1. NAME OF THE MEDICINAL PRODUCT

Brand Name: **ABHAYRAB®**

Generic Name**:** Rabies Vaccine, Human I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Abhayrab® is a freeze dried, purified inactivated Rabies vaccine containing inactivated Rabies Virus (L. Pasteur 2061/Vero Strain propagated in Vero cells). Thiomersal is added as preservative. Rabies is an acute viral disease which causes fatal encephalomyelitis in virtually all the warm blood animals including man. The virus can be found in wild and domestic animals and is transmitted to other animals and humans through their saliva (i.e., bites, scratches, licks on broken skin and mucous membrane).

Composition:

Purified lyophilized Rabies antigen derived from Rabies virus (L. Pasteur 2061/ Vero Strain propagated in Vero Cells) inactivated.

Potency ≥ 2.5 I.U Per vial

Stabilizers: Maltose and Human Albumen…q.s

Preservative: Thiomersal 0.015% w/v

3. PHARMACEUTICAL FORM

Abhayrab® vaccine is Freeze dried vaccine appears as creamy white crystalline pellet. The vaccine should be reconstituted with the Diluent (Sodium chloride injection 0.9%w/v) supplied along with the vaccine. On reconstitution the final vaccine appears as clear solution free of particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

a) A Pre Exposure Vaccination (Prior to exposure to rabies virus): This is indicated for

- All high risks groups of personnel such as veterinarians, Municipal workers, Medical and paramedical personnel, Forest and Zoo personnel, Hunters, Animal handlers, Laboratory personnel working with suspected rabies materials and pet owners.
- Persons staying or visiting in rabies endemic areas

b) Post Exposure Vaccination (after suspected exposure to rabies virus): This is indicated for

- Persons after contact/ bite by as suspected case of or a rabid animal.
- See Table 1 for WHO recommendations for course of action to be taken post contact with a suspected or confirmed rabid animal.

Table 1. Guide for post exposure treatment (W.H.O. TRS931 Recommendations)

Category	Type of contact with a suspect or confirmed rabid domestic or wild [a] animal, or animal unavailable for testing	Type of Exposure	Recommended Post-Exposure Prophylaxis
I	Touching or feeding of animals, licks on intact skin	None	None, if reliable case history is available
II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Minor	Administer vaccine immediately [b] Stop treatment if animal remains healthy throughout an observation period of 10 days [c] or if animal is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques
III	Single or Multiple transdermal bites or scratches, licks on broken skin contamination of mucous membrane with saliva (i.e. licks) Exposures to bats [d]	Severe	Administer rabies immunoglobulin and vaccine Immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days or if animal is found to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques

[a] Exposure to rodents, rabbits and hares seldom, if ever, requires specific anti-rabies post-exposure prophylaxis.

[b] If an apparently healthy dog or cat in or from a low-risk area is placed under observation, the situation may warrant delaying initiation of treatment.

[c] This observation period applies only to dogs and cats. Except in the case of threatened or endangered species, other domestic and wild animals suspected as rabid should be humanely killed and their tissues examined for the presence of rabies antigen using appropriate laboratory techniques.

[d] Post-exposure prophylaxis should be considered when contact between a human and a bat has occurred unless the exposed person can rule out a bite or scratch, or exposure to a mucous membrane.

Reference: WHO Technical Report Series 931, WHO expert consultation on rabies.

4.2 Posology and method of administration

Intramuscular:

- *Pre-Exposure:* 0.5 mL of reconstituted vaccine on 0, 7 and 21 or 28th day followed by annual booster vaccination.

- *Post-Exposure:*
  - For a new case: 0.5 mL of reconstituted vaccine on days 0, 3, 7, 14 and 28.
  - For previously immunized individuals: They should receive a two booster series on days 0 and 3. The administration of passive immunization is not required.
  - For immunocompromised individuals: They should definitely receive rabies immunoglobulin in addition to a full post-exposure vaccination series as listed above evening in category II bite.

