Unit: Technical Assessment Unit

Public assessment report for biological products

VaxiRab N

Administrative information:

Trade name of the medicinal product:	VaxiRab N
INN (or common name) of the active substance(s):	Inactivated Rabies Virus (Pitman Moore Strain) ≥2.5 I.U/VIAL
Manufacturer of the finished product	Zydus Lifesciences Limited., Survey No. 417, 419, 420, Sarkhej Bavla National highway No.8A, Village-Moraiya, Tal- Sanand, Dist-Ahmedabad-382 210, Gujarat state, - INDIA
Marketing Authorization holder	Zydus Lifesciences Limited., Survey No. 417, 419 &420, Sarkhej Bavla National highway No.8 A, Village-Moraiya, Tal Sanand, city: Moraiya -382 210 Dist Ahmedabad -382 210 Gujarat state, INDIA
Applied Indication(s):	for active immunization against rabies virus infection in humans for; ▪ Pre-exposure vaccination (IM). ▪ Post-exposure vaccination in incomplete or unvaccinated persons (IM or ID).
Pharmaceutical form(s) and strength(s):	Lyophilized Powder
Route of administration	Intra muscular (I.M) \ Intradermal (I.D)
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

ID	Intradermal
IM	Intramuscular
IU	International Units
mL	milliliter
WHO	World Health Organization

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

VaxiRab-N vaccine, a purified Chick Embryo Cell Culture Rabies Vaccine ($PCECV^{PM}$), is a freeze-dried vaccine, which uses Pitman Moore Rabies virus strain. The original pitman moore strain; Wistar strain PM-HDCS, 1503- 3M adapted in duck embryo, was further adapted to Duck fibroblast cell cultures by serial passages followed by adaptation in Chick fibroblast cultures by serial passages. It is concentrated by density gradient centrifugation, purified, inactivated by addition of β-propiolactone, mixed with stabilizer solution and lyophilized. The diluent used is sterile water for injection. The ready-to-use vaccine is pyrogen-free and contains no preservative. The vaccine has an antigenic value not less than 2.5 IU per dose as determined by NIH potency test in mice, corresponding to recommendations for highly purified rabies vaccine (WHO technical report series, 1992, No.824) & recommendations for inactivated rabies vaccine for human use produced in cell substrates and embryonated eggs. (WHO technical report series, 2007, No.941 Annex 2).

2. Quality aspects:

- **Introduction**

As mentioned in the aforementioned section.

- **Drug Substance (Active ingredient)**

- **General information**

- **Nonproprietary Name:** Inactivated final bulk of rabies vaccine
- The rabies virus is a species of the Lyssavirus genus of the Rhabdoviridae family with a cylindrical morphology where the outer envelope is covered with spike-like projections corresponding to the glycoprotein (G-protein) which recognize specific viral receptors on susceptible cell membranes; hence the immunogenicity of rabies vaccine is attributed to protein G.
- **Physicochemical Characterization:** Inactivated rabies final bulk has a pH of 7 – 7.8.
- **Biological characterization:** Inactivated rabies final bulk is characterized for its antigen content (Glycoprotein content) by Single Radial Diffusion (SRD). The SRD value should not be less than 6.0 IU/mL.

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

➢ **Manufacturer**:
Zydus Lifesciences Ltd., Survey No. 417, 419 & 420, Sarkhej - Bavla National Highway No. 8A, Village - Moraiya, Tal: Sanand, Dist. Ahmedabad – 382 210, Gujarat State, INDIA.

➢ **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: SPF chicken egg incubation, candling, embryo collection & pooling, trypsinization, preparation of cell suspension, rabies virus infection & adsorption, distribution into roller bottles, virus harvest, pooling & filtration of virus harvest, concentration and purification of rabies virus and inactivation of rabies virus and preparation of final bulk.

- **Control of Materials**

- All the raw materials are tested internally in quality control laboratory as per the relevant pharmacopoeial monograph or in-house procedures.
- List of raw materials of Pharmacopoeial and in- house prepared with relevant CoAs were provided.
- The specifications, test methods, analytical reports & vendor CoAs of raw material have been enclosed in the MA file.

- **Controls of Critical Steps and Intermediates**

- Samples taken from the critical steps in the manufacturing process are analyzed by Quality Control (QC) as part of in-process quality control testing. Tests and specifications on Rabies Master /Pre Working/Working virus seeds were evaluated, and found compliant with the requirements of WHO, Indian Pharmacopoeia, and European Pharmacopoeia.

