PROFESSIONAL INFORMATION FOR

RABIES MAB CIPLA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RABIES MAB CIPLA (100 IU / 2,5 mL, solution for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rabies Human Monoclonal Antibody (rDNA) 100 IU / 2,5 mL

Fully human IgG1 monoclonal antibody

Each 1 mL contains:

Rabies Human Monoclonal Antibody 40 IU

Sugar free

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

3. PHARMACEUTICAL FORM

Solution for injection

Rabies Human Monoclonal Antibody (RABIES MAB CIPLA) is a clear, colourless liquid, free from any visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RABIES MAB CIPLA is indicated as passive antibody component of post-exposure prophylaxis of rabies infection, when given to individuals with suspected rabies exposure.

RABIES MAB CIPLA must always be used in combination with a rabies vaccine as part of the post-exposure prophylaxis, as per recommendations of the World Health Organization (WHO). RABIES MAB CIPLA administration depends 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 RABIES MAB CIPLA

For all categories, immediate washing and flushing of all bite 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

Posology

RABIES MAB CIPLA vial should be inspected visually for extraneous particulate matter and/or discoloration before administration. If these conditions exist, it should not be used.

Post-exposure prophylaxis consists of a regimen of one dose of RABIES MAB CIPLA and a full course of rabies vaccination. RABIES MAB CIPLA and the first dose of rabies vaccine should be given as soon as possible after exposure. Additional doses of rabies vaccine

should be given according to the manufacturer's instructions. The recommended dose of RABIES MAB CIPLA is 3,33 IU/kg body weight, preferably at the time of the first vaccine dose. It may also be given through the seventh day after the first dose of vaccine is given.

The dose of 3,33 IU/kg body weight is the same for children and adults. In case of multiple wounds, the dose of RABIES MAB CIPLA may be diluted in a solution of 0,9 % sodium chloride in order to provide the full amount required for good infiltration of all the wounds.

Because of the risk of interference with the vaccine immune response, neither the dose should be increased nor a repeated RABIES MAB CIPLA dose be given (even if the onset of the simultaneous prophylaxis is delayed).

Paediatric population

Because of the life-threatening risk due to rabies, the use of rabies post-exposure prophylaxis is not contraindicated in children under 5 years.

Method of administration

If anatomically feasible, the full dose of RABIES MAB CIPLA should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly at a site distant from the site of vaccine administration.

RABIES MAB CIPLA should never be administered in the same syringe or into the same anatomical site as rabies vaccine. DO NOT INJECT INTRAVENOUSLY.

4.3 Contraindications

- Because of the life-threatening risk due to rabies, there are no contraindications to the administration of RABIES MAB CIPLA.
- If a patient is known to be hypersensitive to excipients (see **section 6.1)** of the RABIES MAB CIPLA, appropriate precautions must be taken

4.4 Special warnings and precautions for use

If anaphylaxis or severe allergic reactions occur, administer appropriate medications e.g. epinephrine (adrenaline) and provide supportive care as required.

Infiltration of wounds in some anatomical sites (finger tips) must be carried out with care in order to avoid increased pressure in the tissue compartment (compartment syndrome).

The possibility of allergic reactions in individuals sensitive to components of the product should be evaluated. Epinephrine (adrenaline) Hydrochloride Solution (1:1000) and other appropriate agents should be 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 MAB CIPLA be administered in the same syringe or at the same site as rabies vaccine.

A separate sterile needle and syringe must be used for each individual patient to prevent the transmission of infectious agents. RABIES MAB CIPLA must not be administered intravenously. The product must be administered intramuscularly. As with all preparations given intramuscularly, bleeding complications may be encountered in patients with bleeding disorders.

The recommended dose of RABIES MAB CIPLA should not be exceeded since a higher dose could interfere with the immune response to rabies vaccine.

RABIES MAB CIPLA contains sodium

RABIES MAB CIPLA contains less than 1 mmol sodium (23 mg) per unit volume, that is to say essentially ‘sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interaction studies in humans have been conducted with RABIES MAB CIPLA. Repeated doses of RABIES MAB CIPLA should not be administered once the vaccination course has been started as the same may interfere with the immune response of the vaccine.

4.6 Fertility, pregnancy and lactation

Because of the life-threatening risk due to rabies, pregnancy and lactation is not a contraindication to rabies post-exposure prophylaxis.

Pregnancy

It is not known whether RABIES MAB CIPLA can cause fetal harm when administered to a pregnant woman.

Breastfeeding

It is not known whether RABIES MAB CIPLA is secreted in breast milk.

