RABIES VACCINE, HUMAN I.P.
(Purified Chick Embryo Cell Culture Rabies Vaccine) [PCECV^{PM}])
VaxiRab N®

Summary of product characteristics as per Annexure C

1. NAME OF THE MEDICINAL PRODUCT

Rabies Vaccine, Human I.P. (Purified Chick Embryo Cell Culture Rabies Vaccine) [PCECV^{PM}]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lyophilized vial contains:

Inactivated rabies virus (Pitman Moore Strain)
Potency ≥ 2.5 IU
Virus is propagated in chick embryo fibroblast cell culture and Inactivated by β-propiolactone
Excipients: Gelatin, Human Albumin, Sucrose
Diluent: 1ml Sterile Water for Injections I.P.

3. PHARMACEUTICAL FORM

Drug Substance(s)

- Inactivated final bulk of rabies vaccine has been developed by classical method as per the WHO Technical report series no.824, 1992 & 941, 2007, Annexure 2 and Indian Pharmacopoeia.

Drug Product

- Rabies Vaccine (Purified Chick Embryo Cell Culture Vaccine) has been developed by classical method as per the WHO Technical report series no.824, 1992 & 941, 2007, Annexure 2 and Indian Pharmacopoeia.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunization against rabies.

a) Pre-exposure Prophylaxis (preventive, prior to exposure): Immunization prior to possible infection with rabies, particularly for vets, veterinary medicine students, animal keepers, hunters, forestry workers, animal handlers, butchers, personnel in rabies research laboratories, etc., or prior to visits to areas in which rabies in endemic (rabies infected areas).
b) Post exposure Prophylaxis (after exposure): Treatment after contact with animals which are rabid or suspected to be rabid, or after contact with an inoculated rabies carcass.

4.2 Posology and method of administration

Add the diluent (1 ml Sterile Water for Injections I.P) to the Lyophilized vaccine. The vaccine should be visually inspected both before and after reconstitution for any foreign particulate matter and / or change in physical appearance. The vaccine must not be used if any change in the appearance of the vaccine has taken place. A clear solution results after reconstitution of the freeze-dried powder with the clear and colorless diluent.

A) Pre-exposure vaccination:

Pre-exposure vaccination is indicated for persons at high risk of exposure (laboratory personnel, veterinarians, abattoir workers, police engaged in tasks in endemic area, animal dealers, animal handlers, workers in quarantine stations, zoologists and, in endemic areas, gamekeepers, hunters, forest rangers, forestry workers etc.). Pre-exposure vaccination is also recommended for persons (including children) who stay for an extended period (several months) in endemic areas and thus come into frequent contact with potentially rabid animals (dogs, cats, foxes, bats or other animal species at risk of rabies).

Intramuscular Route

Pre-exposure basic immunization consists of a series of three intramuscular injections of full one dose (1 ml) on days 0, 7 and 28 (or 21), given into the deltoid muscle, or in small children, in the anterolateral thigh but never in the gluteal region.

Seroconversion is checked 2-3 weeks after the last dose. It is routinely necessary in persons with suspected immunosuppression (through medication or disease) and in persons with a

high occupational risk of exposure. The titer of neutralizing antibodies should be checked every 6 months in persons at high occupational risk; in all other persons at continued risk, the titre should be determined every year. If the titre is inadequate (≤ 0.5 lU/mL), further booster doses are given until vaccination is successful.

B) Post - exposure measures in incomplete or unvaccinated persons:

1) Treatment of the wound

As first aid, the wound should be thoroughly cleansed with soap and water or with a detergent. A tetanus booster and antibiotic treatment may be indicated in some cases.

2) Active vaccination with VaxiRab N®

Intramuscular Route

A series of 5 Intramuscular injections of 1 ml dose on days 0, 3, 7, 14 and 28 into the deltoid muscle, or in small children, in the anterolateral thigh, but never in the gluteal region. (WHO Technical Report series 2005, No 931)

The success of vaccination (≥ 0.5 lU/mI) in immunocompromised persons at high risk should be checked by measuring the titre on day 14. Patients with a titre that is less than 0.5 IU/ml should be given another two doses of vaccine simultaneously and as soon as possible. Further checks on the antibody titre should be made and further doses of vaccine should be administered as necessary.

Intradermal Route

This vaccine is of sufficient potency to allow its safe use in one of the WHO recommended intradermal post-exposure regimens in countries where relevant national authorities have approved the intradermal route for rabies Post-exposure treatment.

One intradermal dose comprises 0.1 ml of reconstituted vaccine.

