SUMMARY OF PRODUCT CHARACTERISTICS

Abhayrab-PF®
[ATC-Code: J07BG01]

January 2023

Manufactured by

HUMAN BIOLOGICALS INSTITUTE
(A division of Indian Immunologicals Ltd)
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Brand Name: Abhayrab-PF®

Generic Name: Rabies Vaccine, Human I.P.

2. QUALITATIVE AND QUANTITATIVE 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 Albumin: q.s.

Diluent for reconstitution: 0.9% w/v Sodium Chloride Inj. I. P. (0.5 ml)

3. PHARMACEUTICAL FORM

Lyophilized (freeze-dried) powder and diluent for reconstitution. A clear colourless solution results after reconstitution of the lyophilized powder with the accompanying diluent.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Active immunization against rabies.

a) Pre-exposure Vaccination (Prior to exposure to rabies virus)

Particularly recommended for high-risk groups of people such as:

- Laboratory staff handling the virus and infected material
- Clinicians and persons attending to human rabies cases
- Veterinarians, veterinary students
- Animal handlers and catchers
- Wildlife wardens, forest officials
- Quarantine officers; and
- Travellers from rabies free areas to rabies endemic areas

b) Post-exposure vaccination (after known/ suspected exposure to rabies virus):

Recommended for persons after contact/ bite by a suspected case of or a rabid animal and/or persons suspected to have been exposed to live rabies virus.

[See Table 1 for W.H.O recommendations for course of action to be taken after contact with a suspected or confirmed rabid animal.]

4.2. Posology and method of administration

Reconstitution:

Prior to use, reconstitute the lyophilized vaccine with the 0.5 ml diluent supplied. Any reconstituted vaccine should be used as soon as possible.

Dosage and Administration:

Reconstituted vaccine of 0.5 ml to be administered by deep intramuscular route in the deltoid region in adults and in anterolateral aspect of thigh in children.

The vaccine should never be administered by intravascular route.

PRE-EXPOSURE IMMUNIZATION SCHEDULE

One immunization dose (0.5 ml of the reconstituted vaccine) to be administered by deep intramuscular route on days: 0, 7 and 21 or 28 ('0' being the day of receiving the first dose of vaccination).

Booster Doses

Only people whose occupations put them at continual or frequent risk of exposure should receive periodic booster doses (0.5 ml of the reconstituted vaccine to be administered by deep intramuscular route) whenever the rabies virus neutralizing antibody titre drops below 0.5 IU/ml.

POST-EXPOSURE TREATMENT

A. Unimmunized or Previously Incompletely Immunized Individuals:

One single dose (0.5 ml) of vaccine to be administered by deep intramuscular route each on days 0, 3, 7, 14 and 28 ('0' being the day of receiving the first dose of vaccination).

Rabies immunoglobulin should be administered preferably as soon as possible after initiation of post exposure prophylaxis in all cases of category III bites but not beyond 7 days from the first dose of vaccination. In immunocompromised cases, even category II bites require administration of rabies immunoglobulin.

B. Previously Fully Immunised Individuals:

Patients who have previously received a complete course of primary vaccination (pre- or postexposure) should receive only two doses of Abhayrab-PF® as described below:

One dose of 0.5 ml of the reconstituted vaccine to be administered by deep intramuscular route on days 0 and 3.

Administration of rabies immunoglobulin is not required in previously fully immunized individuals (with proof of the immunization).

C. *Immunocompromised Persons***:**

Immunocompromised individuals or individuals receiving chloroquine-based antimalarial treatment or long-term corticosteroid or other immunosuppressive therapy should receive

vaccination by intramuscular route only and not by intradermal route. They should be vaccinated with one dose of vaccine (0.5 ml) to be administered by deep intramuscular route on days 0, 3, 7, 14 and 28.

The immunocompromised individuals should receive rabies immunoglobulin in all category II and III bites.

4.3. Contraindications

- In case of Pre-Exposure prophylaxis, rabies vaccination is contraindicated in severe febrile illness, acute or chronic progressive illness and known hypersensitivity to any of the components of the 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

Warnings:

- *The vaccine should never be administered by intravascular route.*
- Same Syringe or site should not be used for administering the Immunoglobulin and the vaccine.
- Keep out of reach of Children.