Intradermal:

- Pre-Exposure: Two doses of reconstituted vaccine of 0.1 mL each on 0, 7 and 21 or 28th day followed by annual booster vaccination.
- Post exposure:
  - For a new case: 2-site Intradermal Regimen (2-2-2-0-2): Two doses of reconstituted vaccine of 0.1 mL each on days 0, 3, 7 and 28. Vaccine administered intradermally raises a visible and palpable bleb in the skin. Intradermal injections must be carried by staff trained in this technique.
  - For previously immunized individuals: They should receive a two booster series on days 0 and 3. The administration of passive immunization is not required.
  - For immunocompromised individuals: They should definitely receive rabies immunoglobulin in addition to a full post-exposure vaccination series as listed above even in Category II bite .

Method of administration:

Reconstitution:

- Prior to use, reconstitute the freeze dried vaccine with diluent as per the pack supplied.

For Intra muscular:

Reconstitute the freeze dried vaccine with 0.5 mL diluent (0.9% w/v Sodium Chloride inj. IP) only.

In case of 1.0 mL diluent is supplied, reconstitute the freeze dried vaccine with 0.5 mL out of 1.0 mL diluent, the remaining 0.5 mL diluent should be discarded.

For Intra Dermal:

Reconstitute the Freeze dried vaccine with 0.5 mL or 1.0 mL diluent as per the pack supplied.

It is recommended that the reconstituted vaccine should be used immediately. However in case of unforeseen delay it should be stored at +2°C to +8°C and

used within 6 hours. All unused reconstituted vaccine at the end of 6 hours must be discarded.

Dosage and Administration:

- For intramuscular: Reconstituted vaccine of 0.5 mL to be administered by deep intramuscular route in the deltoid region in adults & in anterolateral aspect of thigh in children.

- For intradermal: Reconstituted vaccine of 0.1 mL to be administered at two different lymphatic drainage sites usually the left and upper arm. Vaccine administered intradermally must raise a visible and palpable "bleb" in the skin. Aseptic technique and a sterile needle and syringe must be used to draw up vaccine for each patient and for each dose. The remainder can be used for another patient, provided that the vial is stored in a refrigerator at +2°C to +8°C and the total content is used within 6 hours.

4.3 Contraindications

- In case of Pre-Exposure prophylaxis, rabies vaccination is contraindicated in case of severe febrile illness, acute or chronic progressive illness and known hypersensitivity to any of the components of vaccine.
- As Rabies is a fatal disease, there are no contraindications in case of post exposure vaccination.

4.4 Special warnings and precautions for use

Precautions:

- Concurrent use of immunosuppressive agents like corticosteroids should be avoided as it may hamper in the development of protective antibodies.
- In case of Category III bites as per WHO classification (See Table 1) antirabies immunoglobulin is recommended along with the first dose of rabies vaccination.
- Use intramuscular route in cases of severe or delayed cases of category III bite on day '0'.
- Delay in the commencement of post-bite therapy, incomplete and irregular therapy can cause failure of vaccination and protection against rabies.
- If anti-malarial chemo prophylaxis (e.g. with Chloroquine) is being given concurrently, vaccine should be administered through intramuscular route only.
- Vaccine should never be administered into the gluteal region, where absorption is unpredictable.

- As with any injectable vaccine, hypersensitivity or anaphylaxis can occur with Abhayrab® and thus Inj. Adrenaline (1: 1000) and other anti-histaminics should be ideally available during vaccination.
- Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine.

Warnings:

- The vaccine should never be given by intravascular route
- Same Syringe or site should not be used for administering the Immunoglobulin and the vaccine.

4.5 Interactions with other medicinal products and other forms of interactions

In patients receiving immunosuppressive therapy or antimalarial medications or those with congenital or acquired immunodeficiency, the response to the vaccination may be reduced or absent.

Administration of immunosuppressive medication and antimalarial compounds during post-exposure treatment should be avoided.

Rabies immunoglobulins should be administered at the recommended dose only. The immunoglobulins should neither be given at higher nor lower doses than those recommended, nor should they be repeatedly administered, as this may attenuate the effects of concomitantly administered rabies vaccine.

Time intervals to be observed before other immunizations are given

It is not necessary to observe an interval with regard to other vaccinations.

