SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Proprietary Name: Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S

Non-Proprietary Name*:* Rabies Vaccine Inactivated (Freeze-Dried)

Rabies Vaccine Inactivated (Freeze dried) RABIVAX-S is a sterile, purified inactivated rabies vaccine prepared on vero cells. Rabies Vaccine Inactivated (Freeze-dried) RABIVAX-S is freeze dried and is provided with diluent (Sterile Water for Injections I.P SWFI) (1 dose of powder in vial and 1 ml of diluent SWFI in ampoule). The vaccine has the appearance of a white dry cake. The vaccine conforms to the World Health Organization (W.H.O.) requirements.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 1 ml contains:

Component	Quantity/dose	Specification	Active/ Non-active	Reason for inclusion
Purified Rabies Antigen (Rabies virus Pitman-Moore strain 3218- VERO adapted and grown on Vero cells, inactivated by using β propiolactone)	Not less than 2.5 IU	In-house	Active	Immunogen
Glycine	40 mg	IP/BP/Ph.Eur	Non-active	Stabilizer
Sucrose	40 mg	BP/Ph.Eur	Non-active	Stabilizer
HSA	10 mg	IP/BP/Ph .Eur/ USP/In-	Non-active	Stabilizer

3. PHARMACEUTICAL FORM

Lyophilized vaccine to be reconstituted with Diluent-Sterile Water for Injections I.P.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S is indicated for the prevention of rabies in children and adults. It can be used before or after exposure, as a primary immunization or as a booster dose.

a) Pre-Exposure prophylaxis

Pre-exposure vaccination should be offered to subjects at high risk of contamination by the rabies virus. This vaccination is particularly recommended for veterinarians, veterinary medicine students, animal keepers, hunters, forestry workers, animal handlers, butchers, personnel in rabies research laboratories etc., children at high risk of exposure or prior to visits to areas in which rabies is endemic.

b) Post-Exposure prophylaxis

Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S is indicated in post-exposure prophylaxis of rabies infection, when given to individuals with suspected rabies exposure. Rabies Vaccine Inactivated (Freeze-Dried) must always be used as per recommendations of the World Health Organization (WHO), depending on the type of contact with a suspected rabid animal.

Category	Type of contact	Recommended treatment
I	Touching or feeding animals, licks on the intact skin	No treatment is required
II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Immediate vaccination
III	Single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin, exposure to bats	Immediate vaccination and administration of immunoglobulin

For all categories, immediate washing and flushing of all wounds and scratches is recommended. If indicated tetanus prophylaxis should also be given with tetanus toxoid. Treatment should be started as early as possible after exposure, but in no case should it be denied to exposed persons whatever time interval has elapsed.

4.2. Posology and method of administration

Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S should be reconstituted only with the entire contents of the diluent supplied (Sterile Water for injections I.P.) using a sterile syringe and needle, with gentle shaking the dried cake is easily dissolved. After reconstitution the vaccine should be used immediately. The vaccine vial monitor for this type of vaccine is attached to the vial cap and should be discarded when the vaccine is being reconstituted. The diluent and reconstituted vaccine should be inspected visually for any foreign particulate matter and / or

variation of physical aspects prior to administration. In the event of either being observed, discard the diluent or reconstituted vaccine.

For adults and children aged ≥2 years, the vaccine should always be administered in the deltoid area of the arm; for children aged <2 years, the anterolateral area of the thigh is recommended. Rabies vaccine should not be administered in the gluteal area, as the induction of an adequate immune response may be less reliable.

Intradermal regimen may be used for people with category II and III exposures in countries where the Intradermal route has been endorsed by national health authorities.

a) Pre-Exposure prophylaxis

The following schedule should be followed for pre-exposure prophylaxis in high-risk populations.

Route	Dose	Number of Doses	Schedule
Intramuscular	1 ml	3	Day 0, 7 and 21 or 28
Intradermal	0.1 ml	3	Day 0, 7 and 21 or 28

Periodic booster injections are recommended as an extra precaution only for people whose occupation puts them at continual or frequent risk of exposure. For people who are potentially at risk of laboratory exposure to high concentrations of live rabies virus, antibody testing should be done every 6 months. Those professionals, who are not at continual risk of exposure through their activities, should have serological monitoring every 2 years. Because vaccine-induced immunity persists in most cases for years, a booster should be administered if rabies virus neutralizing antibody titres fall to < 0.5 IU/ml.

b) Post-Exposure prophylaxis

In order to remove as much of the rabies virus as possible, immediately cleanse the wound with soap and wash thoroughly with water. Then treat with alcohol (70%) or an iodine tincture. The following schedule should be followed for post-exposure prophylaxis in previously unimmunized individuals.