Precautions:

- Concurrent use of immunosuppressive agents like corticosteroids should be avoided as it may hamper the development of protective antibodies.
- In case of category III bites as per WHO classification (see Table 1), anti-rabies immunoglobulin is recommended along with the first dose of rabies vaccination, it has to be administered with a different syringe & needle and at a site different and away from the site of vaccination.
- Intramuscular route must be used in cases of inmmunocompromised/ immunosuppressed individuals.
- Immunocompromised/ immunosuppressed individuals should also receive RIG (Rabies Immunoglobulin) even in Category II bites in addition to full post exposure vaccination series.
- Delay in the commencement of post-bite therapy, incomplete and irregular therapy can cause failure of vaccination and inadequate protection against rabies.
- Vaccine should never be administered into the gluteal region, where absorption is unpredictable.
- As with any injectable vaccine, hypersensitivity or anaphylaxis can occur with Rabies vaccine and thus Inj. Adrenaline (1: 1000) and other medications including anti-histaminics should be readily available during vaccination.

- Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine.
- The vaccine recipient should be kept under medical supervision for at least 30 minutes after vaccination to monitor for any undesirable effects.

4.5. Interaction with other medicinal products and other forms of interaction

- 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. This, administration of corticosteroids or other immunosuppressive medication and antimalarial compounds during post-exposure treatment should be avoided.
- Rabies immunoglobulin should be administered at the recommended dose only. The immunoglobulin should neither be given at higher nor lower doses than recommended, nor should it be repeatedly administered, as this may attenuate the effects of concomitantly administered rabies vaccine.

4.6. Safety in Fertility, Pregnancy and Lactation

In suspected cases of post exposure, considering the severity and fatal implications of the disease, pregnancy and lactation are not contraindications for vaccination with Abhayrab-PF® (Rabies Vaccine, Human I.P.).

4.7. Effects on ability to drive and use machines

Post-vaccination dizziness has been reported after use of Anti Rabies Vaccines. This can temporarily affect ability to drive and use machines. In a clinical study, antirabies vaccines, including similar vaccine Abhayrab were found to be safe, immunogenic and protective.

4.8. Undesirable effects

Like all medicines, Abhayrab-PF® vaccine may also have undesirable/ adverse effects which include the following:

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

Systemic mild events: Mild fever, headache, myalgia, malaise, nausea, dizziness.

Very rarely: High fever, gastrointestinal symptoms, lymphadenopathy, erythema multiforme, rash, arthritis and anaphylaxis.

4.9. Overdose

There has been no report of overdose with Abhayrab-PF® **(**Rabies Vaccine, Human I.P**)**.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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Pre-exposure Immunisation

The immunogenicity of Abhayrab® (which varies from Abhayrab-PF® by the only factor that it contains thiomersal as a preservative in addition) 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 anti-rabies antibody titer of 0.5 IU/ml by day 28 or earlier.

In a Phase I clinical trial, subjects received 3 doses by intramuscular route on day 0, 7 and 28. No serious adverse event was reported during the trial period. Mild pain at the injection site was the only adverse event reported in a few volunteers which subsided within 24-48 hours. The geometric mean titers were 17.29 IU/ml and 19.25 IU/ml on 14th and 35th day post vaccination respectively.

In a Phase II clinical trial subjects in the age group of 22 to 50 years were enrolled in two groups who received Abhayrab as Pre-exposure prophylaxis. A total of 60 volunteers (Group 1) who had no history of prior anti-rabies vaccination were administered 3 doses of Abhayrab (reconstituted to 0.5 ml) intramuscularly on days 0, 7 and 28. Another 32 subjects (Group 2) who had the history of prior anti-rabies vaccination received a single booster dose of Abhayrab. The mean serum antibody titers of <0.25 IU/ml and 8.33 IU/ml were noted on day 0 in volunteers of Group 1 and 2 respectively. Post vaccination, the Group-1 volunteers showed geometric mean antibody titers of 12.69 IU/ml and 18.19 IU/ml on 14th and 35th day respectively. In Group-2 volunteers, geometric mean serum antibody titers were 38.85 IU/ml and 22.14 IU/ml on 14th and 35th day post vaccination respectively. No serious adverse reaction was noticed in any of the volunteers during the course of clinical trial. Pain at the injection site was the only adverse event reported in a few volunteers which subsided within 24-48 hours.

In a Clinical Study carried out in a single center in Philippines 73 healthy volunteers had received intradermal Pre-exposure prophylaxis with Abhayrab vaccine (one dose of 0.1 ml administered intradermally on either deltoid on days 0, 7 and 28). The geometric mean concentration values were 3.30 IU/ml and 4.37 IU/ml on days 14 and 28, respectively. The adverse events reported were redness at the injection site (38.4%), itching at the injection site (20.5%), pain at the injection site (1%) and fever (1.4%) all of which were of mild intensity.

