12. Side Effects:

- Local reactions: pain, erythema, edema, pruritus, and induration at the injection site.
- Systemic reactions: fever, shivering, fainting, asthenia, headache, dizziness, arthralgia, myalgia, nausea.
- Exceptional cases of anaphylactic reactions are observed.

If you develop side effects mentioned above or any other undesirable effects, please inform your doctor.

Safety of INDIRAB® has been evaluated in three clinical trials; pain, swelling and fever were reported in 0.05% of subjects (20/389) and the incidence of the adverse events did not vary between the two groups of vaccines (P value >0.05). Itching was reported in 19 of 68 subjects receiving INDIRAB® via intradermal route as compared to 21 of 66 subjects receiving the reference vaccine; the P value was non-significant.

13. Pharmacological properties

13.1 Immune response

Three multi-centre clinical studies with 661 subjects were conducted in India to evaluate the safety and immunogenicity of INDIRAB® in comparison to a reference Rabies vaccine. The studies included both pre-exposure and post-exposure studies.

As per WHO requirement and National guidelines, new Rabies vaccines are approved for intradermal (ID) use only after generating sufficient clinical data on their immunogenicity when administered similar route. A simulated post-exposure study in adult healthy volunteers was undertaken wherein the vaccine was administered via intra dermal route to demonstrate the immunogenicity and safety in comparison with a reference Rabies vaccine.

(A) In the pre-exposure study for intramuscular administration, subjects were randomized to receive INDIRAB® and reference vaccine in 3:1 ratio. Seroconversion was achieved on day 14 in all subjects. Immunogenicity as measured by Rabies Virus Neutralizing Antibody (RVNA) titres achieved with INDIRAB® [GMT=6.1 IU/mL; 95% Confidence Interval (CI) 5.19, 7.17] was similar to reference vaccine [GMT=8.3 IU/mL; 95% CI 5.59, 11.03] on day 35 with no statistically significant difference between the groups. Seroprotection (titres>0.5 IU/mL) was maintained in all subjects upto day 365.

(B) In the post-exposure study with 187 subjects with suspected rabid animal bites, INDIRAB® was administered intramuscularly. RVNA was measured on day 14, 28 and 90; all subjects sero converted by day 14, and sero protection levels were maintained throughout the follow up period.

(C) A clinical trial was undertaken to demonstrate immunogenicity of INDIRAB® when administered by WHO approved intra dermal schedule of vaccination. INDIRAB® was administered to 68 subjects and reference vaccine administered to 66 subjects. The GMTs of RVNA was similar in both groups on day 14, 28 and 90 with no statistically significant difference (p value <0.05); GMT in test group was 3.36 IU/mL (95% CI; 3.26, 3.14) and 3.26 IU/mL (95% CI; 3.14, 3.76) in reference group. Seroconversion was observed in all subjects on day 14 and sero protection (>0.5 IU/mL) was sustained throughout the follow up period of 90 days.

14. Storage:

Do not use the vaccine after expiry.
Vaccine vial and diluent should be stored at +2°C to +8°C; the reconstituted vaccine should be used as soon as possible, but at least within 8 hours.
Shake well before use.
Do not freeze.
Keep out of reach of children.

15. Shelf life:

Lyophilized vaccine: 36 months when stored at +2°C to +8°C
Diluent: 48 months when stored at +2°C to +8°C

16. Presentation:

Mono pack contains one vial of lyophilised vaccine, diluent and disposable syringe with needle.
Multi pack contains 10 vials of lyophilized vaccine and 10 ampoules of diluent. Separate syringes and needles to be used for IM/ID use.

Manufactured & Marketed by:

Bharat Biotech
Lead Innovation

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Ranga Reddy District - 500 078
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Rabies Vaccine, Human IP

(Purified Inactivated, Lyophilized Rabies Vaccine, prepared on Vero cells)

INDIRAB®

1. Name and description of the active immunizing agent

INDIRAB® is a chromatographically purified Vero cell Rabies vaccine (CPRV) containing ≥ 2.5 IU of purified beta propriolactone inactivated Rabies virus of PM strain prepared in Vero cells.

2. Composition:

Each vial of Reconstituted Rabies Vaccine contains:

Sl.No	Ingredients	Quantity
1	Purified BPL Inactivated Rabies virus(PM strain, Prepared in Vero cells)	≥ 2.5 IU
2	Thiomersal (as preservative) IP	0.01% (w/v)
3	Maltose	upto one immunizing dose
4	Human Albumin IP	upto one immunizing dose

Diluent composition

Each 1.0mL contains (0.3% w/v)
Sodium Chloride ..... 3.0 mg
Water for Injections ..... q.s to 1.0 mL

The 1.0 mL presentation is suitable for all WHO recommended Intramuscular / Intradermal pre-exposure & post-exposure vaccination schedules.