Route	Dose	Number of Doses	Schedule
Intramuscular	1 ml	5	Day 0, 3, 7, 14 and 28
Intradermal	0.1 ml + 0.1 ml	4	Day 0, 3, 7 and 28

For Intradermal route, four doses should be administered (2 injections of 0.1 ml at 2 different sites) as per the Updated Thai Red Cross regimen (2-2-2-0-2) as given above.

In those previously immunized by complete vaccination schedule (pre-exposure or post-exposure prophylaxis), 2 doses of 1 ml given by intramuscular route or 2 doses of 0.1 ml by Intradermal route on Day 0 and Day 3 are recommended.

In cases of Category III exposures and of category II exposures in immunodeficient patients, human rabies immunoglobulin (20 IU/kg) or equine rabies immunoglobulin (40 IU per kg) should be given in conjunction with Rabies Vaccine on Day 0. If anatomically feasible, the full dose of rabies immunoglobulin should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly at a site distant from vaccine administration. Rabies immunoglobulin may be diluted to a volume sufficient for all wounds to be effectively and safely infiltrated.

If rabies immunoglobulin is not available at the time of the first vaccination, it must be administered no later than 7 days after the first vaccination since later administration would result in interference with immune response of the vaccine.

4.3. Contraindications

a) Pre-exposure prophylaxis

In case of fever or an acute illness, vaccination should be postponed. In case of previous severe reaction to any components of the vaccine, RABIVAX-S is contraindicated.

b) Post-exposure prophylaxis

Because of the life-threatening risk of rabies, there are no contraindications to the administration of post-exposure prophylaxis using RABIVAX-S.

The Intradermal route must not be used in the individuals receiving long term corticosteroid or other immunosuppressive therapy or chloroquine for malaria treatment or prophylaxis and in immunocompromised individuals. Such individuals may have a reduced response to intradermal rabies vaccination and should instead receive the vaccine intramuscularly.

The vaccine may contain traces of neomycin. Anaphylactic or anaphylactoid reactions to neomycin, history of anaphylactic or anaphylactoid reactions are absolute contraindications.

4.4. Special warnings and special precautions for use

Do not administer vaccine by intravascular route. Immunoglobulins and rabies vaccine should not be combined in the same syringe or injected at the same site. If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., adrenaline) and provide supportive care as required.

The possibility of allergic reactions in individuals sensitive to components of the product should be evaluated. Adrenaline hydrochloride Solution (1:1000) and other appropriate agents should be readily available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs as per the current recommendations.

Special care should be taken to ensure that the product is not injected into a blood vessel. Under no circumstances should Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S be administered in the same syringe or at the same site as rabies immunoglobulin.

A separate sterile needle and syringe must be used for each individual patient to prevent the transmission of infectious agents. Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S must not be administered intravenously. As with all preparations given intramuscularly, bleeding complications may be encountered in patients with bleeding disorders.

Special precautions for the Intradermal route
It is essential that Intradermal administration of Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S be carried out only by medical staff trained in this technique in order to ensure that the vaccine is delivered Intradermally and not subcutaneously.

For the Intradermal route, a sterile syringe with fixed needle (insulin type) is preferred. Correct Intradermal injection should result in a raised papule with an "orange peel" (peau d'orange) appearance. If the vaccine is injected too deeply into the skin, and a papule is not seen, the needle should be withdrawn and reinserted nearby. If papule is not seen after 2 successive attempts, the patient should be given the dose intramuscularly.

Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S does not contain a preservative; therefore, great care must be taken to avoid contamination of reconstituted vaccine. Vaccine may be used up to 6 hours after reconstitution provided it is maintained at 2°C to 8°C. Unused vaccine must be discarded after 6 hours. A new sterile needle and syringe must be used to withdraw and administer each dose of vaccine for each patient to avoid cross infection.

4.5. Interactions with other medicinal products and other forms of interaction
Corticosteroids, chloroquine and other immunosuppressive treatments can interfere with the immune response of the vaccine and lead to the failure of the vaccination. Immunoglobulins must be administered at a different site from that of the vaccine (the contralateral side). The recommended dose of rabies immunoglobulin should not be exceeded nor should repeated doses of the same be administered once the vaccination course has been started since a higher dose could interfere with the immune response to rabies vaccine.

4.6. Pregnancy and lactation
Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S was safe, non-teratogenic and did not cause developmental toxicity in a prenatal developmental toxicity study in pregnant rats.

It is not known whether Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. It is also not known whether Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S is secreted in breast milk.