Post-exposure Immunization

Various clinical studies in persons exposed to rabies virus have demonstrated that Abhayrab® (which varies from Abhayrab-PF® by the only factor that it contains thiomersal as a preservative in addition) when used in the recommended post-exposure WHO schedule of 5 intramuscular injections of 0.5 ml (days 0, 3, 7, 14 and 28) provided adequate anti-rabies antibody titers of neutralising antibodies (> 0.5 IU/ml). Similar results were obtained in studies with healthy volunteers who had been given the WHO recommended post-exposure regimen (or 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 at day 14.

- In a Phase II clinical trial, subjects in the age group of 6 to 40 years were enrolled. A total of 12 subjects with Class II exposure (Group A) received Abhayrab vaccine (reconstituted to 0.5 ml) by intramuscular route rand 16 subjects with Class III exposure (Group B) received Abhayrab vaccine by intramuscular route and rabies immunoglobulin as per WHO guideline. The mean serum antibody titers of Group A on day 0, 14, 30, and 90 post vaccination were <0.25 IU/ml, 10.83 IU/ml, 14.16

IU/ml, and 5.81 IU/ml respectively. The mean serum antibody titers in Group B on day 0, 14, 30, and 90 post vaccination were <0.25 IU/ml, 8.37 IU/ml, 13.62 IU/ml and 4.84 IU/ml respectively. No serious adverse reaction was noticed in any of the volunteers during the course of clinical trial. The adverse events reported were pain at the injection site, irritation at the injection site, fatigue and pyrexia.

- In a Phase III clinical trial carried out to assess the safety, immunogenicity and efficacy of Abhayrab, enrolled a total of 230 subjects between 3 and 60 years of age. Seventy-five subjects were of category II exposure (Group A) who were administered Abhayrab (reconstituted to 0.5 ml) by intramuscular routeand 155 subjects were of category III exposure (Group B) who received Abhayrab vaccine by intramuscular route as per WHO regimen along with rabies immunoglobuins. For Group A, GMT values were < 0.5 IU/ml , 13.58 IU/ml and 7.04 IU/ml on day 0, 14 and 90 respectively. For Group B, GMT values were < 0.5 IU/ml , 12.76 IU/ml and 8.84 IU/ml on day 0, 14 & 90 respectively. Pain at the injection site was the only adverse event reported in a few volunteers which subsided within 24-48 hours.

- In a Clinical Study carried out in a single center in Philippines 76 healthy subjects had followed the modified Thai Red Cross post exposure prophylaxis ID regimen (2-2-2-0-2) using a dose of 0.1 ml Abhayrab vaccine each given intradermally on both deltoids on days 0, 3, 7, and 28. The GMC values were 3.73 IU/ml and 4.82 IU/ml on days 14 and 28 respectively. The adverse events reported were redness at the injection site (38.4%), itching at the injection site (20.5%), pain at the injection site (1%) and fever (1.4%) all of which were of mild intensity.

- In a study carried out at Anti Rabies Vaccination Clinic of VSS Medical College Hospital, Orissa, India 100 subjects between 18 to 70 years of age presenting within 24 hours of WHO category II or III exposure to known or potentially rabid animals were recruited. The subjects were followed up for 365 days long study period with a grace period of 15 days. Seventy-seven patients had exposure of category III and 23 patients of category II. All the category III patients were co-administered ERIG (Equine rabies immunoglobulin). Each patient received two 0.1 ml injection of Abhayrab PVRV intradermally over the deltoid area on days 0, 3, 7 & 28 according to the Updated-TRC Regimen. The overall GMT of anti-rabies antibody titers for both the groups were 0.35 IU/ml, 5.01 IU/ml, 7.81 IU/ml, 4.12 IU/ml and 2.15 IU/ml on days 7, 14, 28, 90 and 365 respectively. The adverse events reported were mild pain at the injection site (58%), swelling at the injection site (23%), erythema at the injection site (11%), itching at the injection site (12%), echymosis at the injection site (2%), headache (12%), fever (8%), dizziness (4%), malaise (7%), nausea (2%) and regional adenopathy (1%). No serious adverse reactions were identified and reported during the one year follow up period.

- In a prospective unicentric randomized single blind study comparative trial Abhayrab vaccine reconstituted to 1 ml was administered through Intradermal route as per updated Thai Red Cross regimen (2-2-2-0-2) in healthy volunteers as a simulated post-exposure study. In total, 53 subjects received the Abhayrab vaccine group out of whom 42 completed the study and were included in immunogenicity analysis. On day 0, all the 42 subjects were having < 0.5 IU/ ml of antibody titer. There was 100% seroconversion and seroprotection on day 14, day 28 and day 38. The GMT (n=42) on day 0 and day 38 were 0.12 IU/ ml and 60.39 IU / ml respectively. No Serious Adverse Events (SAEs) were recorded in the study. The adverse events reported were pain at the injection site, rash at the injection site, fever, headache, body pains, weakness, drowsiness and giddiness.

