PROFESSIONAL INFORMATION FOR

RABIES VACCINE CIPLA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RABIES VACCINE CIPLA (2,5 IU, Lyophilised powder for reconstitution)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative Declaration

RABIES VACCINE CIPLA (Freeze dried) is a sterile, purified inactivated rabies vaccine prepared on vero cells. Rabies Vaccine Inactivated is freeze dried and is provided with a single diluent (1 dose of powder in vial and 1 mL of diluent in ampoule). The vaccine has a milky white friable mass.

Quantitative Declaration

Each 1 mL dose of reconstituted vaccine contains:

Purified Rabies antigen (Rabies virus Pitman-Moore strain 3218) Vero adapted and grown on vero cells, inactivated with beta-propiolactone ≥ 2,5 IU.

RABIES VACCINE CIPLA contains sugar: 40 mg of sucrose.

For full list of excipients, see section **6.1**.

3. PHARMACEUTICAL FORM

Lyophilised powder for reconstitution

The vaccine milky white friable mass appearance.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

RABIES VACCINE CIPLA is indicated for the prevention of rabies in all age groups (adults and children). It can be used before or after exposure, as a primary immunisation or as a booster dose (see sections **4.4** and **5.1**).

Pre-exposure prophylaxis

Pre-exposure vaccination should be offered to people at high risk of exposure to the rabies virus. This vaccination is primarily recommended for veterinarians, veterinary medicine students, animal keepers, hunters, forestry workers, animal handlers, butchers, personnel working in rabies diagnostic and research laboratories as well as children at a high risk of exposure to rabies.

Post-exposure prophylaxis

RABIES VACCINE CIPLA is indicated for post-exposure prophylaxis of rabies infection. It should be administered immediately to individuals with suspected rabies exposure. Administration of RABIES VACCINE CIPLA must always be based on the official recommendations of the World Health Organization (WHO), depending on the type of exposure with a suspected rabid animal.

Table 1: Contact categories

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 irrespective of the time interval that has elapsed.

4.2. Posology and method of administration

Posology

RABIES VACCINE CIPLA should only be reconstituted with the entire contents of the diluent supplied (Sterile Water for Injections), using a sterile syringe and needle. It should be gently shaken until the dry cake is entirely dissolved. The vaccine should be used immediately after reconstitution. The vaccine vial monitor for this type of vaccine is attached to the vial cap (if attached) 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 characteristics prior to administration. In the event of observing any physical variations or particulate matter in either the diluent or reconstituted vaccine, it should be discarded.

PRE-EXPOSURE PROPHYLAXIS

The pre-exposure prophylaxis course comprises of 3 injections at day 0, day 7 and day 21 or day 28, this schedule complies with WHO recommendations.

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 for people whose occupation continually puts them at risk of exposure. Antibody testing should be done every 6 months for people who are potentially at risk of laboratory exposure to high concentrations of live rabies virus. Serological monitoring should be done every 2 years for professionals who are not at continual risk of exposure through their activities. Moreover, since vaccine-induced immunity persists for years in most cases, a booster dose should be administered if the rabies virus neutralising antibody titres fall below 0,5 IU / mL.

POST-EXPOSURE PROPHYLAXIS

In order to remove as much of the rabies virus as possible, the wound should be immediately cleansed with soap and washed thoroughly with water, then treat with an alcohol (70 %) or a povidone iodine tincture.

The vaccination must be administered under medical supervision and should be started as soon as possible after exposure.

The treatment must be adapted according to the type of contact (see table 1) and the immunization status of the subject.

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 people who were previously immunised by complete vaccination schedule (pre-exposure or post- exposure prophylaxis), 2 doses of 1 mL administered intramuscularly, or 2 doses of 0,1 mL administered intradermally on day 0 and day 3 are recommended.

In cases of category II and III exposures in immunodeficient patients, human rabies immunoglobulin (20 IU / kg) or equine rabies immunoglobulin (40 IU per kg) should be given concurrently with RABIES VACCINE CIPLA on day 0. The full dose of rabies immunoglobulin should be thoroughly infiltrated in the area around and into the wounds, if it is anatomically practical. The remaining volume should be injected intramuscularly at a site distant from the vaccine administration site. 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 as later administration would result in interference with the immune response of the vaccine.

Recommendations for the use of RABIES VACCINE CIPLA must be strictly adhered to, in order to reach a sufficient level of antibody protection. An insufficient immune response may lead to fatal cases of rabies.

