PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CHIRORAB freeze dried suspension

Powder and solvent for suspension for injection.

PCEC (Purified chicken embryo cell) rabies vaccine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 vial (1,0 ml) contains:

Inactivated rabies virus (strain flurry LEP), potency ≥ 2,5 IU

Host system: primary chicken fibroblast cell cultures

This vaccine contains residues of chicken proteins (e.g., ovalbumin), human serum albumin, and may contain traces of neomycin, chlortetracycline and amphotericin B, see section 4.4.

Contains sugar (sucrose): 20 – 100 mg per vial

Sodium: 4,0 – 5,0 mg per vial

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

CHIRORAB is a white, freeze-dried vaccine for reconstitution with the solvent prior to use.

The solvent is clear and colourless.

A clear colourless solution results after reconstitution of the white freeze-dried powder with the clear and colourless solvent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CHIRORAB is indicated for active immunisation against rabies in individuals of all ages.

This includes pre-exposure prophylaxis (i.e. before possible risk of exposure to rabies) in both primary series and booster dose and for post-exposure prophylaxis (i.e. after suspected or proven exposure to rabies). CHIRORAB is to be used on the basis of WHO official recommendations.

4.2 Posology and method of administration

Posology

The recommended single intramuscular (IM) dose is 1,0 ml in individuals of all ages.

The recommended single intradermal (ID) dose is 0,1 ml in individuals of all ages.

Pre-exposure prophylaxis (PrEP)

Primary immunisation

Intramuscular (IM) administration

In previously unvaccinated individuals, an initial course of pre-exposure immunisation consists of three doses (each of 1,0 ml), administered intramuscularly on days 0, 7 and 21 (or 28).

Pre-exposure prophylaxis is recommended for anyone who is at continual, frequent or increased risk for exposure to the rabies virus, as a result of their residence or occupation, such as laboratory workers dealing with rabies virus and other lyssaviruses, veterinarians and animal handlers. Travellers in high-risk areas should be vaccinated after a risk assessment. Children living in or visiting rabies-affected areas are at particular risk and should be given pre-exposure prophylaxis on an individual basis or in mass campaigns when there are no economic, programmatic or logistical obstacles (WHO 2013 recommendations).

Intradermal (ID) administration

In previously unvaccinated individuals, an initial course of pre-exposure prophylaxis consists of three doses (each of 0,1 ml) administered ID on days 0, 7 and 21 (or 28).

Booster doses

Intramuscular (IM) administration

The individual IM booster dose is 1,0 ml.

CHIRORAB may be used for booster vaccination after prior immunisation with human diploid cell rabies vaccine (HDCV).

The need of intermittent serological testing for the presence of antibody ≥ 0,5 IU/ml and the administration of booster doses should be assessed in accordance with official recommendations.

A booster would be recommended only if rabies virus neutralizing antibody (RVNA) concentration falls to less than 0,5 IU/ml (assessed by rapid fluorescent focus inhibition test [RFFIT] or fluorescent antibody virus neutralisation test [FAVNT]).

According to WHO, periodic booster doses of rabies vaccine are not necessary for people living in or travelling to high-risk areas who have received a complete primary series of pre- or post-exposure prophylaxis with rabies vaccine. Periodic booster injections are recommended only for people whose occupation puts them at continual or frequent risk of exposure as an extra precaution in the absence of recognized exposure.

If possible, antibody monitoring of personnel at risk is preferred to the administration of routine boosters. 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. If the RVNA concentration falls below 0,5 IU/ml of serum, one booster dose of vaccine should be given intramuscularly or intradermally.

Those professionals who are not at continual risk of exposure through their activities, such as certain categories of veterinarians and animal health officers, should have serological monitoring every 2 years (WHO 2013).

Alternatively, booster doses may be given at official recommended intervals without prior serological testing according to the perceived risk. Experience shows that reinforcing doses are generally required every 2-5 years.

Intradermal ID administration

The individual ID booster dose is 0,1 ml.

Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis consists of:

- local treatment of the wound as soon as possible after exposure
- a course of potent, effective rabies vaccine that meets WHO recommendations, and
- administration of rabies immunoglobulin, if indicated.

The indication for post-exposure prophylaxis depends on the type of contact with the suspected rabid animal, as provided in Table 1, Recommended post-exposure prophylaxis according to type of exposure. Post-exposure immunisation should begin as soon as possible after exposure and should be accompanied by local measures to the site of inoculation so as to reduce the risk of infection.

According to WHO, prompt local treatment of all bite wounds and scratches is an important step in post-exposure prophylaxis. The recommended first-aid procedures include immediate, thorough flushing and washing of the wound with soap and water, detergent, povidone iodine or other medicines with virucidal activity. If soap or a virucidal medicine is not available, the wound should be thoroughly and extensively washed with water. People who live in areas endemic for rabies should be taught simple local wound treatment and warned not to use procedures that may further contaminate or enlarge the wound.

