THRABIS®

RECOMBINANT RABIES G PROTEIN VACCINE

1.0 Generic Name

Recombinant Rabies G Protein Vaccine

2.0 Qualitative and Quantitative composition

Each 0.5 mL contains

rRabies G Protein…….	50.00 µg
Disodium Hydrogen Phosphate Anhydrous IP….	0.87 mg
Monobasic Sodium Phosphate Monohydrate BP.	0.88 mg
Sodium Chloride IP……..	8.76 mg
Tergitol NP9…….	0.1 µL
Sodium Hydroxide……...	q.s

3.0 Dosage form and strength

THRABIS® is clear, colorless solution free from visible particles and it contains 50 µg of Rabies G Protein per 0.5 mL of vaccine.

4.0 Clinical particulars

4.1 Therapeutic Indication:

Active immunization against rabies for Post-exposure treatment (after exposure): Treatment after contact with animals, which are rabid or suspected to be rabid, or after contact with an inoculated rabies carcass.

4.2 Posology and Method of administration

THRABIS® should be administered as a single 0.5 mL intramuscular injection in the region of the deltoid muscle in adult population of 18 to 65 years of age as per the schedule given in the Table - 1.

Table 1:- Post-exposure vaccination schedule

Route	Volume	Regimen	Vaccination Schedule (1 dose each on days)
IM	50 µg/0.5 mL	3-dose	1st dose Day 0
			2nd dose Day 3
			3rd dose Day 7

For WHO exposure categories II and III, and in category I cases where there is uncertainty regarding the correct classification of exposure (see Table 2 below), vaccination should be performed as recommended in Table 1.

Table 2 WHO rabies exposure categories		
WHO exposure category	**Description**	**Recommended treatment**
I	Touching or feeding animals, animal licks on intact skin (no exposure)	None, if reliable case history is available. In case of unreliable case history, treat according to Table 1.
II	Nibbling of uncovered minor scratches or abrasions without bleeding (exposure).	Administer vaccine immediately according the vaccination schedule in Table 1.
III	Single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (Severe exposure).	Immediately administer vaccine according the vaccination schedule in and rabies immunoglobulin

The vaccine should be visually inspected for any foreign particulate matter and/or change in physical appearance. The vaccine must not be used if any change in the appearance of the vaccine has taken place.

4.3 Contraindication

THRABIS® vaccine is contraindicated in individuals with known history of a severe hypersensitivity reaction to the vaccine, or to any of the excipients listed.

4.4 Special Warning and precaution for use

Do not administer by intravascular / intradermal route. Do not use the vaccine after the expiry date.

4.5 Drug interactions

The response to the vaccination may be reduced in patients receiving immunosuppressive therapy or with congenital or acquired immunodeficiency. Concomitant use of Immunosuppressant / antimalarial during treatment after exposure should be avoided unless necessary.

4.6 Use in special populations

Pregnancy and Lactation: THRABIS® has no prior experience to use in pregnant and lactating females.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with THRABIS® vaccine.

4.8 Undesirable effects

The most commonly reported adverse reactions were mild and transient in nature. THRABIS® vaccine has been evaluated for safety and immunogenicity in Phase I/II and Phase III clinical studies in Indian population by Cadila Pharmaceuticals Limited, India. THRABIS® vaccine was found to be safe and immunogenic in all clinical trials.

Phase-I Clinical Trial

Out of total 170 subject, 56 subjects reported AEs and headache was the most frequent AE, followed by muscle pain and tiredness. In this study one patient reported a serious adverse event (SAE), abscess at penoscrotal junction, which was unrelated to study vaccine and resolved with medication. Most frequent body system affected by AEs were general disorders and administration site conditions (11% subjects), musculoskeletal and connective tissue disorders (11% subjects) and gastrointestinal disorders (11% subjects).

Phase-II Clinical Trial

No SAE or anaphylactic reaction was reported in phase-II. Out of total 225 subjects, 40 subjects reported AEs and headache was the most frequent adverse event, followed by muscle pain and tiredness. Most frequent body system affected by AEs was general disorders and administration site conditions (12% subjects), musculoskeletal and connective tissue disorders (9% subjects) and nervous system disorders (8% subjects).

Phase-III Clinical Trial

No Serious adverse event or anaphylactic reaction was observed. Out of total 800 subjects, 99 subjects reported AEs. Most frequently observed AEs were localized pain, redness and swelling at the injection site. Most frequent body system affected by AEs was general disorders and administration site conditions (11.88% subjects). No clinically significant abnormality was observed in laboratory results observed during the clinical trials.

4.9 Overdose

No data is available on overdose with THRABIS® vaccine.