Fertility

Animal reproduction studies have not been conducted with RABIES MAB CIPLA. It is not known whether RABIES MAB CIPLA can affect reproductive capacity.

4.7 Effects on ability to drive and use machines

Effect of RABIES MAB CIPLA on ability to drive and use machines is not known.

4.8 Undesirable effects

Summary of the safety profile

The majority of side effects reported were local injection site reactions. These reactions were mild to moderate and resolved without sequelae.

Tabulated summary of adverse reactions

Following adverse reactions have been reported during the phase II/III clinical trial of RABIES MAB CIPLA administered along with rabies vaccine as per WHO recommended post-exposure prophylaxis regimen. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Frequencies are reported as:

Very common; ≥ 1/10

Common; ≥ 1/100 to < 1/10

Uncommon: ≥ 1/1 000 to < 1/100

Very rare: ≤ 1/10 000

MedDRA system organ Class	Frequency	Side effects
Nervous system disorders:	Very common	Headache
Gastrointestinal disorders	Common	Nausea
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
General disorders and administration site conditions	Very common	Fatigue
	Common	Fever, chills, pain, redness, swelling
	Uncommon	Itching at wound site

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 requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP ((Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: 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

Pharmacological classification

Pharmacotherapeutic group: A 30.1 Antibody

ATC code: J06BB05

RABIES MAB CIPLA is a sterile solution of fully human IgG1 monoclonal antibody specific to the rabies virus surface G glycoprotein for infiltration in local wound and intramuscular administration following a suspected rabies exposure.

RABIES MAB CIPLA binds to a conformational epitope of the ectodomain at antigenic site III and minor site a of the rabies G glycoprotein. Binding of RABIES MAB CIPLA to the G glycoprotein probably prevents viral attachment to target cells.

RABIES MAB CIPLA neutralizes a wide variety of terrestrial and bat isolates of rabies virus tested by a standardized rapid fluorescence focus inhibition test (RFFIT).

5.2 Pharmacokinetic properties

In the phase I study of RABIES MAB CIPLA, one group of nine adults with a complete set of antibody measurements through study day 84 was used for pharmacokinetic analysis. The pharmacokinetics was determined using ELISA to measure anti-rabies antibody concentrations on days 0, 3, 7, 14, 28, 42, 56 and 84 from participants who received a single dose of RABIES MAB CIPLA 6,66 IU/kg. The median maximum concentration (C_{max}) was 2,79 mcg / mL, the median time to C_{max} was 72 hours and the median elimination half-life ($t_{½}$) of RABIES MAB CIPLA was calculated to be 18,4 days.

5.3 Preclinical safety data

Acute toxicity studies were conducted in Sprague Dawley rats and New Zealand white rabbits by intramuscular route. Maximum tolerated dose was greater than 420 IU/kg (Sprague Dawley rats) and 248 IU/kg (New Zealand white rabbits).

Repeat dose toxicity studies were conducted in Sprague Dawley rats and New Zealand white rabbits by intramuscular route. No observed adverse effect level was greater than 420 IU/kg and 248 IU/kg.

Weekly intramuscular administration of over a 4-week dosing period was well tolerated in the hamsters at up to 10 mg/ kg/dose. There was no evidence of systemic toxicity and no microscopic abnormalities were observed at the injection sites.

Tissue cross reactivity studies in human and Syrian hamster tissues did not reveal significant findings.

Allergenicity/hypersensitivity testing conducted in guinea pigs showed that RABIES MAB CIPLA was a non-sensitizer to the guinea pigs.

Non-clinical data revealed no special hazard for humans based on studies of acute and repeated dose toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Citrate buffer
    - Citric acid
    - Sodium Citrate
- Sodium Chloride (NaCl)
- Polysorbate-80.

6.2 Incompatibilities

Under no circumstances should RABIES MAB CIPLA be administered in the same syringe or at the same site as rabies vaccine or any other medicinal products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

- Store at or between 2 °C to 8 °C.
- DO NOT FREEZE. Product which has been exposed to freezing should not be used. RABIES MAB CIPLA contains no preservatives and unused portions must be discarded immediately. Do not use after expiry date.

6.5 Nature and contents of container

RABIES MAB CIPLA is filled in 4 mL, 13 mm clear USP Type 1 tubular glass vials. Vials are stoppered with a 13 mm halobutyl rubber stopper and sealed with 13 mm blue coloured flip off aluminium seal.

pack sizes:

100 IU/2,5 mL (40 IU/mL) vial.

Mono carton – 1 vial packed in a carton

50 vials packed into a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

58/30.1/0161

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: To be allocated.

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

To be allocated.