A bleeding wound at any site indicates potentially severe exposure and must be infiltrated with either human or equine rabies immunoglobulin. Most severe bite wounds are best treated by daily dressing, followed by secondary suturing when necessary. If suturing after wound cleansing cannot be avoided, the wound should first be infiltrated with human or equine rabies immunoglobulin and suturing delayed for several hours to allow diffusion of the immunoglobulin through the tissues before minimal sutures are applied. Secondary sutures are less likely to become infected and present better cosmetic results if carried out under optimal conditions. An infected bite wound is no contra-indication to injection of rabies

immunoglobulin. Bites on the finger or toe tip, ear lobe or nasal area can be safely injected with rabies immunoglobulin, provided excessive pressure is not applied, as this can cause compression syndromes.

Other treatments, such as administration of antibiotics and tetanus prophylaxis, should be applied as appropriate for potentially contaminated wounds (WHO 2013).

Table 1: Recommended post-exposure prophylaxis according to type of exposure

Category of exposure	**Type of exposure to a domestic or wild[a)] animal suspected or confirmed to be rabid, or animal unavailable for testing**	**Recommended post-exposure prophylaxis**
I	Touching or feeding animals Licks on intact skin Contact of intact skin with secretions or excretions of a rabid animal or human case	None, if reliable case history is available.
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding	Administer vaccine immediately [b)] Stop treatment if animal remains healthy throughout an observation period of 10 days[c)] or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques.
III	Single or multiple transdermal bites[d)] or scratches, licks on broken skin. Contamination of mucous	Administer rabies vaccine immediately, and rabies immunoglobulin, preferably as soon as possible after initiation of post-exposure prophylaxis. Rabies

Category of exposure	**Type of exposure to a domestic or wild[a)] animal suspected or confirmed to be rabid, or animal unavailable for testing**	**Recommended post-exposure prophylaxis**
	membrane with saliva (i.e. licks). Exposure to bats[e)].	immunoglobulin can be injected up to 7 days after first vaccine dose administration. Stop treatment if animal remains healthy throughout an observation period of 10 days or is proven to be negative for rabies by reliable laboratory using appropriate diagnostic techniques

[a)] Exposure to rodents, rabbits or hares does not routinely require rabies post-exposure prophylaxis.

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

[c)] 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.

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

[e)] Post-exposure prophylaxis should be considered when contact between a human and a bat has occurred, unless the exposed person can rule out a bite or scratch or exposure of a mucous membrane.

1. Post-exposure prophylaxis of previously unvaccinated individuals

IM administration

- 5 dose Essen regimen (1-1-1-1-1): one 1,0 ml IM injection on each of days 0, 3, 7, 14, and 28.
- 4 dose Zagreb regimen (2-1-1): two 1,0 ml IM injections on day 0 (one in each of the two deltoids or thigh sites) followed by one 1,0 ml IM injection on each of days 7 and 21.

ID administration

Updated two site Thai Red Cross (TRC) regimen (2-2-2-0-2): two 0,1 ml ID injections at different anatomical sites (e.g., deltoid and thigh) each on days 0, 3, 7 and 28.

The 8-site intradermal (Oxford) regimen (8-0-4-0-1-1) can alternatively be used: One 0,1 ml ID injection at each of the following 8 sites: the left and right deltoids, lateral thighs, suprascapular regions and lower quadrants of the abdomen on day 0; one 0,1 ml ID injection at each 4 sites: the left and right deltoids and lateral thighs on day 7 and one 0,1 ml ID injection at a single site on deltoid on day 28 and day 90.

2. Post-exposure prophylaxis in previously vaccinated individuals

IM administration

In previously vaccinated individuals, post-exposure prophylaxis consist of two doses (each of 1,0 ml) administered IM on days 0 and 3. Rabies immunoglobulin is not indicated in such cases.

ID administration

In previously vaccinated individuals, post-exposure prophylaxis consist of two doses (each of 0,1 ml) administered ID on days 0 and 3. Rabies immunoglobulin is not indicated in such cases.

3. Dosing in different populations

Paediatric patients

Paediatric individuals receive the same 1,0 ml IM dose or 0,1 ml ID dose as adults.

Elderly patients

Elderly individuals receive the same 1,0 ml IM dose or 0,1 ml ID dose as adults.

Immunocompromised individuals

In immunocompromised individuals, a complete series of 5 doses according to the Essen (1-1-1-1-1 on days 0, 3, 7, 14, and 28) regimen in combination with comprehensive wound management and local infiltration of rabies immunoglobulin is required for individuals with category II and III exposure.