- In a multicentric study carried out by ICMR (Indian Council of Medical Research), responses to different intradermal TCARVs (which also includes Abhayrab vaccine) were compared with that of French PVRV (Aventis) administered intramuscularly on 0, 3, 7, 14 and 28 days. All the vaccines administered intradermally were well tolerated. No adverse drug reactions were reported from any of the vaccinated volunteers and none of the volunteers was withdrawn from the trial on account of vaccine related reasons. All the volunteers who received Abhayrab PVRV were sero-protected on days 14, 28 and 90.

- In a Clinical Study carried out in a single center in Vietnam evaluated immunogenicity and safety of Abhayrab in Post Exposure regimens administered by intradermal route in 100 healthy volunteers aged between 18-66 years. The subjects were administered intradermal doses (0.1 ml each on deltoid area) on days 0, 3, 7, and 28. GMT values on 28^{th} and 180^{th} day was 2.618 IU/ml and 0.695 IU/ml respectively. The local adverse events were itching (17%), redness (10%), swelling (3%) and pain (6%). Similarly, the systemic adverse events were headache (13%), fatigue (12%), erythema (9%), fever (5%), joint pain (2%), myalgia (6%) and dizziness (6%). The frequencies of these adverse events gradually decreased with subsequent vaccinations. Most of these AEs were mild and occurred within first three days post-vaccination. No SAEs were reported.

- A PMS study for safety evaluation was carried out for Abhayrab vaccine reconstituted to 1 ml, when administered by either intramuscular route or intradermal route in category II animal exposure subjects in India. In this prospective, open label, two arm, single centric study, a total of 120 subjects with Category II exposure were enrolled into the study. Out of them, 111 subjects completed the study as per the protocol as nine subjects were lost-to follow up. Subjects recruited in the first arm received one dose of Abhayrab reconstituted to 1 ml by intramuscular route on days 0, 3, 7, 14 and 28 as per ESSEN regimen. In the second arm, the subjects received two doses of 0.1 ml of Abhayrab reconstituted to 1 ml administered intradermally, one on each deltoid region on days 0, 3, 7 and 28 as per Updated Thai Red cross regimen. The subjects were followed up for 7 days post last dose of vaccination. At the end of the study, a total of 87 mild or moderate local and systemic adverse events were reported (33 in intramuscular route group and 54 in intradermal route group) in the study. No serious adverse event was reported during the study period. Among the local adverse events, in intramuscular route group, 18 (30%) subjects were having pain at the injection site and it was the only local adverse event observed. In intradermal route group as well, pain at the injection site was the most common local adverse event and was found in 13 (21.7%) subjects followed by local redness in 12 (20%) and local itching in 8 (13.3%) subjects. Among the systemic adverse events, in intramuscular route group, fever was the most common and was found in 7 (11.7%) of the subjects followed by body pains in 3 (5%), headache in 3 (5%), backache in 1 (1.7%) and tingling sensation in the lower limbs in 1 (1.7%) of the subjects. In intradermal route group fever was the most common systemic AE and was found in 7 (11.7%) of the subjects followed by body pains in 6 (10%), headache in 6 (10%), joint pain in 1 (1.7%) and dizziness in 1 (1.7%) of the subjects. The severity assessment of all the local and systemic adverse events showed that they were either mild or moderate only.

- In another prospective PMS study, safety evaluation was carried out for Abhayrab vaccine reconstituted to 1 ml when administered intradermally in category II animal exposure subjects in India. Out of 101 subjects, 96 (95 %) subjects completed the study as per the protocol. A total of 88 mild or moderate local and systemic adverse

events were reported in the study. No serious adverse event occurred during the study period. Among the local reactions, pain at the injection site was the most common and was found in 26 (25.7%) subjects followed by erythema at the injection site in 23 (22.7%) subjects and itching at the injection site in 16 (15.8%) subjects. Most of the local adverse events were mild except few which were assessed as moderate. No severe local adverse event was observed. Among the systemic reactions, fever was the most common adverse event and was found in 10 (9.9%) subjects followed by body pains in 6 (5.9%) subjects, headache in 3 (3%) subjects, joint pains in 2 (2%) subjects and dizziness in 2 (2%) subjects. All the systemic adverse events were assessed as mild by the Investigator. No moderate or severe systemic adverse event was observed.