For VaxiRab N® the administration schedule recommended in India in both non-immunized and fully immunized individuals is; the 2-site Intradermal WHO endorsed

regimen (known as Updated Thai Red Cross intradermal regimen, "2-2-2-0-2" regimen) that prescribes 1 injection of 0.1 ml at 2 sites on day 0, 3, 7 and 28. Two different lymphatic drainage sites, usually the left and right upper arms are selected. Updated Thai Red Cross intradermal regimen is endorsed by WHO.

It is essential that intradermal administration of VaxiRab N® be carried out only by medical staff trained in this technique in order to ensure that the vaccine is delivered intradermally and not subcutaneously. For the intradermal route a sterile syringe with fixed needle (insulin type) is preferred. Correct intradermal injection should result in a raised papule with an "orange peel" appearance.

If the vaccine is injected too deeply into the skin, and a papule is not seen, the needle should be withdrawn and reinserted nearby. In the event that a dose of vaccine is inadvertently given subcutaneously or intramuscularly, a new dose should be administered intradermally.

The intradermal route must not be used in the following instances:

- Individuals receiving long term corticosteroid or other immunosuppressive therapy or chloroquine,
- Immunocompromised individuals,
- Individuals, particularly children, with severe wounds, especially to the head and neck or presenting late for consultation.

Special Storage Conditions for Intradermal Usage

VaxiRab N® does not contain preservative; therefore, great care must be taken to avoid contamination of reconstituted vaccine. Vaccine may be used up to 6 hours after reconstitution provided it is maintained at 2 - 8° C. Unused vaccine must be discarded after 6 hours. Using aseptic technique, a dose of vaccine may be withdrawn from a vial and the remainder used for another patient provided that the vial is stored in a refrigerator between 2 - 8° C. A new sterile needle and syringe must be used to withdraw and administer each dose of vaccine for each patient to avoid cross infection.

Note: If dogs or cats suspected of having rabies remain healthy after an observation period of 10 days, or tissue tests show that the animal was not rabid, the active immunization can be stopped.

3) Passive Immunization with Human Rabies immunoglobulin

After a possible contamination with rabies virus through single or multiple bites or scratches, or as a result of contact of mucous membranes with saliva, post-exposure prophylaxis should be initiated with a dose of 20 lU/kg of Human rabies immunoglobulin. It is recommended that where practicable, as much of the dose as possible is infiltrated around the wound and the rest injected intramuscularly (into the gluteal region). A first dose of the rabies vaccine VaxiRab N® is given intramuscularly (deltoid region) at the same time. If human immunoglobulin is not available, anti-rabies serum of equine origin must be given in a dose of 40 lU/kg and infiltrated around the wound if possible. Before administering such a heterologous serum, an intradermal test injection must be given to check tolerability.

Rabies immunoglobulin is not necessary if the skin remains intact, scratches or grazes are small and have not drawn blood.

C) Post-exposure immunization in previously vaccinated persons

Persons who have already received a complete series of pre- or post- exposure vaccinations with VaxiRab N® or in whom an antibody titre of at least 0.5 lU/mI has been previously documented, are given only two intramuscular doses of VaxiRab N ® one on day 0 and the other on day 3 and do not require any rabies immunoglobulin.

Wounds should be thoroughly cleaned with soap and water or detergent. In some cases, a tetanus booster and antibiotic treatment are indicated.

Persons previously vaccinated with a vaccine of unknown potency and in whom no documented neutralizing antibody titer of at least 0.5 lU/mI can be demonstrated, should receive a complete course of post-exposure vaccination including rabies Immunoglobulin.

4.3 Contraindications

There are no absolute contraindications after exposure to rabies.

The vaccine should not be administered to subjects with a history of a severe hypersensitivity reaction to any of the ingredients in the vaccine and should receive an alternative rabies vaccine if a suitable product is available.

4.4 Special warnings and precautions for use

As with all vaccines, appropriate medical treatment should be immediately available for use in the rare event of an anaphylactic reaction to the vaccine.

It is advisable to use rabies vaccines derived from non-avian sources for persons with known sensitivity to avian proteins. If such vaccines are not available, all necessary preparations should be made to treat complications which might arise in the event of an anaphylactic reaction.

Do not administer by intravascular injection. If the vaccine is inadvertently administered into a blood vessel there is a risk of severe adverse reactions, including shock

4.5 Interaction with other medicinal products and other forms of interaction

VaxiRab N® can be given concurrently with other vaccines (particularly tetanus toxoid). No intervals need to be observed between other vaccinations. Different injectable inactivated vaccines should be administered into separate injection sites.

It is essential to check the antibody titer when vaccination is undertaken during treatment with immunosuppressants, and if necessary, to continue post-exposure immunization until the appearance of a protective antirabies antibody titer (≥ 0.5 lU/ml).