4.6 Pregnancy and lactation

In suspected post exposure, considering the severity and fatal implications of the disease, the pregnancy is not a contraindication.

4.7 Effects on ability to drive and use machines

Post-vaccination weakness/ dizziness have been frequently reported. This can temporarily affect ability to drive and use machines.

4.8 Undesirable effects

Local minor events: Mild pain, erythema, induration, pruritus, rash, oedema at the site of injection

Systemic mild events: Mild fever, headache, myalgia, malaise

Very rarely: High fever, gastrointestinal disorders, lymphadenopathy, arthritis and anaphylaxis.

4.9 Overdose

No symptoms of overdose are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-Code: J07B G01

A protective antibody titre is achieved in nearly all subjects after a series of three injections of Abhayrab® if given according to recommended schedules.

Injection of the vaccine induces production of an antibody titer which markedly exceeds

0.5 IU/ml serum. This threshold is considered to provide adequate immunogenicity. As the antibody concentration slowly falls, booster doses are required to maintain antibody levels above the acceptable level of 0.5 IU/ml.

Pre-exposure Immunisation

The immunogenicity of Abhayrab® has been demonstrated in clinical trials conducted in India and Philippines. When administered according to the recommended immunization schedule (days 0, 7, 21 or 28), 100% of subjects attained an adequate titer of 0.5 IU/ml by day 28 or earlier.

Persistence of antibody titres ≥ 0.5 IU/ml for 2 years after immunization with Abhayrab® has been proven to be common in clinical trials.

Post-exposure Immunization

Various clinical studies in persons exposed to rabies virus have demonstrated that Abhayrab® , when used in the recommended post-exposure WHO schedule of 5 intramuscular injections of 0.5 ml (days 0, 3, 7, 14, 28) or 4 intradermal doses at 2 sites each with 0.1 ml of reconstituted vaccine (two ID sites each on days 0, 3, 7 and 28), provided adequate titers of neutralising antibodies (> 0.5 IU/ml) in 100% of patients within 14 days and that was found to be maintened in patients on day 28 - 90. Very similar results were obtained in several studies with healthy volunteers who had been given the WHO recommended post-exposure regimen ("simulated" post-exposure immunisation).

In clinical trials involving Abhayrab® patients with previous history of immunization with anti rabies vaccine demonstrated a good and quick immune response with > 4 fold increase in anti body titers at day 14.

Immediate and thorough wound cleansing with foaming soap and water, appropriate schedule and number of doses applied to the correct vaccination site (deltoid area) and passive immunization with Rabies Immunoglobulin (RIG) within appropraiate time line and at all indicated sites are essential to treatment success.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Toxicology

This vaccine conforms to WHO requirements.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Human Serum Albumin (25% w/v)
- Maltose (50% w/v)
- Thiomersal (7.5% w/v)

6.2 Incompatibilities

Do not mix with Rabies Immunoglobulin in the same syringe.

6.3 Shelf life

The shelf-life of the vaccine is 3 years.

Abhayrab® should not be used after the expiry date printed on the pack and container.

The vaccine should be used immediately after reconstitution.

While being used for intradermal dose for more than one person, the reconstituted vaccine should be used within 6 hours of opening and residual, if any, must be discarded appropriately.

6.4 Special precautions for storage

Abhayrab® should be stored at +2 to +8° C.

6.5 Nature and contents of container

Each mono carton (combo pack) contains:

- One Freeze dried vaccine vial
- One pack insert
- One ampoule containing 0.5mL/ 1.0 mL sterile diluent for reconstitution
- One sterile disposable syringe with needle
- Alcohol swab

6.6 Instructions for use/handling

The lyophilisate should be reconstituted immediately using the diluent supplied, and carefully agitated prior to injection. The reconstituted vaccine should be used immediately.

Dispose any vaccine unused within 6 hours of opening appropriately.

7. MARKETING AUTHORISATION HOLDER

Human Biologicals Institute
(A division of Indian Immunologicals Limited)
Survey No. 281 to 284 and 321, Biotech Park Phase – III,
Karakapatla Village, Mulugu Mandal,
Medak District – 502 281
Andhra Pradesh, INDIA.

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

September, 2013

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