- **Process Validation**

Validation is done for the following steps involved in the manufacturing process:

- Stage I: From egg receipt to preparation of raw virus harvest, 3 batches were validated with a batch size of 6000 Eggs.
- Stage II: From Raw virus harvest filtration, purification and concentration up to the manufacturing of virus concentrate, where 3 batches were validated with a batch size of 1250 ml.
- Stage-III: From dilution of virus concentrated with phosphate buffer saline solution, inactivation with beta propiolactone and blending of inactivated bulk with stabilizer solution for preparation of the final bulk ready for filling, 5 batches were validated with a batch size of NLT 38,000 mL).
- The critical process parameters were found to meet the predefined limits and met all the critical quality attributes.
- The protocols and reports of raw virus harvest (Stage I), Concentration and Purification (Stage II) and Inactivation of Rabies Virus (Stage III) of drug substance were provided in the MA file.

- **Manufacturing Process Development**

- The Manufacturing process was developed as per the WHO Technical Report Series No. 824, 1992 “WHO Expert Committee on Rabies” & 941, 2007 Annex-2“Recommendations for Inactivated Rabies Vaccine for Human Use Produced in Cell Substrates and Embryonated Eggs” as well as relevant pharmacopoeial standards. The existing knowledge of manufacturing process of duck embryo based rabies vaccine was utilized to develop the purified chicken fibroblast cell culture-based rabies vaccine.

- **Characterization**

  - Physicochemical characterization included pH test.

- Biological characterization included absence of contaminants, glycoprotein content, and inactivation in cell culture tests.

- **Specification**
  The drug substance is analyzed as per In-house, Indian Pharmacopeia, British Pharmacopeia and WHO TRS specifications.

- **Analytical Procedures**
  The analytical methods and in-process testing procedures that are intended to be used for batch-release and stability samples analysis during commercial batch production of Inactivated final bulk of Rabies Vaccine drug substance are listed below:
  - Test for Inactivation in Cell Culture
  - Absence of Contaminants
  - pH
  - Glycoprotein Content
  - Bacterial Endotoxin

- **Batch analysis**
  - Batch-to-batch quality consistency was observed with drug substance.
  - Certificate of analyses of Inactivated bulk as well as Final Bulk of Rabies Vaccine has been enclosed in this section.

- **Reference Standards or Materials**
  - Detailed protocol and summary report for establishment of internal reference standard and their validation were provided.
  - Zydus has made In-House Reference Standard (IHRS) designated as Batch no: RV90017 which was calibrated against WHO 7th International Standard for Rabies Vaccine.
  - The respective report of In-House Reference Standard of Rabies Vaccine against WHO International Standard of Rabies Vaccine (NIBSC Code:16/204) for Determination of Rabies glycoprotein by Single Radial Immunodiffusion (SRD) along with the Certificate of Analysis of In-house Reference Standard RV90017 have been submitted.

- **Container closure system**
  - Prior to the inactivation, the virus concentrate is preserved in polypropylene containers below -65°C.
  - Purified Chick embryo cell culture Rabies Vaccine Inactivated Final Bulk can be held for 12 days in EVA bag 2 to 8 °C until its final filling based on the hold time study.
  - Packaging material specifications, CoAs and standard testing procedure were provided.

- **Stability of drug substance**

Based on available stability data**:**

- ✓ **Approved Shelf Life:** 12 days
- ✓ **Approved Storage Conditions:** 2-8 °C

Drug product:

- **Description and Composition of the Drug Product:**
  Purified Chick Embryo Cell Culture Rabies Vaccine (PCECV^{PM}) is a freezedried vaccine, which uses Rabies virus strain, Pitman Moore.
  Composition: Inactivated virus (Pitman Moore Strain) in chick embryo fibroblast cell culture is provided as 1 dose of lyophilized powder in vial along with 1 mL of Diluent-Sterile Water for Injections in ampoule.
  The primary container consists of 3 ml USP type I Glass Vial with 13 mm grey bromobutyl rubber stopper used as container closure and 13 mm aluminum flip off seals.
  The secondary package: The vials shall be labeled with approved sticker label and packed with 1 ml ampoule of sterilized water for Injections BP.

- **Pharmaceutical Development**
  Components of drug product
  Rabies Vaccine (Purified Chick Embryo Vaccine) PCECV^{PM} is a sterile, white to off white freeze dried cake. A clear Solution is produced after reconstitution with water for Injection. Inactivated final bulk of rabies vaccine has been developed by classical method as per the WHO Technical report series no.824, 1992 & 941, 2007.
  The excipients are gelatin, human albumin, sucrose, sodium chloride, sodium hydroxide and water for injection. Beta Propiolactone is used for Inactivation.

  Formulation Development
  For each batch, the volume of cell culture concentrate will differ based on its antigen content (SRD value) to achieve final antigen content of NLT 9.0 IU/ml in the inactivated bulk. Batches with appropriate antigen content and stabilizers are selected for formulation of Rabies Vaccine inactivated.

