procedures either pharmacopeia or in house developed were described. The analytical procedures that need validation are clearly mentioned and well described.

  - **Reference Standards or Materials.**

All reference standards used during manufacturing are well described in the MA file

  - **Container closure system**

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The concentrated bulk is filled into 15 mL High Density Polyethylene vials, with a polypropylene stopper.

- **Stability of drug substance**

- The results of stability studies for three production batches of each DS component support the claimed shelf-life when stored in its proper container.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

Verorab is a freeze-dried inactivated purified vaccine to be administered by the intramuscular route. It is a white homogeneous pellet.
Each dose of freeze-dried vaccine is reconstituted using a sterile solution of 0.4% sodium chloride to provide a single dose of 0.5 mL.
After dissolution, the product is limpid and homogeneous.
The nominal dose of the vaccine is 0.5 mL.

- Container closure system and their compatibility.

The Freeze-Dried Product is presented in a Type I glass vial with a stopper and a cap.
Container
Method of Closure
• Chlorobutyl stopper. 13 mm diameter.
• Flip-off cap (aluminum and polypropylene parts).

- **Manufacture of the drug product:**

- Description of manufacturing process and process controls along with manufacturers and responsibilities.

- Sanofi Winthrop Industrie, 1541, Avenue Marcel Merieux- Marcy l'etoile-69280- France.
- **Description of Manufacturing Process and Process Controls**

- Manufacturing process is simply divided into two processes: formulation or blending process and filling and packaging of the vial process.

- **Control of critical steps and intermediates**

There are no intermediate in the DP manufacturing process.
The critical steps of the DP manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- **Process validation and / or evaluation**

- sterile filtration and freeze drying: carried out in three manufacturing consistency batches and the study reports enclosed

- **Control of excipients**

- excipients and their use during the DP manufacturing are mentioned.
- no excipient of animal origin is used during DP manufacture. No novel excipients were used

- **Control of drug product**

-The specifications include physical characters, general tests, tests for identity, tests for purity, activity, quantity, tests for contaminants.
- Justification of the DP specifications at the release and during stability studies are provided.
- The analytical procedures, principles and validity criteria used for control testing of the vaccine were provided.

- **Container closure system.**

- the product is filled in type I glass vials (3ml) stoppered with chlorobutyl rubber stopper and sealed with flip off aluminum seals. The product supplied 0.5ml solvent in PFS type I glass with a plunger stopper attached with needle and needle shield.
- Identity of materials of construction together with their specifications are described

- **Stability of the drug product.**

-Approved shelf life for the Finished product: 48 months when stored at 2-8°C
-Approved Storage Conditions:
- Store at temperature 2-8ºC
- After the first opening / reconstitution:
For intramuscular use: the product must be used immediately.
For intradermal use, the physical-chemical stability after reconstitution was shown to last for 6 hours at 25°C protected from light. From a microbiological perspective, the product must be used immediately.
In case of non-immediate use, the duration and conditions of storage and use are the responsibility of the user.
If Verorab is administered intramuscularly, the vaccine must be used immediately after reconstitution.
If Verorab is administered intradermally, the vaccine may be used up to 6 hours after reconstitution on the condition that is stored at a temperature not exceeding 25°C and protected from light. After reconstitution with 0.5 mL of solvent, using aseptic techniques, a 0.1 mL vaccine dose must be taken from the vial. The rest may be used for another patient. Before each withdrawal, shake the vial gently to obtain a homogenous suspension. A new sterile needle and a new sterile syringe must be used to withdraw and administer each vaccine dose to each patient to avoid cross-infection. The unused reconstituted vaccine must be thrown away after 6 hours.

3. **Non –clinical aspect:**

Verorab is a purified, inactivated whole virus rabies vaccine. The vaccine activity was confirmed after administration of increasing dilutions of the reference vaccine & Verorab followed by a booster dose seven days later to female Albinos mice.
Pharmacokinetics studies were not conducted as they are not required for vaccines.
The toxicity of Rabies vaccine produced on Vero cells has been evaluated in single or repeated administration in rats, mice and monkeys either by subcutaneous (SC) or intravenous (IV) route

of up to 13 months duration. In addition, local hypersensitivity in guinea-pig was evaluated. These studies were conducted in the early 1980's, and that they were not conducted in compliance with Good Laboratory Practices (GLP) standards as these principles have been formally introduced in Europe in 1987.