- In a study by an independent investigator, nineteen patients aged 6–70 years, of both sexes, who presented at the outpatient clinic of the Civil Hospital, Ahmednagar, with a history of fox bite (all category 3 bites) were administered Abhayrab vaccine as part of post-exposure prophylaxis and followed up. All received one intramuscular dose each on days 0, 3, 7, 14, and 28. Six patients were treated with equine rabies antiserum (Central Research Institute), which was infiltrated around the wounds. Eleven patients were administered a booster dose of Abhayrab vaccine on day 1020 after the first dose The geometric mean antibody titre days 30, 90, 870, 1020, and 1050 were 3.16, 25.00, 0.77, 0.48 and 30.08 IU/ml respectively.

- Fourteen pregnant women who received rabies post-exposure prophylaxis (PEP) at the anti-rabies clinic (ARC) of Kempegowda Institute of Medical Sciences (KIMS, Bengaluru, India) were followed up for assessing the safety of modern rabies vaccines and equine rabies immunoglobulin (ERIG) in pregnancy. The women were in the age range of 18 to 28 years. Abhayrab was one of the vaccines used in this study. None of the pregnant women reported any adverse event to either vaccine or equine rabies immunoglobulin. All had safe vaginal deliveries, and in all cases, both the mother and the child were found to be healthy and normal.

[To achieve maximum possible protection, immediate and thorough wound cleansing with soap and running water, passive immunization with Rabies Immunoglobulin (RIG) whenever recommended and proper vaccination as per schedule are important.]

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Preclinical toxicology study data of Abhayrab-PF® found it confirming to the regulatory requirements.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Maltose
Human Albumin

Diluent for reconstitution: 0.9% w/v Sodium Chloride Inj. I. P.

6.2. Incompatibilities

Do not mix with Rabies Immunoglobulin in the same syringe.

6.3. Shelf life

36 months from the date of manufacture.

6.4. Special precautions for storage

- Keep out of reach of Children.
- Protect from light.
- Store and transport between +2°C and +8°C. However, storage temperature of -20°C for vaccine vial is recommendeded for long term storage.
- DO NOT FREEZE THE DILUENT.
- Discard the diluent ampoule if frozen.
- Do not keep the vaccine and the diluent along with other medicinal product including other vaccine(s) that could create confusion and lead to admixture.

6.5. Nature and contents of container

Abhayrab-PF® **(**Rabies Vaccine, Human I.P.**)** is available as Lyophilized vaccine in a transparent glass vial and 0.5 ml sterile diluent in a transparent glass ampoule.

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The lyophilzed powder should be reconstituted immediately prior to administration using the diluent supplied. Please refer section 4.2 for further details.

Disposal: As per the applicable Biomedical Waste Disposal guidelines/ rules.

7. MARKETING AUTHORISATION HOLDER

Human Biologicals Institute
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Survey No.: 281-284 and 321, Biotech Park,
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Web:www.indimmune.com

8. MARKETING AUTHORISATION NUMBER

The Marketing Authorization Number is country specific. In India, the country of origin, the Marketing Authorization Number is: 01/MD/TS/2016/V/G.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of First Authorization in India, the country of origin: 11 May 2018.

10. DATE OF COMPILATION OF THE TEXT

December 2023.

Table 1: Appropriate rabies treatment based on different categories of exposure

Category of exposure	**Type of exposure to a domestic or wild animal suspected or confirmed to be rabid or animal unavailable for testing**	**Recommended post-exposure prophylaxis**
Category I	Touching or feeding animals, licks on intact skin (no exposure)	None, if reliable case history is available[a] (in case of uncertainty, vaccine to be administered)
Category II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding (exposure)	Administer vaccine immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days[b] or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques. Treat as category III if bat exposure involved[c].
Category III	Single or multiple transdermal[d] bites or scratches; contamination of mucous membrane or broken skin with saliva from animal licks; exposures due to direct contact with bats (severe exposure).	Administer rabies vaccine immediately, and rabies immunoglobulin, preferably as soon as possible after initiation of post-exposure prophylaxis. Rabies immunoglobulin can be injected up to 7 days after administration of first vaccine dose. Stop treatment if animal remains healthy throughout an observation period of 10 days or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques.

(Based on the WHO TRS-1012)

[a] If an apparently healthy dog or cat in or from a low-risk area is placed under observation, treatment may be delayed.

[b] This observation period applies only to dogs and cats. Except for threatened or endangered species, other domestic and wild animals suspected of being rabid should be euthanized and their tissues examined for the presence of rabies antigen by appropriate laboratory techniques.

[c] Bat rabies has not been conclusively proven in India and hence exposure to bats does not warrant treatment[1].

[d]Bites especially on the head, neck, face, hands and genitals are category III exposures because of the rich innervation of these areas.