Method of administration

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

Special Populations

Serology testing:

To ensure continuous protection, a serological test should be performed every 6 months in people with continuous risk of exposure. The serological test may be performed every 2 years after the booster dose administered at 1 year and every 5 years in individuals with a frequent risk of exposure to rabies.

The minimal acceptable antibody level is defined as ≥ 0,5 IU / mL when using this test.
If the result is below the acceptable level, a booster dose should be administered.

Immunocompromised subjects

In people with congenital or acquired immunodeficiency, the immune response to the vaccine may be inadequate. In such patients, it is recommended to monitor serological antibody levels to ensure that an acceptable response has been induced by the pre-exposure schedule. Moreover, if post-exposure vaccination is required, rabies immunoglobulin should be given in association with the vaccine for category II & III exposures.

Patients with bleeding disorders

Intramuscular injection can cause a haematoma at the injection site, therefore it is not advisable to give rabies vaccine to persons with any bleeding disorder, such as haemophilia, thrombocytopenia or to persons on anticoagulant therapy unless the potential benefits clearly outweigh the risk of administration. If RABIES VACCINE CIPLA is administered in such individuals, caution should be observed, and the necessary steps should be taken to avoid the risk of a haematoma forming after injection.

Prior to administration of any dose of RABIES VACCINE CIPLA, the parent or guardian of the recipient or the adult recipient himself must be asked about their personal history, family history as well as recent health status, including immunisation history, current health status and any adverse event experienced following previous immunisations. The course of the vaccination must be carefully considered in individuals who have a history of serious or severe reactions within 48 hours after an injection with similar vaccine components.

The person responsible for administration must take all precautions known for the prevention of allergic or any other reactions, prior to the injection of any biological. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following administration of the vaccine.

Epinephrine injection (1:1000) must be immediately available in case of unexpected anaphylactic or serious allergic reactions.

4.3. Contraindications

a) Pre-exposure prophylaxis

Vaccination should be postponed in case of fever or and acute illness. RABIES VACCINE CIPLA is contraindicated in individuals who experienced a previous severe reaction to any of the vaccine components.

b) Post-exposure prophylaxis

- There are no contraindications to the administration of post-exposure prophylaxis using RABIES VACCINE CIPLA because there is a life-threatening risk associated with rabies.
- The intradermal route must not be used in the individuals receiving long term corticosteroid, other immunosuppressive therapy, 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. A history of anaphylactic or anaphylactoid reactions to neomycin are absolute contraindications.

4.4. Special warnings and precautions for use

Special precautions for the Intradermal route

It is essential that intradermal administration of RABIES VACCINE CIPLA 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. The 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 the papule is not seen after 2 consecutive attempts, the patient should be given the dose intramuscularly.

RABIES VACCINE CIPLA does not contain a preservative, therefore, great care must be taken to avoid contamination of the reconstituted vaccine. The 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.

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. Special care should be taken to ensure that the product is not injected into a blood vessel.

4.5. Interaction with other medicines 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 dose be administered once the vaccination course has been started as a higher dose could interfere with the immune response to rabies vaccine.

4.6. Fertility, pregnancy and lactation

Pregnancy

Prenatal developmental toxicity studies were conducted in pregnant rats and RABIES VACCINE CIPLA was safe, non-teratogenic and did not cause developmental toxicity in

pregnant rats. However, data on the toxicity of RABIES VACCINE CIPLA in pregnant women has not been established.

It is advisable to carefully weigh the expected benefits against the potential risks prior to pre-exposure prophylaxis with RABIES VACCINE CIPLA during pregnancy and breastfeeding. Due to the life-threatening risk of rabies, pregnancy and lactation are not contraindications for post-exposure prophylaxis with RABIES VACCINE CIPLA.

Breastfeeding

Secretion of RABIES VACCINE CIPLA in breast milk has not been established, therefore, caution should be employed when this vaccine is administered to a nursing mother.

Fertility

Animal reproductive studies have not been conducted with rabies vaccine inactivated. Data on the use of this vaccine in pregnant women is limited, hence, the administration of this vaccine during pregnancy is not recommended.

4.7. Effects on ability to drive and use machines

The effect of RABIES VACCINE CIPLA on the ability to drive and operate machinery is unknown.