Alternatively, two doses of vaccine may be given on day 0, that is, a single dose of 1,0 ml vaccine should be injected into the right deltoid and another single dose into the left deltoid muscle. In small children, one dose should be given into the anterolateral region of each thigh. This would result in a total of 6 doses (2-1-1-1-1 on days 0, 3, 7, 14 and 28).

When feasible, the rabies virus neutralising antibody response should be measured 2 to 4 weeks (preferably on day 14) following the start of vaccination to assess the possible need for an additional dose of the vaccine. Immunosuppressive medicines should not be administered during post-exposure therapy unless essential for the treatment of other conditions (see section 4.5).

Method of administration

Intramuscular (IM) Regimen: For adults and children ≥ 2 years of age, the vaccine should be administered into the deltoid; for children < 2 years, the anterolateral area of the thigh is recommended.

Intradermal (ID) Regimen: Intradermal administration is an acceptable alternative to the standard intramuscular route, in countries where ID administration is endorsed by national health authorities, leading to significant vaccine savings.

The vaccine must not be given by intravascular injection, see section 4.4.

Rabies vaccine must not be given by intra-gluteal injection or subcutaneously, see section 4.4.

Instructions for reconstituting CHIRORAB

Parenteral medicines should be inspected visually for particulate matter and discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered. The vaccine should only be reconstituted using the solvent supplied in the package.

A clear colourless solution results after reconstitution of the white freeze-dried powder with the clear and colourless solvent.

The powder for solution should be reconstituted using the solvent for solution supplied and carefully agitated prior to injection. The reconstituted vaccine should be used immediately.

During manufacturing, the vial is sealed under vacuum. Therefore, to prevent problems in withdrawing the reconstituted vaccine from the vial after reconstitution of the vaccine, it is recommended to unscrew the syringe from the needle to eliminate the negative pressure.

After that, the vaccine can be easily withdrawn from the vial. It is not recommended to induce excess pressure, since over-pressurization will create the problems in withdrawing the proper amount of the vaccine.

Any unused vaccine or waste material should be disposed of in accordance with local requirements (see section 6.6).

4.3 Contraindications

- Hypersensitivity to the active pharmaceutical ingredient (see section 2) or to any of the excipients (see section 6.1)

- *Post-exposure prophylaxis (PEP)*

  In view of the almost invariably fatal outcome of rabies, there is no contraindication to post-exposure prophylaxis, including pregnancy.
- Individuals with acute diseases requiring treatment should not be vaccinated until at least 2 weeks after recovery. Minor infections are not a contraindication to vaccination.

4.4 Special warnings and precautions for use

Reports of anaphylactic reactions including anaphylactic shock have occurred following CHIRORAB vaccination. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Hypersensitivity reactions (PEP only)

Patients considered to be at risk of a severe hypersensitivity reaction to the vaccine or any of the vaccine components should receive an alternative rabies vaccine if a suitable product is available.

CHIRORAB contains residues of egg and chicken proteins, such as ovalbumin. In instances in which individuals have developed clinical symptoms of anaphylaxis such as generalised urticaria, upper airway (lip, tongue, throat, laryngeal or epiglottal) oedema, laryngeal or bronchospasm, hypotension and shock, following exposure to egg or chicken protein, the vaccination should only be administered by personnel with the capability and facilities to manage anaphylaxis post-vaccination.

Central nervous system effects

Encephalitis and Guillain-Barré Syndrome have been reported to be temporally associated with the use of CHIRORAB (see section 4.8). The use of corticosteroids to treat adverse reactions such as these may inhibit the development of immunity to rabies (see section 4.5). A patient’s risk of developing rabies must be carefully considered, before deciding to

discontinue immunisation.

Route of administration

Unintentional intravascular injection may result in systemic reactions, including shock. Do not inject intravascularly.

CHIRORAB must not be given by intra-gluteal injection or subcutaneously, as the induction of an adequate immune response may be less reliable.

The vaccine must not be mixed in the same syringe with other medicines. If rabies immunoglobulin is indicated in addition to CHIRORAB vaccine, then it must be administered at an anatomical site distant to the vaccination (see section 4.5)).

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions, may occur in association with vaccination as a psychogenic response to the needle injection (see section 4.8). It is important that procedures are in place to avoid injury from fainting.

Excipient with known effect:

CHIRORAB contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take CHIRORAB.

Sucrose may have an effect on the glycaemic control of patients with diabetes mellitus.

CHIRORAB contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Immunosuppressive medicines can interfere with the development of an adequate response to the rabies vaccine. Therefore, it is recommended that serological responses should be monitored in such subjects, and additional doses administered as necessary (see section

4.2).

