4.9.3 Study 2 (Post-exposure Intramuscular):
A total of 188 (aged 5–55 years) cases bitten by suspect rabid animal and having either category II or III exposure participated in the study, out of which 141 subjects were given **INDIRAB®** vaccine (potency 6.08 IU/dose) and 47 subjects were given Verorab vaccine (potency >2.5 IU/dose). Majority of animal bite victims in India belong to this age group. Category III patients were administered rabies immunoglobulin (Equine rabies Immunoglobulin) as per WHO recommended dose. Both test and reference vaccines were reconstituted with 0.5 mL diluent. Vaccine was administered intramuscularly on days 0, 3, 7, 14 and 28 and blood samples of 5mL were collected on days 0, 14, 28 and 90
All subjects tested for RVNA had 100% sero-converted in both the vaccine groups by day 14. More than adequate levels of RVNA titers were observed on days 28 and 90 and there was no significant difference in the titers on all days tested. These people were alive and quite healthy after 1-year observation period.

4.9.4 Study 3 (Simulated post-exposure intradermal)
As very good antibody titers were obtained after the conventional IM schedule of vaccination, study was conducted with intradermal (ID) route to determine if Indirab vaccine is equally immunogenic.
A total of 134 healthy volunteers (aged 18–55 years) participated in the study, 68 were given **INDIRAB®** vaccine (potency 5.7 IU/dose) and 66 subjects were given Verorab vaccine (potency >2.5 IU/dose). Vaccine was administered ID as per updated Thai Red Cross Regimen(2-2-2-0-2) on days 0, 3, 7 and 28 and blood samples of 5mL were collected on day 0, 14, 28 and 90.
The results showed that Indirab was immunogenic as Verorab even when administered by ID route of vaccination. The incidence of side effects was negligible, did not differ significantly between the two groups and did not require medication in all three studies.
INDIRAB® has proved to be safe and immunogenic by both IM and ID routes. In addition, this is the only purified Vero cell Rabies vaccine that is purified by chromatographic technique, reducing the cellular DNA content to less than 100 pg/dose.
The quantitative test for correlate of protection for Rabies is neutralization and the level required is 0.5 IU/mL.

4.10 Post-Marketing Experience
A phase 4 study was conducted to evaluate the safety and immunogenicity of 0.1mL **INDIRAB®** reconstituted with 1 mL diluent, administered intradermally at two upper arms on day 0, 3, 7 and 28 using updated THAI Red Cross regimen in post-animal bite cases. Equirab immunoglobulins were used in category III bite cases along with the vaccine administration. The common local symptoms were itching, pain and swelling at the injection site in the category III bite subjects who have received rabies immunoglobulin injection along with **INDIRAB®**. The general symptoms reported were fever & body pain. The symptoms resolved in 48 hours with symptomatic treatment. No adverse events were observed/ recorded during the first 30 minutes. There were no serious adverse reactions reported. None of the enrolled subjects were withdrawn from study for vaccine related adverse reaction.
The RFFIT assay was carried out at National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore with samples withdrawn on day 0, 14 and 90.The anti-rabies antibody titers were negative at baseline i.e., day 0. The day 14 and 90 anti-rabies titers by RFFIT analysis were above the minimum clinical protective levels of >0.5 IU/mL in all the subjects enrolled in the study. 100% of subjects both in the vaccinated and vaccine and rabies immunoglobulin injected sero converted by day 14 & maintained titers of >0.5 IU/mL up to day 90 (WHO specifies minimum antibody titers of 0.5 IU/mL as protective against rabies virus).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic Properties: Not applicable

5.2 Pharmacokinetic Properties: Evaluation of pharmacokinetic properties is not required for vaccines.

6. PHARMACEUTICAL PARTICULARS: Category: Vaccine
6.1 List of Excipients

Thiomersal IP	0.01% w/v
Maltose NF	upto 1 immunizing dose
Human Albumin IP	upto 1 immunizing dose

6.2 Incompatibilities: INDIRAB® must not be mixed in the same syringe 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 Storage: Vaccine vial and diluent should be stored at +2°C and +8°C; the reconstituted vaccine must be stored at +2°C and +8°C and be used within 6 hours from reconstitution.
Shake well before use. Do not freeze. Keep out of reach of children.