A total of five acute toxicity studies were performed: two studies in rats (via SC and IV routes), two studies in mice (via SC and IV routes) and one study in non-human primates (via IV route). All these studies demonstrated that when administered subcutaneously or intravenously in rats, mice and monkeys, the vaccine was well tolerated and not associated with any clinical signs, nor changes in body weight and food consumption. No gross lesions were reported at necropsy in rats and mice.

Two repeated dose toxicity studies (thirteen weeks each) were conducted by SC administration. In both studies, no effects on body weight and food consumption nor hematology were noted. In rats, no changes in the behavior were observed in the animals of the three groups; a few changes in blood biochemistry (including the slight increase of alpha-2 and beta-globulin in treated animals) were regarded to be of very low magnitude and of no toxicological significance. All macroscopic and microscopic findings recorded were considered to be within the background pathology of rats of this age, with no toxicological significance. Meanwhile in Monkeys, no abnormal clinical signs nor vaccine related changes in biochemistry parameters were observed. Local reactions at the injection sites were minor and consisted only of transitory and very slight occasional indurations. At microscopy, only inflammatory changes were seen at the injection sites in treated groups.

Assessment of hypersensitivity in Guinea pigs revealed that vaccine administration did not show any potential for sensitization in animals treated and challenged with 0.2 mL of this vaccine by intradermal route. Moreover, considering the large background information from the marketed vaccine and all clinical studies conducted with the vaccine so far, there are no risks of particular severity from toxicology point of view that would preclude the initiation of a proposed clinical trial.

4. Clinical aspect:

➢ Clinical Overview

Sanofi Pasteur’s Purified Vero Cell Rabies Vaccine (PVRV) has been extensively evaluated throughout its clinical development and post-marketing use since its first licensure in France in 1985. Clinical studies have demonstrated the immunogenicity, efficacy, and safety of the vaccine when administered for both pre-exposure vaccination and post-exposure prophylaxis (PEP), including use in rabies-endemic regions.

The vaccine is prequalified by the World Health Organization (WHO) for pre-exposure vaccination and for post-exposure prophylaxis using the Essen, Zagreb, and Thai Red Cross (TRC) regimens. Sanofi Pasteur’s PVRV is indicated for pre-exposure vaccination, including

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primary immunization and booster doses, as well as for post-exposure prophylaxis against rabies in all age groups. Two routes of administration are currently recognized by WHO: intramuscular (IM) and intradermal (ID).

Approximately 14,000 subjects have been exposed to PVRV in clinical trials, including 260 pregnant women, more than 1,400 children under 18 years of age, and 1,159 patients with severe exposures following bites from confirmed rabid animals. These studies consistently demonstrated the immunogenicity, efficacy, and safety of the vaccine.

Sanofi Pasteur's PVRV has been shown to reliably induce rabies virus-neutralizing antibodies at concentrations exceeding the WHO protective threshold of 0.5 IU/mL in 100% of vaccinated individuals by Day 14 following initiation of post-exposure prophylaxis. Field studies conducted in rabies-endemic areas demonstrated a 100% survival rate during follow-up periods ranging from 6 months to 3 years among patients who received appropriate PEP according to WHO recommendations.

Clinical studies have also demonstrated long-term antibody persistence and immune memory for up to 20 years following primary immunization. To further evaluate the immunogenicity and safety profile of the vaccine, Sanofi Pasteur conducted three clinical studies. According to the applicant, all studies were performed in compliance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

- **Benefit-Risk Assessment**

The available clinical evidence demonstrates that Sanofi Pasteur's PVRV is highly immunogenic and effective for both pre-exposure vaccination and post-exposure prophylaxis against rabies. The vaccine consistently induces protective rabies virus-neutralizing antibody responses and has demonstrated excellent effectiveness in preventing rabies when administered according to WHO-recommended protocols.

The safety profile of the vaccine is well characterized and remains favorable, with reported adverse events generally limited to mild and transient local reactions. No new safety concerns were identified in the reviewed studies.

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- **Clinical Conclusion**

Sanofi Pasteur's PVRV is among the most widely used cell-culture rabies vaccines worldwide, with well-documented safety and efficacy in both pre-exposure and post-exposure rabies prophylaxis. Over more than 25 years of extensive use, more than 85 million doses have been distributed across over 100 countries in Europe, Asia, Africa, and Latin America.

Given its extensive clinical use, substantial post-marketing experience, and demonstrated ability to induce protective immune responses, PVRV provides one of the most comprehensive and long-standing bodies of clinical evidence supporting rabies prevention and management. Based on the available data, the benefit-risk profile of PVRV remains favorable when used in accordance with approved prescribing information and current vaccination recommendations.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.

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