3. Pharmaceutical Form:

Lyophilized powder for injection with diluent ampoule.

4. Clinical Particulars

4.1 Therapeutic Indications:

INDIRAB® is indicated for active immunization against Rabies.

(A) Pre- Exposure Prophylaxis:

immunization **before** possible exposure to Rabies, especially in case of high risk professionals e.g. Veterinarians, Animal care personnel, Hunters, Doctors, Rabies Laboratory personnel, production personnel, Army personnel, Postmen and Children who are exposed to the risk of Rabies.

(B) Post-Exposure Treatment:

Immunization with Rabies Vaccine is part of post-exposure treatment of individuals after contact with animals that are rabid or suspected to be rabid.

5. Dosage

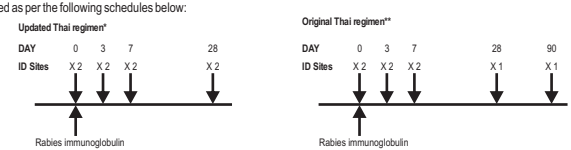
INDIRAB® may be used to vaccinate persons of any age.
INDIRAB® may be administered by intramuscular or intradermal routes.

Dose for children and adults: 1.0mL by intramuscular route.
Dose for children and adults: 0.1 mL per site by intradermal route (Updated Thai Regime).
The vaccination schedule should be adapted according to the category of exposure and the person's immune status against Rabies.

6. Method and Route of Administration:

Reconstitute the lyophilized vaccine with 1.0 mL of diluent supplied in ampoule and gently shake until the powder is completely suspended. The solution should be homogenous, clear and free from particles. Withdraw required quantity of the solution into a syringe for administration.

The vaccine must be injected immediately after reconstitution and the syringe must be destroyed after use. The reconstituted vaccine may be administered as per the following schedules below:



Intramuscular route: 1.0 mL of vaccine, administered intramuscularly in the deltoid muscle of adults and in the antero-lateral region of the thigh in young children respectively.
Intradermal route: Two doses of 0.1mL each is administered intradermally in each upper arm (over the left & right deltoids).When the vaccine is administered intradermally it causes a visible and palpable "bleb" in the skin.

In the event of a subcutaneous or an intramuscular injection, a new dose should be immediately administered intradermally in the adjacent site.

Do not inject in the gluteal region.
Do not inject intravascularly.

6.1 Pre-Exposure Immunization
This vaccination is recommended for prevention of Rabies in persons who are at a higher risk of exposure. All persons at a permanent risk, such as diagnostic, research and production laboratory staff working on Rabies virus, should be vaccinated. The recommended schedule is as per Table 1.

Table 1: Pre-Exposure Immunization Schedule (Intramuscular / Intradermal Administration)

1st dose	Day Zero
2nd dose	Day 7
3rd dose	Day 28
1st Booster dose	1 year later
2nd Booster dose	Every 5 years

6.2 Post-Exposure Treatment
Vaccination with Rabies vaccine should begin immediately after exposure to Rabies has either been confirmed or suspected. Other post-exposure treatment measures include first aid and local treatment of wound, and administration of Rabies immunoglobulin, if indicated.

The choice of immunization schedule for post-exposure prophylaxis is dependent on the type of wound or exposure and the status of the animal.

6.2.1 Immediate wound treatment
Immediate local treatment of all bite wounds and scratches that may be contaminated with Rabies virus is important. It is recommended to thoroughly wash the wound with ample water and soap or detergent for 15 minutes and disinfect the site with 70% alcohol or tincture of iodine.

6.2.2 Post-Exposure Immunization
Post exposure vaccination must be administered under medical supervision as per schedule in Table 2, as per the recommendations listed in Table 3 (Exposure category).

The schedule includes 1.0 mL via intramuscular injection on D0, D3, D7, D14, D28 and D90 (Optional) **or** 0.1mL via intradermal injection on D0, D3, D7 and D28. Table below provides definition of category of exposure (I, II & III) and recommended treatment.

In the case of category III exposure (see Table 3), Rabies immunoglobulin must be co-administered with the Rabies vaccine.

Table 2: Post-Exposure Immunization Schedule (Intramuscular / Intradermal Administration)

Dose	Route of Administration	
	Intramuscular	Intradermal
1st dose	Zero day (D0)	Zero day (D0)
2nd dose	Day 3 (D3)	Day 3 (D3)
3rd dose	Day 7 (D7)	Day 7 (D7)
4th dose	Day 14 (D14)	Day28 (D28)
5th dose	Day 28 (D28)	-
6th dose	Day 90 (optional)	-

Post-Exposure Immunization by Intradermal route: Updated Thai Red Cross ("2-2-2-0-2") regimen:
One dose of vaccine, in a volume of 0.1mL is to be administered intradermally at two different lymphatic drainage sites, usually in the deltoid muscle on the left and right upper arm, on days 0,3,7and 28.