7. PRESENTATION
- Mono pack contains one vaccine vial, one diluent ampoule (0.5 mL or 1.0 mL) and one disposable syringe with needle.
- Multi pack contains 10 vaccine vials, 10 diluent ampoules (0.5 mL or 1.0 mL), separate syringes and needles to be used for IM/ID.

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Manufactured & Marketed by:

BHARAT BIOTECH
Lead Innovation

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For use by a Registered Medical Practitioner or Hospital or Laboratory only

Rabies Vaccine, Human IP

(Purified, Inactivated, Lyophilized Rabies Vaccine Prepared on Vero Cells)

INDIRAB®

1. NAME AND DESCRIPTION OF THE MEDICINAL PRODUCT
INDIRAB® is Purified Inactivated, Lyophilized Rabies Vaccine, prepared from Pitman Moore strain of Rabies Virus grown in Vero cells.
The potency of one single human dose of **INDIRAB®** vaccine is ≥ 2.5 IU of rabies antigen.

The freeze-dried vaccine is reconstituted immediately before use as stated on the label to give a clear or slightly opalescent suspension. The vaccine meets WHO requirements.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition: After reconstitution, 1 vial contains:	
Vero Cell derived purified BPL inactivated Pitman Moore strain of Rabies virus potency	≥2.5 IU
Thiomersal IP	NMT 0.01% w/v
Maltose NF	upto 1 immunizing dose
Human Albumin IP	upto 1 immunizing dose

Each 0.5 mL Diluent ampoule contains:
Sodium Chloride IP ..... 1.5 mg
Water for Injections IP ..... q.s. to 0.5 mL
OR

Each 1.0 mL Diluent ampoule contains:
Sodium Chloride IP ..... 3 mg
Water for Injections IP ..... q.s. to 1.0 mL

3. PHARMACEUTICAL FORM
Lyophilized powder to be reconstituted for injection.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications:
INDIRAB® is indicated for active immunization against rabies in individuals of all ages.

A) Pre-exposure prophylaxis: Immunization **before** possible exposure to rabies, especially in case of high-risk individuals e.g. veterinarians, animal care personnel, hunters, healthcare professionals, laboratory personnel, personnel involved in manufacturing of rabies virus vaccine, army personnel, postmen and children who are exposed to the risk of rabies.

B) Post-exposure Treatment: Immunization **after** exposure/ contact with suspected rabid animal.

4.2 Posology, Schedule and Method of Administration
INDIRAB® vial containing lyophilized powder should be reconstituted with the accompanying either 0.5 mL or 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. If not clear, the vaccine should not be administered. 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.

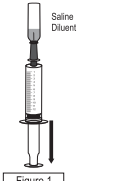

Figure 1

Figure 1. Clean and break the neck of the ampoule. Withdraw Saline from the ampoule.

Figure 2

Figure 2. Transfer the Saline into the lyophilized vaccine vial.

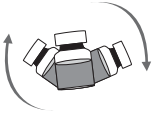
Figure 3

Figure 3. Shake the vial well.

Figure 4

Figure 4. After reconstitution, withdraw dose volume of reconstituted vaccine and administer intramuscularly or intradermally.

INDIRAB® is administered by intramuscular or intradermal route.

- **Intramuscular route:** Single dose for children and adults: 0.5mL or 1.0 mL in the deltoid muscle of adults and in the antero-lateral region of the thigh in young children <2 years of age.

- **Intradermal route:** Single dose for children and adults: 0.1 mL per site in the upper arm. Vaccine administered intradermally using a tuberculin/insulin syringe must raise a visible and palpable "bleb" in the skin. In the event that a dose of vaccine is inadvertently given subcutaneously or an intramuscular injection, a new dose should be administered intradermally immediately in the nearby site.

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

The vaccination schedule should be adapted according to the category of exposure.

4.2.1 Pre-Exposure Prophylaxis Schedule (Intramuscular/ Intradermal Administration)

1st dose	Day 0
2nd dose	Day 7
3rd dose	Day 28
1st Booster Dose	1 Year later
Booster Dose	Every 5 years

4.2.2 Post-Exposure Treatment
Vaccination with **INDIRAB®** should begin immediately after exposure to rabies which 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.

4.2.3 Immediate Wound Treatment
Immediate local treatment of all animal 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.