5.0 Pharmacological Properties

5.1 Mechanism of Action

In this THRABIS® vaccine , the virus like particles (VLPs) self-assemble from this recombinant G protein which is produced from genes cloned into baculovirus expression vectors and expressed in Spodoptera frugiperda (Sf9) insect cells. The interaction of the G protein and specific cell surface receptors is involved in fusion of the rabies virus to the host cell membrane. The adsorption initiates the infection process, the virus penetrates the host cell and enters the cytoplasm by pinocytosis (via clathrin-coated pits). Recombinant Rabies G protein vaccine generates antibodies against rabies G protein and in turn affects virus neutralization as well as

prevent virus attachment to the cell and confers protection against rabies. Being a subunit vaccine, there are no chances of reversal with THRABIS® vaccine as compared to inactivated vaccines.

5.2 Pharmacodynamic Properties

Phase-I/II and phase-III clinical trials have shown that THRABIS® vaccine was immunogenic and provided adequate seroprotection as per WHO recommendation of Rabies virus neutralizing antibody (RVNA) titre of >0.5 IU/ML.

Summary of clinical trials conducted

Phase-I clinical trial

Rabies G Protein vaccine was evaluated in total of 170 healthy subjects (10 subjects in each of the 17 arms) to assess safety and immunogenicity of IM THRABIS® vaccine administered indifferent doses (5, 10, 20 & 50 μg per 0.5 mL) and schedules (On days: 0,3 / 0,3,7 / 0,7 / 0,7,10). A complete seroprotection (100%) was achieved for all dose schedule regimens of THRABIS® vaccine at Day 14 and sustained the same at day 42. All doses & schedules of THRABIS® vaccine were reported to be safe & immunogenic as per seroprotection criteria of WHO.

Phase-II Clinical trial

Phase-II Clinical trial design (n=225) consisted of 5 study arms [4 in Rabies G protein vaccine (200) and 1 in comparator vaccine (n=25)]. THRABIS® vaccine arms included dose (10 and 50 μg) and schedule (0, 3 and 0, 3, 7 days). A complete seroprotection (100%) was achieved for all dose schedule regimens at Day 14 and sustained the same at day 42.

Phase-III Clinical Trial

A phase-III clinical trial conducted in 800 volunteers were randomized in 2:1 ratio (THRABIS® vaccine and comparator rabies vaccine as a reference vaccine, respectively). On Day 14, 99.24% volunteers showed seroprotection with THRABIS® vaccine. No statistically significant difference was observed for seroprotection at day-14 and Day 42 post vaccination with THRABIS® vaccine compared to the reference vaccine. In summary, all the clinical trials conducted in Indian population, THRABIS® vaccine produced seroprotection levels of RVNA titers i.e. ≥0.5 IU/mL as per WHO recommended level for seroprotection, by Rapid Fluorescent Focus Inhibition Test (RFFIT).

5.3 Pharmacokinetic Properties

Not applicable

6.0 Non-Clinical Properties

6.1 Animal Toxicology and Pharmacology

Results of the preclinical acute toxicity studies in mice and subacute toxicity studies in mice and rabbits, revealed no serious hazard for human use. When the rabbits were exposed to repeat intramuscular injections of THRABIS® vaccine on days 1, 4, 8, 15, 29 & 43, there were no adverse

effects observed on any parameters up to 58 days. Therefore, the administration of six doses of the THRABIS® vaccine up to the 60 µg/0.1 mL intramuscularly was considered well tolerated and concluded as NOAEL (no-observed-adverse-effect-level). THRABIS® vaccine has not been evaluated for genotoxicity, carcinogenic or mutagenic potential, or for impairment of fertility.

7.0 Description

THRABIS® vaccine is clear, colorless solution free from visible particles.

8.0 Pharmaceutical Particular

8.1 Incompatibilities:

Do not mix the THRABIS® vaccine with other drugs in same syringe.

8.2 Shelf Life

Expiry date of the THRABIS® vaccine is indicated on label and carton of the product.

8.3 Package Information

The Single dose (0.5 mL) of THRABIS® vaccine supplied along with one disposable syringe with needle.

8.4 Storage and handling instruction

- Store at +20°C to +8°C.
- Do not freeze.
- Discard if frozen.
- Shake well before use.
- Keep out of reach of children.
- Protect from light
- Do not use THRABIS® vaccine after the expiration date shown on the label.

9.0 Patient counselling Information

Consult the physician for personalized medical advice

10.0 Details of Manufacturer

CADILA PHARMACEUTICALS LIMITED

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11. Market Authorization

Market Authorization:- MF/BIO/20/000040 dated 08-May-2020

12. Date of Rivision

May-2022