| Bharat Biotech Lead Innovation | ARTWORK APPROVAL | |
|---|---|---|
| Product: **INDIRAB® (0.5mL / IM)** | Name of the artwork: **Package Insert** | Market: **Export** |
| Artwork code: **62ANPIE.02** | Change control No: | Item code: |

# INDIRAB® Package Insert

Safety of **INDIRAB®**, when given intramuscularly, has been evaluated in two clinical trials; adverse events such as pain and swelling at injection site, fever were present in 5% (9/180) and in 6% (9/141) of subjects in pre-exposure and post-exposure studies respectively. However, the incidence of adverse events was not statistically significant when compared with a reference vaccine in each of these studies.

**14. PHARMACOLOGICAL PROPERTIES**
**14.1 Immune response**

Two multi-centre clinical studies with 427subjects 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.

(A) In the pre-exposure study with 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 that with reference vaccine [GMT=8.3 IU/mL; 95% CI 5.59, 11.03] on day 14with no statistically significant difference between the groups. Seroprotection (titres>0.5 IU/mL) was maintained in all subjects up to day 365, post vaccination.

(B) In the post-exposure study with 188 subjects with suspected rabid animal bites, **INDIRAB®** was administered intramuscularly. RVNA was measured on days 14, 28 and 90; all subjects sero-converted by day 14, and sero protection levels were maintained throughout the follow up period.

**15. STORAGE:**
Vaccine vial and diluent should be stored at +2°C to +8°C; the reconstituted vaccine must be stored at +2°C to +8°C and used within 6-8 hours from reconstitution (WHO Expert Consultation on Rabies – 2013).

Shake well before use.
Do not freeze.
Keep out of reach of children.
Do not use the vaccine after expiry.

**16. SHELF LIFE:**
The expiry date of the vaccine is indicated on the label and carton of the product.

**17. PRESENTATION:**
Mono pack contains one vial of lyophilized 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 with multi-pack vials.

Last Revision date: February 2018

*Manufactured by*

Bharat Biotech
Lead Innovation

**Bharat Biotech International Ltd.,**
Genome Valley, Shameerpet Mandal,
Medchal District - 500 078,
Telangana, India.
e-mail: feedback@bharatbiotech.com,
www.bharatbiotech.com

62ANPIE.02



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

## Rabies Vaccine BP

Purified Inactivated, Lyophilized Rabies Vaccine, Prepared in 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 dose (0.5mL) of **INDIRAB®** vaccine is equal to or greater than 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. It does not contain preservative. The vaccine meets WHO requirements.

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each dose (0.5mL) of reconstituted vaccine contains:
Vero cell derived Purified BPL Inactivated Pitman Moore strain of Rabies Virus, Potency ≥ 2.5 IU
Thiomersal BP ..... NMT 0.01% w/v
Maltose NF ..... upto 1 immunizing dose
Human Albumin BP .....upto 1 immunizing dose

**Each 0.5 mL Diluent ampoule contains:**
Sodium Chloride IP/BP ..... 1.5mg
Water for Injections IP/BP ..... q.s to 0.5mL
The 0.5 mL presentation is suitable for all WHO recommended intramuscular, pre - exposure & post - exposure vaccination schedules against animal bites.

**3. PHARMACEUTICAL FORM:**
Lyophilized powder for injection

**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. Reconstitution**
**INDIRAB®** is to be reconstituted only with the accompanying saline diluent. The reconstituted vaccine should be a clear and colorless solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

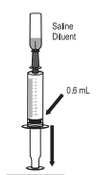

Figure 1

**Figure 1.** Cleanse both vial stoppers. Withdraw 0.6 mL of Saline from diluent vial.

Figure 2

**Figure 2.** Transfer saline diluent into the lyophilized vaccine vial.


Figure 3

**Figure 3.** Shake the vial well

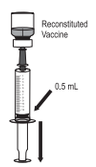

Figure 4

**Figure 4.** After reconstitution, withdraw 0.5 mL of reconstituted vaccine and administer **intramuscularly.**



| Date: | 23-02-2018 | INDIRAB® Package Insert artwork for Export | | | | | | | Colors CMYK/Pantone |
|---|---|---|---|---|---|---|---|---|---|
| Specs | Product | Size | Strength | Paper | GSM | Fold | | | 90% Black C |
| | INDIRAB® | 210 X 145 mm | 0.5mL Vial | News Print | 45±10 | H-1 V-2 105x37 mm | | | |
| Approval | QA - RA | Corp comm | Packing Incharge | HOD - QC | HOD Production | Marketing (Domestic / Export ) | MED | HOD - QAO | |
| Signature | | | | | | | | | |

**6. DOSAGE**

**INDIRAB®** is used to vaccinate persons of any age. **INDIRAB®** is administered by intramuscular route.

Dose for children and adults: 0.5mL by intramuscular route. The vaccination schedule should be adapted according to the category of exposure.

**7. Method and Route of Administration:** Reconstitute the lyophilized vaccine with 0.5 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 should be administered as per the schedules listed below in Tables 1 and 2.

Intramuscular route: 0.5 mL of vaccine, administered intramuscularly in the deltoid muscle in adults and in the antero-lateral region of the thigh in young children.

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

**7.1 Pre-Exposure Prophylaxis**

Pre-exposure 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 Prophylaxis Schedule (Intramuscular Administration)**

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

**7.2 Post-Exposure Treatment**

Vaccination with Rabies vaccine 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.

**7.2.1 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.

**7.2.2 Post-Exposure Immunization**

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

The schedule includes 0.5 mL via intramuscular injection on D0, D3, D7, D14, D28 and D90. 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 Administration)**

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

**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 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. |

**7.2.3 For Category III bites, additional passive immunization on day 0 is recommended with Rabies immunoglobulin (RIG).**

For all category **III** bites, additional passive immunization on day 0 is recommended with Rabies Immunoglobulin (RIG). Please refer to the package insert of RIG product from the respective manufacturer for its use.

**7.2.4 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 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 should be considered to have an uncertain immunization status.

**8. 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.

**9. DRUG INTERACTIONS AND OTHER INTERACTIONS:**

Corticosteroids and immunosuppressive treatment may interfere with antibody production and may 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/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.

**10. PRECAUTIONS/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 diseases.
- 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.

**11. 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.

**12. SPECIAL WARNINGS:**

- 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 to +8°C and must be used within 6-8 hours from reconstitution (WHO Expert Consultation on Rabies – 2013).
- Vaccine contains traces of neomycin sulphate and may cause cutaneous sensitization or other allergic reactions.
- Epinephrine injection (1:1000) must be immediately available in case anaphylactic or other allergic reactions occur.

**13. SIDE EFFECTS:**

- 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 pains) may occur in some cases.
- In exceptional cases, anaphylactic reactions may be observed.

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





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