4.8. Undesirable effects

a) Summary of the safety profile

RABIES VACCINE CIPLA may cause injection site reactions such as pain, erythema, oedema, pruritus, induration and systemic reactions such as fever, shivering, faintness, asthenia, headache, dizziness, myalgia, nausea, abdominal pain and arthralgia. Usually these reactions are mild in severity, transient and resolve within 3 days without any serious consequences.

b) Tabulated summary of adverse reactions

List of adverse reactions:

The following adverse reactions have been reported during clinical trials of Rabies Vaccine Inactivated (Freeze-Dried) administered with or without HRIG (Human Rabies Immune Globulin) as per the WHO recommended post-exposure prophylaxis regimen. In each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Common:	Lymphadenopathy

Immune system disorders

Common:	Skin allergic reactions rash, pruritus (itching), and oedema urticaria
Rare:	Angioedema, dyspnea

Nervous system disorders

Common:	headache, dizziness, somnolence

Gastrointestinal disorders

Common:	Abdominal pain, nausea
Rare:	Diarrhoea

Musculoskeletal and Connective tissue disorders

Common:	Arthralgia, myalgia, chills (shivering)

General disorders and administration site conditions:

Common:	Fever, asthenia, pain, induration, erythema, oedema, pruritus, shivering

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

4.9. Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: A 30.2 Antigens

ATC code: J07BG01

RABIES VACCINE CIPLA is a lyophilised, stabilised suspension of inactivated Pitman-Moore rabies virus strain (PM-Vero) which is grown and modified on vero cells and inactivated by beta-propiolactone.

a) Pre-exposure Prophylaxis:

In a phase I clinical trial in previously unimmunised 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) 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) in patients with potential category II and III rabies exposure, all individuals achieved a protective antibody titre (≥ 0,5 IU/mL) by day 7 of a primary series of five injections of the rabies inactivated vaccine. The injections were given according to the WHO recommended schedule of day 0, 3, 7, 14 and 28, using the intramuscular injection of 1 mL each or a primary series of four injections given on day 0, 3, 7, and 28 given intradermally using the 0,1 mL injection on each deltoid muscle. Patients with category II exposure only received the vaccine and patients with category III exposure received human rabies immunoglobulin and the vaccine on day 0.

5.2. Pharmacokinetic properties

Pharmacokinetic properties are not applicable as this is a vaccine.

5.3. Preclinical safety data

RABIES VACCINE CIPLA has undergone single dose and repeated-dose toxicity studies in rats and mice administered by intramuscular route and local tolerance by intradermal route in rats. The results of single dose toxicity studies concluded that RABIES VACCINE CIPLA did not cause any noticeable 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. The inactivated rabies vaccine was also found to be safe in repeated dose toxicity and local tolerance study by intradermal route.

RABIES VACCINE CIPLA was safe, non-teratogenic and did not cause developmental toxicity in a prenatal developmental toxicity study in pregnant rats. Non-clinical data revealed any special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose

Glycine

Human Serum Albumin (HSA)

6.2. Incompatibilities

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

6.2. Shelf Life

36 months

6.3. Special precautions for storage

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

Once reconstituted, the product must preferably be used immediately. However, RABIES VACCINE CIPLA is stable for 12 hours at 2 ºC and 8 ºC under photolytic conditions.

6.4. Nature and contents of container

For vial (Lyophilised vaccine):

RABIES VACCINE CIPLA is filled in 13 mm USP type-I clear tubular glass vials of 16,5 mm diameter and 40 mm height and 4,0 mL overflow volume. Vials are stoppered with a 13 mm Rubber ‘Lyo’ stopper and sealed with 13 mm red coloured flip off aluminum seal.

For diluent:

1 mL sterile clear, transparent, OPC, USP type-I ampoule.

One monocarton with a tray containing 1 vaccine vial with 1 diluent ampoule –Sterile water for injection 1 mL, packed together + syringe-needle.

One monocarton with a tray containing 1 vaccine vial +1 diluent ampoule –Sterile water for injection 1 mL, packed together.

Multipack of 5 (5 vaccine vials + 5 diluent ampoules –Sterile water for injection 1 mL, packed together).

Box of 50 vials of Rabies vaccine and Box of 50 ampoules of sterile water for injection 1 mL packed separately.

Not all pack sizes will be commercialised.

6.5. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements**.**

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

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8. REGISTRATION NUMBER(S)

56/30.2/0294

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 September 2023

Date of latest renewal: TBC

10. DATE OF REVISION OF THE TEXT

TBA