Administration of rabies immunoglobulin may be necessary for management but may attenuate the effects of concomitantly administered rabies vaccine. Therefore, it is important that rabies immunoglobulin should be administered once only for treating each at-risk exposure and with adherence to the recommended dose.

Concomitant ingestion of chloroquine for malaria prophylaxis can reduce the antibody formation after intradermal administration of rabies vaccine. Therefore, the pre-exposure vaccination with VaxiRab N® should be given by intramuscular route in persons using chloroquine in a concomitant manner.

4.6 Special Population

Pregnancy category C: Controlled studies in neither animals nor pregnant women are available. In life-threatening Indications, VaxiRab N® can be administered because the potential benefits outweigh the possible risks.

Lactation: Administration of VaxiRab N ® during breast-feeding has no negative effects on the child.

4.7 Effects on ability to drive and use machines

Effect of VaxiRab N® on ability to drive and use machines is not known.

4.8 Undesirable effects

- In rare cases, local reactions including lymphadenopathy may be observed.
- Transient fever can occur following vaccination.
- Despite the high degree of purity of the vaccine, there is a theoretical risk of inducing anaphylactic reactions in persons sensitized to avian proteins.
- Rabies vaccine may cause Erythema Multiforme.

4.9 Overdose

No experience is available on the consequences of over dosage.

5. PHARMACOLOGICAL PROPERTIES

The Inactivated virus contained in VaxiRab N® vaccine undergo phagocytosis by macrophages and is then transported with them into the reticuloendothelial tissue, where they stimulate the immune system to produce virus- neutralizing anti-rabies antibodies.

5.1 PHARMACODYNAMICPROPERTIES

VaxiRab N® has been evaluated in total of 5 pre-licensure studies (1 Phase I, 2 Phase II and 2 Phase III studies). In the various pre-licensure clinical studies of VaxiRab N®, all subjects who were considered for immunogenicity at various time points post-vaccination (day 14, day 28, day 90 or day 180) had an antibody titre above the seroprotective cut-off titre recommended by the WHO (0.5 IU/ml) which suggests that the vaccine generates a sufficient immune response for protection against the disease. The GMTs of antibodies at various time points were 6.4 to 26.4-fold higher than the WHO recommended seroprotective cut-off titre. Further, the antibody titres were also maintained above the WHO recommended seroprotective cut-off titre till 6 months (180 days) as assessed in one phase III clinical study.

With respect to the safety, all the adverse events reported in these studies were mild or moderate in intensity and resolved completely during the course of the study. There was also no serious adverse event reported in any of the studies

5.2 PHARMACOKINETIC PROPERTIES

Not applicable

5.3 Preclinical safety data

5.3.1 Animal Toxicology & Pharmacology:

Rabies Vaccine, Human I.P. (Purified Chick Embryo Cell Culture Rabies Vaccine) formulation developed by Zydus Life Sciences Ltd. has been adequately tested in toxicology studies, with two acute dose toxicity studies in mice and rats by intramuscular route & intradermal route and two repeat-dose studies in rats and rabbits by intramuscular route & intradermal route. No unexpected toxicity and safety concerns were identified in these non-clinical studies during in-life Phase and terminal Phase including histopathological evaluation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Cell Culture Concentrate
- Stabilizer Solution
- Beta Propiolactone (βPL)
- Sodium Hydroxide
- Water for Injection

6.2 Incompatibilities

- This product must not be mixed with other medicinal products.

6.3 Shelf life

- The expiry date of the vaccine is indicated on the label and carton of the product.

6.4 Special precautions for storage

Store at 2°C to 8°C.
Do not freeze. Protect from Light

Every packing shows an expiry date of VaxiRab N® and Diluent; the product should not be used after VaxiRab N® expiry date. Reconstituted vaccine should be used immediately or can be stored for up to 6 hours at 2-8°C as described in intradermal administration section.

6.5 Nature and contents of container

Vaccine is filled in flint tubular USP-I glass vial fitted with Bromo butyl Rubber stopper and sealed with aluminum flip off seal.

6.6 Special precautions for disposal

Used containers shall be disposed of either as per bio-medical waste disposal instructions of respective country or through autoclaving / incineration.

7. Details of manufacturer

Zydus Lifesciences Limited
Survey No. 417, 419 & 420
Sarkhej - Bavla N.H. No. 8A,
Moraiya,
Taluka: Sanand,
Dist. Ahmedabad – 382 210, Gujarat

8. MARKETING AUTHORISATION NUMBER(S)

Permission No. MF – 320/2011

9. DATE OF FIRST AUTHORISATION

16th Aug, 2011