The potency, immunogenicity & safety data as obtained from clinical trials allow safe use of this vaccine through intradermal route. (WHO guide for Post Exposure Prophylaxis, TRS 931, 2005), WHO/EMC/ZOO/96.6, WHO recommendations on Rabies Post-Exposure Treatment and Correct Technique of Intradermal Immunization against Rabies)

Table-3: WHO guide for Post Exposure vaccination of non-immunized subjects against Rabies

Exposure Category	Type of contact with a suspect rabid domestic or wild animal or animal unavailable for observation	Recommended Treatment
1	Touching or feeding of animal, licks on intact skin, contact with animal but definitely not with its saliva	None; if reliable case history is available. In case of uncertainty, vaccine may be administered as per schedule in Table 1.
2	Nibbling of uncovered skin, minor scratches, superficial bites (except on head, neck shoulder girdle, arms or hands) or abrasions without bleeding/ licks on broken skin	Vaccination must begin immediately as per schedule in Table 2. Stop treatment if animal remains healthy throughout the observation period of 10 days or if animal is killed humanely and is found to be negative for Rabies by appropriate laboratory examination.
3	Single or multiple major transdermal bites/scratches especially on head, face, neck shoulder girdle, arms or hands or contamination of mucous membrane with saliva (i.e. licks on broken skin), contact with bats	Immediately initiate Rabies vaccination along with Rabies immunoglobulin (passive immunization). Administer Rabies vaccine as per table 2 schedule. Stop treatment if animal remains healthy throughout the observation period of 10 days or if animal is killed humanely and is found to be negative for Rabies by appropriate laboratory examination.

6.2.3 For Category III bites, additional passive immunization day 0 is recommended with Rabies immunoglobulin (RIG).
The dose for Human Rabies Immunoglobulin (HRIG) is 20 IU/Kg body weight and for Equine Rabies Immunoglobulin (ERIG) and F (ab') 2 products 40 IU/Kg body weight. The total recommended dose should not be exceeded. The full dose of Rabies immunoglobulin, or as much as is anatomically feasible, should be administered into and around the wound site. Any remainder should be injected intramuscularly at a site distant from the site of active vaccine administration. Multiple needle injections into the wound should be avoided. If the correct dose of Rabies immunoglobulin is too small to infiltrate all wounds, as might be true of a severely bitten individual, it can be diluted in physiological buffered saline to ensure greater wound coverage. If RIG is unavailable on first visit and vaccine injection, its administration can be delayed by a maximum of 7 days from date of that first injection.

6.2.4 Vaccination of subjects already immunized against Rabies:
If the vaccine is administered to the subject within 5 years of previous immunization (cell culture Rabies vaccine), two booster doses of vaccine are to be administered via intramuscular or intra dermal route on days 0 &3. If vaccine was administered more than 5 years ago, vaccination schedule as per Table 2 may be followed.

In practice, if the last booster dose was administered more than 5 years ago or if the vaccination is incomplete, the person is considered to have an uncertain immunization status.

7.Additional Information:
Wound should not be sutured for 7 days, and RIG should always be administered before suturing. Antibiotics can be prescribed and tetanus vaccination status should be checked as per institutional anti-tetanus procedures.

8.Drug Interactions and other Interactions:
Corticosteroids and immunosuppressive treatment may interfere with antibody production and cause the vaccine to fail. In order to avoid possible drug interactions, any ongoing medical treatment should be reported to your doctor. In case of contraindications, risks related to vaccination should be weighed against those of a possible infection and if necessary, the vaccination should be carried out after taking appropriate precautions.

9.Contraindications:
This vaccine must NOT be used in the following cases:

Pre-Exposure
- It is preferable to postpone vaccination in severe febrile infection, acute disease, and progressive chronic disease.
- Known hypersensitivity to any of the ingredients of the vaccine.

Post-Exposure
- Due to the fatal progression of declared Rabies infection, there are **absolutely no contraindications** to curative anti-Rabies vaccination.

10.Pregnancy and Lactation:
Adequate Human data on use during pregnancy and adequate animal reproductive studies are not available. It is recommended that pre-exposure prophylaxis be postponed during pregnancy and lactation. During pregnancy and lactation, it is recommended to ask your doctor for advice before using the vaccine.

In post-exposure vaccination, pregnancy is not a contraindication to vaccination since Rabies is a fatal disease.

11.Special Warnings:
- Intradermal injections must be administered by staff trained in this technique.
- Do not inject intravascularly. Make sure that the needle does not enter a blood vessel.
- Do not use same syringe for administering Rabies vaccine and immunoglobulin. Do not inject the vaccine and immunoglobulin at the same site.
- Keep out of reach of children.
- Vaccine vial and diluent should be stored at +2°C and +8°C; the reconstituted vaccine should be used as soon as possible.