Unit: Technical Assessment Unit

Public assessment report for biological products

Rabivax-S

Administrative information:

Trade name of the medicinal product:	Rabivax-S
INN (or common name) of the active substance(s):	Purified Rabies Antigen (Rabies virus Pitman-Moore Strain 3218-VERO adapted and grown on vero cells, inactivated by using b - propiolactone) not less than 2.5 IU Reconstitute with 1 ml of Sterile Water for Injections.
Manufacturer of the finished product	Serum institute of india PVT.LTD.212/2,Hadapsar pune 411028 Maharashtra state, India.
Marketing Authorization holder	Serum institute of india PVT.LTD.212/2,Hadapsar pune 411028 Maharashtra state, India
Applied Indication(s):	prevention of rabies in children and adults. It can be used before or after exposure, as a primary immunization or as a booster dose.
Pharmaceutical form(s) and strength(s):	Lyophilized powder not less than 2.5 IU
Route of administration	Intramuscular or Intradermal
Registration track	Normal Tracks(343/2021)
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

AEs	Adverse Events
D	Day
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titre
HRIG	Human Rabies Immune Globulin
ID	Intradermal
IM	Intramuscular
mL	milliliter
p	p-value

PEP	Post-exposure Prophylaxis
PVRV	Purified Vero Cell Rabies Vaccine
RIG	Rabies Immune Globulin
SAEs	Serious Adverse Events
SIIL	Serum Institute of India Ltd
VERO	A sterile, purified inactivated rabies vaccine
WHO	World Health Organization

Dossier initial submission and evaluation process.

- The product was submitted for registration via 343/2021 ministerial decree.
- The dossier evaluation by the registration administration units was started on 20.11.2023 after providing all the required documents according to the Checklist for documents of new biological products registration file.
- Full CTD along with detailed SOPs were provided.

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1. General introduction about the product including brief description of the Active Pharmaceutical Ingredient, its mode of action and indications

-Serum Institute of India Pvt. Ltd's Rabies Vaccine Inactivated (Freeze Dried) (RABIVAX-S) is a lyophilized single dose in vial along with 1 mL of Diluent-Sterile Water for Injections in ampoule. The vaccine confirms to I.P., B.P. and World Health Organization (WHO) requirements.

-Rabies Vaccine Inactivated (Freeze Dried) is indicated for the prevention of rabies in children and adults. It can be used before or after exposure, as a primary immunization or as a booster dose.

2. Quality aspects:

1.2.1 Introduction

As mentioned in the aforementioned section.

1.2.2 Drug Substance (Active ingredient)

- **General information**

-International non–proprietary name (INN): Purified Rabies antigen

-The rabies virus has a cylindrical morphology and is the type species of the Lyssavirus genus of the Rhabdoviridae family.

-The outer envelope covered with spike-like projections (10 nm in length) corresponding to G-protein trimers which recognize specific viral receptors on susceptible cell membranes; Hence pathogenicity of Lyssavirus is attributed to protein G.

- **Physicochemical Characterization**

Purified rabies antigen is a Milky white to clear colorless liquid.

- **Biological characterization**

The purified rabies antigen is characterized for its antigen content (Glycoprotein content) by Single Radial Immuno Diffusion (SRID). The SRID value should not be less than 4.20 IU/ mL. The method is based on immuno-precipitation reaction of rabies antigen against anti-rabies glycoprotein sera.

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

-The drug substance is manufactured & controlled at Serum institute of India

-The site complies with the GMP requirements

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

-the detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPCs.
-the DS is manufactured through various steps including: Revival of Cells, Cell Passaging, Virus Propagation, Virus Inactivation, Antigen Purification and Stabilizer addition.

- **Control of Materials**

-List of raw materials of Pharmacopoeial and In-House Standard with relevant COAs are provided.
-information regarding the used strain & cell substrate is mentioned in detail in the MA file.

- **Controls of Critical Steps and Intermediates**

-Critical process steps and critical process parameters are mentioned in the manufacturing process and process control flow chart
-The quality control of the intermediates (pre-working seed virus, working seed virus, control cell cultures, MCB, MWCB and MSL) provided.
-Tests and specifications on Rabies Master /Pre Working/Working virus seeds were evaluated, and found compliant with the requirements of WHO, Indian Pharmacopoeia, European Pharmacopoeia.
-Tests on Master Cell Bank or Manufacturer's Working Cell Bank were evaluated, and found in compliance with the requirements of Annex 3 of WHO TRS 978, Indian Pharmacopoeia, European Pharmacopoeia (5.2.3), ICH Q5D, and ICH Q5A (R1).