  Manufacturing Process Development
  Final bulk is filled in 3 mL USP Type I glass vials and half stoppered using presterilized bromobutyl rubber stopper (slotted). Nominal fill volume range will be 1.00 ml to 1.10 ml per vial. The filled vials are lyophilized. Full stoppered lyophilized vials are sealed with blue aluminum flip off seal and stored in cold room at 2 to 8 ºC till further processing.
  Each batch is subjected to 100% visual inspection after cap sealing. Visually accepted vials are labeled and packed as per approved pack style and stored in cold room at 2 to 8 ºC.
  Purified Chick Embryo Cell Culture Rabies Vaccine (PCECV^{PM}) is packed for 3 ml,13 mm, Flint Tubular Vials USP-I with 13 mm grey bromobutyl Rubber Stopper.

Compatibility tests were carried out including visual clarity of washed vials, sterility, BET, fill volume, sealing check, container closure integrity, and visual inspection of filled vials.

Microbiological Attributes
The product is manufactured using aseptic techniques, and all operations associated with aseptic manufacturing have been strictly controlled to reduce bioburden.
The final bulk of rabies vaccine is filtered with 0.2µ filter into EVA bags.
The product has been maintained in controlled environment during the processing to restrict the bioburden of the product. The endotoxin limit for the product has been adopted from Pharmacopoeia. There are no preservatives used in the finished product.

Compatibility
Before reconstitution the product is white to off white freeze-dried cake. After reconstitution it is clear solution with water for injection. It may be colored owing to the presence of pH indicator.
Compatibility study was provided for three batches of Rabies Vaccine post reconstitution using diluent of Sovereign Pharma Private Ltd. indicating the stability of the reconstituted vaccine for up to 12 hours.
For IM injection use immediately after reconstitution and for ID injection store at 2-8°C after reconstitution.
Reconstituted vaccine can be used up to 6 hours, provided it is stored at 2-8°C.

- **Manufacture of the drug product:**
  Description of manufacturing process and process controls along with manufacturers and responsibilities.
  Manufacturer:
  The manufacturing and testing activities of Rabies Vaccine (Purified Chick Embryo Vaccine) are performed as per cGMP standards at Zydus Lifesciences Limited (Formerly known as Cadila Healthcare Limited).
  Vaccine R facility is dedicated for the filling and packing activity of drug product and there are no other manufacturers involved in production, storage and quality control testing.

  Description of drug product manufacturing process that summarizes the following information was provided for the steps shown below:
  - Receipt of final bulk
  - Vial Washing, depyrogenation
  - Filling & Half Stoppering
  - Lyophilization
  - Cap sealing
  - Visual inspection
  - Labelling and 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 (Purified Chick Embryo Vaccine) PCECV^{PM} drug product; Final Bulk Vaccine and Filled Product, were provided and found satisfactory.

Process validation and / or evaluation
Aseptic process simulation (Media fill):
- Aseptic filling process validation is carried out every six months to validate the aseptic processing activity
- Media fill simulation is performed for two working shifts to cover extended hours of filling activity. As the filling time of maximum batch size is not more than 8 hours, hence two different shifts were covered during the study.
- Process performance qualification (PPQ): - PPQ has been performed for 03 commercial scale batches and for stability batches.
- Process Performance Qualification Batch Details were provided.

- **Product specification**
  - All the excipients are from bovine spongiform encephalitis (BSE) and transmissible spongiform encephalitis (TSE) free sources.
  - The specifications of all excipients were listed and found in compliance with IP/BP/EP/USP.
  - All in process testing procedures and CoAs were enclosed in this section.
  - No novel excipients are used in the formulation of Rabies Vaccine.
  - The drug product is analyzed as per Indian Pharmacopoeia (I.P), British Pharmacopoeia (B.P.) and WHO TRS No 941, 2007 Annex 2.
  - Overview of the analytical procedures for the testing of VaxiRab N (Purified Chick Embryo Cell Culture Vaccine) along with their validation reports were provided.
  - 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.

- **Reference Standards or Materials**
  - The In-House reference standard (batch number:RV90017) for determination of glycoprotein content was calibrated against WHO 7th International standard for rabies vaccine.
  - The certificate of analysis of reference standard and the detailed validation report were attached.

- **Container closure system**

- USP Type I Vial that is Flint Tubular vial has been considered as a container for Rabies Vaccine drug product.
- The suitability of the container closure system has been evaluated including Delamination studies of Glass Vials. The reports were provided.
- Component Details: Container: 3 mL, 13 mm Flint Tubular Vial USP-1. Closure: 13 MM, Blue BE2 aluminum Flip off Seal for VaxiRab N Injection. 13 mm grey bromobutyl Rubber Stopper.
- The standard operation procedures of all packing materials were attached.