It is advisable to carefully weigh expected benefits against potential risks prior to pre- exposure prophylaxis with Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S during pregnancy and

breastfeeding. Because of the life-threatening risk due to rabies, pregnancy and lactation are not contraindications for post-exposure prophylaxis with Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S

4.7. Effects on ability to drive and use machines

Effect of Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S on ability to drive and use machines is not known.

4.8. Undesirable effects

Following adverse reactions have been reported during the phase II/III clinical trial of Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S administered with or without HRIG as per WHO recommended post-exposure prophylaxis regimen. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

System	Frequency	Adverse reactions
General disorders and administration site conditions	Very common (> 1/10)	Fever, asthenia, pain, induration, erythema, oedema, pruritus.
	Common (>1/100, < 1/10)	Shivering.
Nervous system disorders	Very common (> 1/10)	Headache, dizziness, faintness.
Musculoskeletal and Connective tissue disorders	Very common (> 1/10)	Arthralgia, myalgia.
Gastrointestinal disorders	Very common (> 1/10)	Abdominal pain.
	Common (>1/100, < 1/10)	Nausea.

Most of the events were of mild severity and resolved within 3 days without any sequelae. Incidence was comparable with the comparator licensed rabies vaccine.

4.9. Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S is a lyophilized, stabilized suspension of inactivated Pitman-Moore rabies virus strain (PM-Vero), adapted and grown on vero cells and inactivated by beta-propiolactone.

Pharmacotherapeutic group: Vaccines
Rabies, inactivated, whole virus, ATC code J07BG01.

Mechanism of Action
Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S stimulates the development of neutralizing antibodies against the rabies virus.

a) Pre-exposure Prophylaxis:
In a phase I clinical trial in previously unimmunized healthy adults, all subjects achieved a protective antibody titre (≥ 0.5 IU/ml) by day 21 of a primary series of three injections of Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S when given according to the recommended schedule of Day 0, 7 and 21 by the intramuscular and intradermal route.

b) Post-exposure Prophylaxis:
In a phase II/III clinical trial of Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S in patients with potential rabies exposure of category II and III, all subjects achieved a protective antibody titre (≥ 0.5 IU/ml) by day 7 (with only 2 doses) of a primary series of five injections of Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S when given according to the WHO recommended schedule of Day 0, 3, 7, 14 and 28 by the intramuscular injection of 1 ml each OR a primary series of four injections of Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S when given on Day 0, 3, 7, and 28 by the intradermal injection of 0.1 ml on each deltoid. Patients with category II exposure received only vaccine and patients with category III exposure received human rabies immunoglobulin and Day 0 along with vaccine.

5.2. Pharmacokinetic properties
Not applicable.

5.3. Preclinical safety data
Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S had undergone single dose and repeated-dose toxicity studies in rats and mice by intramuscular route and local tolerance by intradermal route in rats. Results of single dose toxicity studies concluded that Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S did not cause any observable toxicity in mice at a dose equal to one human dose in absolute terms and in rats at a dose equal to 2 times the human dose in absolute term. Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S also was found safe in repeated dose toxicity and local tolerance study by intradermal route.
Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S was safe, non-teratogenic and did not cause developmental toxicity in a prenatal developmental toxicity study in pregnant rats. Non-clinical data revealed no special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S contains the following Excipients;

S.No	Excipients	Quantity/ Dose	Specification

1	Sucrose	40 mg	BP/ Ph.Eur
2	Glycine	40 mg	IP/ BP/ Ph.Eur
3	Human Serum Albumin (HSA)	10 mg	IP/ BP/ Ph.Eur/ USP/ In-house

6.2. Incompatibilities

Under no circumstances should Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S be administered in the same syringe or at the same site as rabies immunoglobulin or any other medicinal products.

6.3. Shelf-life

Rabies Vaccine Inactivated (Freeze-Dried) RABIVAX-S - 36 months
Sterile Water for Injection (SWFI) – 60 months

6.4. Special precautions for storage

The vaccine should be stored between 2ºC and 8ºC. The diluent should not be frozen, but should be kept cool.

6.5. Nature and contents of the container

Rabies Vaccine Inactivated (Freeze Dried) is filled in 13 mm USP Type 1 clear tubular glass vials of 16.5 mm diameter and 40 mm height and 5.0 mL overflow volume. Vials are stoppered with a 13 mm Bromobutyl Rubber 'Lyo' stopper and sealed with 13 mm red coloured plastic Flip top aluminum seal.

6.6. Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION

Serum Institute of India Pvt. Ltd.
212/2, Hadapsar, Pune-411028 India.

8. MARKETING AUTHORIZATION NUMBER (S)

04988/07008/NMR/2018

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization: 10th February2020
Date of latest renewal: N.A

10. DATE OF REVISION OF TEXT

July 2023