- **Process Validation**

-The Critical Process Parameters and Critical Control Parameters of the manufacturing process were identified and validated.
-A risk assessment shall be performed to identify critical process steps and the risk mitigation activities in the form of setting of critical process parameters and in-process checks shall be performed during process validation and subsequent manufacturing activities.
-All critical manufacturing processes were validated by taking three consistency runs at commercial scale.
-validation protocols and reports are attached to the MA file illustrating the details of the batches used.

- **Manufacturing Process Development**

-purified rabies antigen. The required technology for upstream and downstream has been developed at Serum Institute of India Pvt. Ltd. (SIIPL). This includes cell bank preparation and characterization, Seed viruses preparation and characterization, vaccine virus propagation,

virus concentration and inactivation, inactivated antigen purification, stabilization of antigen, lyophilization.
-detailed description for each step development is mentioned in the MA file.

- **Characterization**

-Physicochemical characterization: The purified rabies antigen is milky white to clear colourless fluid.
-Biological characterization: The phenotypic characterization of Rabies virus is performed using Fluorescence Antibody Test (FAT), Single Radial Immuno-Diffusion (SRID), Lethal Dose test (LD50).
-The glycoprotein (GP) is the structural protein of the virus that induces the formation of virus neutralizing antibodies which confers immunity in animals / humans. Selective immune fluorescent membrane staining and immunecytosis of rabies virus infected cells were shown to be G protein specific.
-Detailed procedures for characterization of the rabies virus were provided and evaluated.
-The potential impurities during the production of Purified Rabies antigen are classified into product related (BSA and neomycin content) and process related (Endotoxin content).
-Results of 3 representative batches were provided and values were within the limits indicating the consistency of the purification process.

- **Specification**

-The tests performed on the drug substance comply with the requirements of I.P, B.P, Ph. Eur, WHO and In-house practices.
-detailed SOPs are provided with their validation report.
-the purity, potency, physicochemical properties & sterility of The Purified Rabies Antigen are tested.

- **Batch analysis**

-The consistency in manufacturing process of Purified Rabies Antigen (Vero) was observed in all the batches manufactured at SIIPL
-Batch analysis for commercial batches of Purified Rabies Antigen have complied with test specification ensuring the consistency of the manufacturing process.

- **Reference Standards or Materials**

-SIIPL has made In-House Reference Standard (IHRS) designated as Batch no: IHRS/01/19 which was calibrated against WHO 7th International Standard for Rabies Vaccine (NIBSC CODE: 16/204). All the batches of Purified Rabies antigen are tested in comparison with above mentioned reference standard for Antigen content.
-Certificate of analysis of IHRS/01/19 and summary of calibration report are provided.

- **Container closure system**

-Purified Rabies Antigen will be filled and stored in presterilized, ready to use 10 L and 20 L capacity Ethyl Vinyl Acetate (EVA) bags at 2-8ºC. The bags are for single use and comply with USP Class VI requirements. Characterization and Certificate of Analysis are provided.

- **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:**

-Rabies Vaccine Inactivated (Freeze Dried) RABIVAX-S is a sterile, purified inactivated rabies vaccine prepared on Vero cells with milky white friable mass appearance.
-The vaccine conforms to I.P, B.P. and World Health Organization (WHO) requirements.
- Composition: Rabies Vaccine Inactivated (Freeze Dried) is provided as 1 dose of lyophilized powder in vial along with 1 mL of Diluent-Sterile Water for Injections in ampoule.
Each vial of 1 dose contains not less than 2.5I.U from purified rabies antigen, 40mg glycine, 40mg sucrose & 10mg human serum albumin.
-Rabies Vaccine Inactivated (Freeze Dried) is filled in 13 mm USP Type 1 clear tubular glass vials of 16.5 mm diameter and 40 mm height and 5.0 mL overflow volume. Vials are stoppered with a 13 mm Rubber stopper and sealed with 13 mm red coloured plastic Flip top aluminum seal.

- **Pharmaceutical Development**

- **Components of drug product**

-The development of Rabies Vaccine Inactivated (Freeze Dried) includes the process development and standardization, characterization of cell banks and seed viruses, validation of production processes. Rabies virus Pitman Moore (PM) 3218 is grown in Vero cells, concentrated, inactivated and purified to obtain purified rabies antigen.
-No fresh excipients are added during blending. All excipients are already present in the Purified Rabies Antigen and have been introduced during the manufacturing process. Hence, the compatibility of the drug substance with excipients is not applicable. The ingredients already present in the purified rabies antigen are Glycine, Sucrose, and Human Serum Albumin.