4.2.4 Post-Exposure Immunisation
Updated Thai Red Cross intradermal regimen (2 -2-2-0-2):
The schedule for the updated Thai Red Cross intradermal regimen is as follows: One dose of vaccine, in a volume of 0.1mL is given intradermally on the left andanother dose in the right upper arm (deltoids) separately on days 0,3, 7, and 28.

Dose	Day of Administration	Intramuscular (0.5 mL/1.0 mL)	Intradermal (0.1mL)
1st dose	Day 0	1 dose	2 doses (1 dose on each arm)
2nd dose	Day 3	1 dose	2 doses (1 dose on each arm)
3rd dose	Day 7	1 dose	2 doses (1 dose on each arm)
4th dose	Day 14	1 dose	—
5th dose	Day 28	1 dose	2 doses (1 dose on each arm)
6th dose	Day 90	(Optional)	—

4.2.5 WHO guide for Post-Exposure Vaccination of Non-Immunized Subjects against Rabies

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 4.2.1.
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 4.2.4. 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)	Immediately initiate Rabies vaccination along with Rabies immunoglobulin (passive immunization). Administer Rabies vaccine as per schedule in 4.2.4. 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.

4.2.6 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 intradermal route on Day 0 & 3. If vaccine was administered more than 5 years ago, vaccination schedule as per 4.2.4 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.

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

4.2.8 Special Warnings
- Intradermal injection 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 must be stored at +2°C and +8°C and must be used within 6 hours from reconstitution
- Epinephrine injection (1:1000) must be immediately available in case anaphylactic or other allergic reactions occur.

4.3 Contraindications
INDIRAB® should not be administered or repeated to persons known to be hypersensitive to any of the components.

4.4 Precautions
This vaccine must NOT be used in the following cases:

4.4.1 Pre-Exposure
It is preferable to postpone vaccination in severe febrile infection, acute disease, and progressive chronic disease.

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

4.5 Interactions with Other Medicinal Products
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 precautions and 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.

4.6 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. It is recommended to ask your physician for advice before using the vaccine.
In post-exposure vaccination, pregnancy is not a contraindication to vaccination since Rabies is a fatal disease. The benefits outweigh the risks.

4.7 Effects on Ability to Drive and Use Machines
No studies on the effect of **INDIRAB®** on the ability to drive and use machines has been performed.

4.8 Adverse Reactions
- Local reactions: pain, erythema, edema, pruritus, and induration at the injection site may occur.
- Systemic reactions: fever, shivering, fainting, asthenia, headache, dizziness, arthralgia, myalgia, gastro -intestinal disorders (nausea. abdominal pain) may occur in some cases.
- Exceptional cases of anaphylactic reactions may be observed.

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

4.9 Pre-Clinical & Clinical Trial Experience
4.9.1 To assess the safety of the vaccine, a 28-day subcutaneous toxicity study in Swiss albino mice with **INDIRAB®** was conducted. Two groups of mice, each compromising of 10 males and 10 females, were injected with control and **INDIRAB®** on days 0, 7, 14, and 21. Animals were observed for clinical signs of the toxicity for 28 days. There were no significant changes observed due to administration of **INDIRAB®** in the animals at the doses tested, when repeatedly injected on day 0, 7, 14, and 21 when compared with control.
Several multi-centric clinical studies[1] were conducted in India to evaluate the safety and immunogenicity of **INDIRAB®** who were pre- and post-exposed to animal bites.

4.9.2 Study 1 (Pre-exposure intramuscular)
A total of 239 healthy volunteers aged between 10 and 65 years participated in the study;180 were given **INDIRAB®** vaccine (potency 5.84 IU/dose) and 59 subjects were given Verorab vaccine (potency >2.5 IU/dose). Both test and reference vaccines were reconstituted with 0.5 mL diluent provided along with the vaccine vial. Vaccine was administered intramuscularly on days 0, 7and 28 and blood samples of 5mL were collected on days 0, 28 and 35. All subjects in both vaccine groups attained more than adequate levels of RVNA titers by day14 which increased substantially on day 35. Though the geometric mean titer (GMT) on day 14 in the Verorab group was higher, it was not statistically significant ($p > 0.05$). In some of the subjects, whose serum was tested at 1-year period, adequate antibody titers were seen in both test and reference groups.