- **Stability of the drug product**
  Based on available stability data:
  Approved Shelf Life:
  Finished product: 3 years
  Diluent: 5 years

  Approved Storage Conditions: Store in a refrigerator (2 °C - 8 °C). Do not freeze. Do not shake. Keep the vial in the outer carton in order to protect from light.

3. Non –clinical aspect:

- **VaxiRab N** is a sterile, freeze-dried, inactivated rabies vaccine that uses Pitman Moore strain and **is** indicated for active immunization against rabies virus infection in humans. It is WHO prequalified in February 2019.
- **Pharmacology:** No dedicated studies were conducted to assess the efficacy of VaxiRab N. However, the immunogenicity profiles, expressed as anti-rabies antibody titer, were evaluated in rats and rabbits as part of the repeated dose toxicity studies. The immunogenicity profiles revealed good antibody titers in all experimental groups at the end of the study period.
- **Pharmacokinetics:** Not applicable according to WHO guidelines on nonclinical evaluation of vaccines Annex 1 (TRS, No. 927, 2005).
- **Toxicology:** Single-dose toxicity studies concluded that the tested VaxiRab N ID & IM doses (3.5 and 10.5 IU/animal, respectively, in Swiss albino mice and 7 and 21 IU/animal, respectively, in Wistar rats) did not show any toxicity. From the repeat-dose toxicity studies results, it was evident that the ID & IM doses up to 3.5 and 10.5 IU/animal, respectively, did not show any toxicity in both NZW rabbits and Wistar rats. **Reproductive and Developmental Toxicity** (including range-finding studies and supportive toxicokinetics evaluations) is not applicable, according to the WHO Guideline on non-clinical testing of vaccines and Guideline on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004). No Stand-alone **local tolerance** study was performed but investigated within the toxicity studies.
  Overall conclusion: Based on the toxicology data, the nonclinical evaluation of this product supports its efficient and safe use in the proposed patient population.

4. Clinical aspect:

Clinical efficacy (immunogenicity) and safety of the product were demonstrated through 5 Clinical trials (Phase I, II & III);

Clinical Efficacy: (Clinical Immunogenicity analysis)

All subjects had an antibody titer of ≥ 0.5 IU/ml which is considered as a protective titer for rabies as per WHO specifications, which clearly indicates that Purified Chick Embryo Cell Culture Vaccine ($PCECV^{PM}$):

- is a highly immunogenic vaccine when **administered intramuscularly** for pre-exposure prophylaxis in healthy subjects as per the WHO schedule.
- is a highly immunogenic vaccine when **administered intramuscularly** in healthy volunteers on a simulated post-exposure prophylaxis regimen as per the WHO schedule.
- when **administered by intramuscular injection** in post-exposure animal bite (both category-II and III) cases, has excellent immunogenicity as per the established standards for Rabies Vaccines.
- when **administered intradermally** by Updated Thai Red Cross regimen (2-2-2-0-2) for simulated post-exposure prophylaxis in healthy volunteers (as per the post-exposure vaccination schedule as recommended by WHO), has excellent immunogenicity as per the established standards for Rabies Vaccines.

Clinical Safety:

- No "serious", "severe" or "unexpected" adverse event was reported.
- All adverse events reported of whatsoever nature, either local or systemic were "mild" to "moderate" intensity only. All these adverse events settled completely with/without symptomatic treatment.
- Further, there was no significant alteration in any of the general physical examination parameters or vital signs as assessed at each visit in any of the healthy adult volunteers.
- None of the adverse events reported led to discontinuation of the study.
- the majority of the volunteers were rated to have an "excellent" tolerability to the vaccine as per the 4- point assessment of tolerability scale.
- Accordingly, on the tolerability front, Purified Chick Embryo Rabies Vaccine $PCECV^{PM}$ was found to be excellently tolerated when administered intramuscularly or intradermally.

Benefit/ Risk discussion:

Based upon the results of phase I, phase II and phase III clinical trials, it can be concluded that the Purified Chick Embryo Rabies Vaccine ($PCECV^{PM}$) is safe & immunogenic. The immunogenicity was proved in the dose same as that recommended for immunization. Vaccine recipients had AEs similar to those reported in the published literature and the benefit associated with the receipt of this vaccine greatly outweighs the minimal risk associated with vaccination.

In conclusion, the overall benefit/risk of VaxiRab N is favorable for active immunization against rabies virus infection in humans for;

- **Pre-exposure vaccination (IM)**
- **Post- exposure vaccination in incomplete or unvaccinated persons (IM or ID)**

5. General Conclusion and Recommendations if any:

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