- **Formulation Development**

-The drug substance used in the formulation of Rabies Vaccine Inactivated (Freeze Dried) is QC tested and released Purified rabies antigen.

-Batches with appropriate antigen content and volume are selected for formulation of Rabies Vaccine Inactivated (Freeze Dried).
-Volume based overage in terms of fill volume of 1.025 ± 0.025 mL is provided to ensure a guarantee of not less than 1.0 mL/container.

- **Manufacturing Process Development**

-The manufacturing process of purified rabies antigen is implemented in a step wise manner with the large scale production of Vero cells, rabies virus propagation, virus inactivation, purification of inactivated antigen and antigen stabilization. Small lots of Purified rabies antigen were taken and freeze dried to produce finished product.
-The rationale for selection and optimization of stabilizers was provided by the manufacturer.
-The quality parameters obtained using the freeze dried compositions of 4% sucrose, 4% Glycine and 1% HSA and the optimized lyophilization cycle complies with the WHO requirement. The product showed desired stability profile. The selected and optimized critical process parameters are provided.

- **Microbiological Attributes**

-Compliance with specification for sterility was shown up to 42 months of storage, indicating the stability of the container closure system for prevention of microbial contamination.
-There is no significant decrease in potency of vaccine as a result of lyophilized cake contact with the primary packaging materials during storage for 42 months. Moisture levels remains within specifications.

- **Compatibility**

-Stability studies on the final product provide the evidence of compatibility of the container closure system with the drug product.

Manufacture of the drug product:
Description of manufacturing process and process controls along with manufacturers and responsibilities.

- **Manufacturer**:

-The Drug Product Rabies Vaccine Inactivated (Freeze Dried)& the diluent sterile water for injection are manufactured by Serum Institute of India Private Limited (SIIPL)

Description of drug product manufacturing process that summarizes the following information was provided for the steps shown below:

- ✓ Formulation
- ✓ Primary Packaging Material and Process Equipment Preparation and Processing
- ✓ Filtration & Blending
- ✓ On-line Filtration and Aseptic Subdivision (Filling)
- ✓ Lyophilization

- ✓ Vial Sealing (Capping)
- ✓ Visual Inspection
- ✓ Labeling and Packing
- ✓ Dispatch packing & Dispatch

➢ **Control of critical steps and intermediates**

-Detailed data for the identification, and control of critical steps involved in the manufacturing of Rabies Vaccine Inactivated (Freeze Dried) RABIVAX-S Final Bulk Vaccine and Filled Product were provided and found satisfactory.
-The Rabies Vaccine Inactivated (Freeze Dried), Final Bulk Vaccine is considered as an intermediate in the manufacturing process of Drug Product. The specification applied for release of Final Bulk of Rabies vaccine is provided

➢ **Process validation and / or evaluation**

-All critical manufacturing processes were validated by taking three consistency runs at commercial scale.
-All the analytical methods used during process validation shall be prior validated. Process validation batches shall also be subjected to stability studies to evaluate its impact on product quality over the period of time and to justify shelf life of the product.
-The submitted Process validation study provided documented evidence, and high degree of assurance that the process stages were satisfactory.

➢ **Product specification:**

-Specifications proposed for release and stability testing of the finished product comply with WHO/BP/IP except for description.
-Detailed SOPs validation protocols & reports are provided for the in-house methods
-The specifications include general characteristics, biological& general safety tests, potency &identity tests
-Justification of the drug product specifications at the release and during stability studies are provided.
-The excipients are purchased in compliance to the pharmacopeial specifications. A test certificate accompanies each batch supplied to guarantee compliance with the specifications.

➢ **Reference Standards or Materials.**

- **Reference antigens and antisera**

-SIIPL has made In-House Reference Standard (IHRS) designated as B. no: IHRS/01/19 which was calibrated against WHO 7th International Standard for Rabies Vaccine (NIBSC CODE: 16/204). IHRS/01/19 is being used for estimation of Glycoprotein content by

ELISA and NIH Potency of all the batches of Rabies Vaccine Inactivated in comparison with above mentioned reference standard.

- **Container closure system**

-Rabies Vaccine Inactivated (Freeze Dried) is filled in 4.0 mL U.S.P Type I vial stoppered with grey butyl rubber closure and sealed with an aluminium flip-off seal.

- **Stability of the drug product**

-Based on available stability data,

- ✓ **approved Shelf Life:**
  36 months

- ✓ **approved Storage Conditions:**

-The vaccine should be stored between 2ºC to 8ºC.
-Vaccine maybe used up to 6 hours after reconstitution provided it is maintained at 2°C to 8°C. Unused vaccine must be discarded after 6 hours.
-Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S should be reconstituted only with the entire contents of the diluent supplied (Sterile Water for injections I.P.) using a sterile syringe and needle, with gentle shaking the dried cake is easily dissolved. After reconstitution the vaccine should be used immediately.

-Information regarding the used diluent are provided in the MA file.

- **Adventitious agents:**

Considering the risk of adventitious agents being present in the product, the manufacturing process of Rabies Vaccine Inactivated (Freeze Dried) is designed to take sufficient precautions. The control/checks are established at various levels in the manufacturing process, which repeatedly check and assure the absence of such adventitious agents in the product/process.
1. Viral adventitious agents
2. Non-viral adventitious agents

The assessment is performed on Master Seed Lots (MSL), Working Seed Lots (WSL) and also during the blending process of Drug Product.

The control of adventitious agents relies on several parameters listed below:
• Compliance with the GMP requirements of Central Drugs Standard Control Organization (CDSCO) - Indian Central Licensing/Regulatory Authority, State Licensing Authority (State FDA) and National Control Laboratory (CDL Kasauli) and WHO. The different steps of manufacturing process are set up in classified area to control external sources of microbial contamination. The air is filtered and over pressure is maintained in the production area.
• Selection and control of starting and raw materials

• Sterilization (filtration/heat steam) or heat treatment of culture media and solutions
• The design of drug substance manufacturing process.
• In-process controls and quality control tests applied through the production process.

Raw materials of animal origin used in the manufacture of purified rabies antigen are Adult Bovine Serum (ABS), Foetal Bovine Serum (FBS) and Trypsin. These are used during the cell culture in the manufacturing process of purified rabies antigen. The suitability for the use of the biological raw material is provided.

3.Non–clinical aspect:

- **Rabivax-S®** is a sterile, purified, inactivated rabies antigen prepared on Vero cells and indicated for the prevention of rabies in children and adults. It can be used before or after exposure, as a primary immunization or as a booster dose. It is WHO prequalified for sale to United Nations agencies on 20 December 2018.
- **Pharmacology:** Not applicable. The efficacy of the vaccine was verified in human clinical studies.
- **Pharmacokinetics:** Not applicable according to WHO guidelines on nonclinical evaluation of vaccines Annex 1 (TRS, No. 927, 2005).
- **Toxicology:** Rabies Vaccine Inactivated (VERO) has been studied in extensive single and repeated dose toxicity studies, repeated dose local tolerance and developmental toxicity studies in mice, rats and rabbits. **Reproductive and Developmental Toxicity** (including range-finding studies and supportive toxicokinetic evaluations) is not applicable according to the WHO Guideline on non-clinical testing of vaccines. However, the applicant submitted a study to evaluate the prenatal developmental toxicity of the test article. No maternal toxicity, embryotoxicity or fetotoxicity was observed at and up to the dose of 1.5 ml/rat of VERO. Therefore, Rabivax-S® at the doses of 0.5 ml, 1 ml and 1.5 ml/rat is not teratogenic in Wistar rat. The NOAEL for maternal toxicity, fetotoxicity and teratogenicity was greater than 1.5 ml/rat (greater than 3 times the intended human dose). **Local tolerance** was evaluated following repeated ID injections for 28 days in Wistar rats. Rabivax-S® induced reaction at the site of injection (skin) which was found to be comparable with that of the diluent treated animals. Therefore, the local reaction at injection site may be due to post-traumatic changes following repeated needle inoculation. It is concluded that the product was found non-toxic even at more than twice the human dose. The absence of toxicity paved the way for Phase I human studies.
- **Overall conclusion:** Based on the toxicology data, the nonclinical evaluation of this product supports its use in the proposed patient population.

4.Clinical aspect:

Clinical Efficacy: Efficacy (Clinical Immunogenicity) was established in 2 controlled clinical trials;

Phase-I study

- The investigational vaccine **was immunogenic** when given as 0.1ml **by intradermal** route and 1ml **by intramuscular route** as three dose regimens given on Day 0, Day 7 and Day 21 as pre-exposure immunization. All subjects achieved protective titers after 3 doses.
- The **GMTs were similar across groups**. The difference in the GMTs were not statistically significant between Group I (SILS's PVRV, IM) and Group II (SILS's PVRV, ID), between Group I (SILS's PVRV, IM) and III (Verorab®, IM) Day on Day 7, Day 21 and Day 42 as well as between Group II and III on Day 7 and Day 21. However, difference in the GMTs between Group II and Group III **was statistically significant** on Day 42; however, the difference is **not clinically relevant.**

Phase-II/III Study

- **The primary efficacy endpoint** of the study **to demonstrate non-inferiority** of SIIL PVRV IM and SIIL PVRV ID in subjects with both category II and III exposures **has been met**.
- **GMCs were comparable** between the groups at baseline **in both category II (**SIIL PVRV IM) **and category III (**SIIL PVRV ID) **exposure** subjects. **Difference in GMCs were not statistically significant** on days 0, 7, 14, 28 and 42 in patients with category II exposure and category III exposure except for day 7 when SIIL PVRV IM + HRIG group GMCs were significantly higher than Rabipur® IM + HRIG (p=0.0253).
- **On Day 7, all the subjects in all groups had seroprotection with only 2 doses of vaccine** and seroprotection was maintained through days 14, 28 and 42.

This shows that SIIL PVRV is highly immunogenic vaccine when administered by both IM and ID routes.

Clinical Safety: Safety was established in 2 controlled clinical trials;

Phase-I study

Most of the solicited local and systemic events, reported in the phase-I study were mild in severity and resolved without any sequelae, without requirement of any concomitant medications. The incidence of solicited events is in line with the incidence reported earlier with other modern tissue culture rabies vaccines. The incidence was similar to those reported in the control arm of the licensed Verorab®. Few unsolicited adverse events, unrelated to study vaccines were also reported. One SAE with criteria being in patient hospitalization for urinary tract infection was reported. The SAE was unrelated to study vaccine and resolved without any sequelae. There was neither death nor any significant AE resulting in any withdrawal. Almost all the hematological,

biochemistry and urinalysis parameters showed no significant change from baseline across three groups. The few mild changes reported were unrelated to study vaccines. Physical examination and vitals showed no abnormal findings across three groups.

Thus, SIIL's PVRV vaccine when given as 1 ml by intramuscular route and 0.1ml by intradermal route as pre-exposure immunization on D0, D7 and D21 was safe, well tolerated with no significant reactogenicity.

Phase II/III Study

Most of the solicited local and systemic events, reported in this study were mild in severity and resolved without any sequelae, without requirement of any concomitant medications. Slightly higher frequency of solicited local reactions in subjects administered SIIL PVRV by ID route is in line with published literature. The incidence of solicited events is in line with the incidence reported earlier with other rabies vaccines. There were no unexpected adverse reactions reported with the study vaccines. No SAE was reported. Thus, SIIL's PVRV vaccine when given as 1 ml by intramuscular route and 0.1 ml by intradermal route on each deltoid as per WHO recommended post-exposure prophylaxis regimen was safe, well tolerated with no significant reactogenicity.

Thus, SIIPL PVRV when given by intramuscular route or intradermal route with or without HRIG was safe and tolerable when given as per WHO recommended PEP regimen in subjects with category II and III exposures.

- **Benefit/ Risk discussion:**

Rabies is a universally fatal disease. Worldwide, there are 61,000 deaths caused by rabies each year, mostly in Asia and Africa (58,300); 16,450 of them are in India and 23,800 in Africa. Most deaths could be prevented with post-exposure prophylaxis (PEP) which includes proper wound care, rabies vaccination and passive protection with hyperimmune rabies immune globulin (RIG) in Category III exposures. The safety of cell culture-based rabies vaccines is very well established and they have been in use for more than 4 decades globally. The Vero cell-based rabies vaccine has been in use since last 30 years and no safety concerns have been reported till date.

- SII PVRV by both IM and ID regimen for PEP induced high immunogenicity which was non-inferior to Rabipur when given as per WHO recommended post-exposure immunization regimens. Immune responses were similar in all three groups on all visits.

- Both the phase I and phase II/III clinical trials of Rabies Vaccine Inactivated demonstrated comparable safety profiles to comparator vaccines (Verorab and Rabipur, respectively). Solicited local and systemic reactions were comparable between the groups. The majority of these were mild in severity and resolved without any sequelae. No SAEs occurred

during the study. No related unsolicited AEs were reported during the study. SII PVRV was safe and well tolerated by both routes.

- Based on the satisfactory safety and efficacy results, SII PVRV seems to be a very sound option for rabies prophylaxis.

In conclusion, the overall benefit/risk of RABIVAX-S is favorable in the prevention of rabies in children and adults. It can be used before or after exposure, as a primary immunization or as a booster dose.

5.General Conclusion and Recommendations if any:

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