All of the rabies immunoglobulin, or as much as anatomically possible (but avoiding possible compartment syndrome), should be administered into or around the wound site or sites. The remaining immunoglobulin, if any, should be injected intramuscularly at a site distant from the site of vaccine administration to avoid possible interference with simultaneously administered rabies vaccine.

Concomitant vaccines should always be administrated at separate injection sites and preferably contralateral limbs.

The ID route must not be used in the following instances:

- individuals receiving long term corticosteroid or other immunosuppressive therapy or chloroquine
- immunocompromised individuals.

4.6 Fertility, pregnancy and lactation

Pregnancy

No cases of harm attributable to use of CHIRORAB during pregnancy have been observed. CHIRORAB may be administered to pregnant women when post-exposure prophylaxis is required.

The vaccine may also be used for pre-exposure prophylaxis during pregnancy if it is considered that the potential benefit outweighs any possible risk to the foetus.

Breastfeeding

While it is not known whether CHIRORAB enters breast milk, no risk to the breastfeeding infant has been identified. CHIRORAB may be administered to breastfeeding women when post-exposure prophylaxis is required.

The vaccine may also be used for pre-exposure prophylaxis in breastfeeding women if it is

considered that the potential benefit outweighs any possible risk to the infant.

Fertility

Non-clinical reproductive and developmental toxicity studies have not been performed.

4.7 Effects on ability to drive and use machines

No studies have been carried out with CHIRORAB to assess the effect on the ability to drive or use machines (see section 4.8).

Some of the adverse effects, e.g. headache and dizziness, described in section 4.8, may affect the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

In clinical trials, the most commonly reported solicited adverse reactions were injection site pain (30 – 85 %) or injection site induration (15 – 35 %). Most injection site reactions were not severe and resolved within 24 to 48 hours.

b. Tabulated summary of adverse reactions

Adverse reactions from clinical trials are listed according to System Organ Classes in MedDRA. Within each System Organ Class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse reaction: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000) very rare (< 1/10 000).

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Common	Lymphadenopathy
Immune system disorders	Rare	Hypersensitivity
	Frequency unknown*	Anaphylaxis including anaphylactic shock
Metabolism and nutrition disorders	Common	Decreased appetite
Nervous system disorders	Very common	Headache, dizziness
	Rare	Paraesthesia
	Frequency unknown*	Encephalitis, Guillain-Barré syndrome, presyncope, syncope, vertigo
Gastrointestinal disorders	Common	Nausea, vomiting, diarrhoea, abdominal pain/discomfort
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Urticaria
	Rare	Hyperhidrosis (sweating)
	Frequency unknown*	Angioedema
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia
General disorders and administration site conditions	Very common	Injection site reactions, malaise, fatigue, asthenia, fever
	Rare	Chills

* Additional adverse reactions from spontaneous reporting

c. Description of selected adverse reactions

Once initiated, rabies post-exposure prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine.

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

4.9 Overdose

No symptoms of overdose are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification A 30.2 Biologicals – antigens

ATC code: J07B G01

Mechanism of action

The vaccine consists of inactivated rabies virus which activates the immune system in forming antibodies against rabies.

The minimum rabies virus antibody titre recommended as being proof of an adequate immune response after vaccination is ≥ 0,5 IU/ml concentration as specified by the WHO. In healthy vaccinees, this level should be achieved in most individuals by Day 14 of a post-exposure regimen, with or without simultaneous administration of RIG and irrespective of age.

Post-exposure prophylaxis: In clinical studies CHIRORAB elicited adequate neutralising antibodies (≥ 0,5 IU/ml) in almost all subjects by day 14 or 30, when administered according to the WHO recommended 5- dose* (day 0, 3, 7, 14, 28; 1,0 ml each, intramuscular) Essen regimen, or to the WHO recommended 4-dose (day 0 (2 doses), 7, 21; 1,0 ml each, intramuscular) Zagreb regimen as well as the former WHO recommended 2-sites (day 0, 3, 7, 28; 0,1 ml per dose, 2 doses per each day, intradermal) TRC regimen, * former WHO recommended Essen regimen consisted of 6 doses (day 0, 3, 7, 14, 28, 90; 1,0 ml each, intramuscular).

Concomitant administration of Human Rabies Immunoglobulin (HRIG) with the first dose of rabies vaccine caused a slight decrease in GMCs (Essen regimen). However, this was not considered to be clinically relevant nor statistically significant.

Pre-exposure prophylaxis: In clinical trials with previously unimmunised subjects, almost all subjects achieve an adequate immune response (RVNAs ≥ 0,5 IU/ml) 3 to 4 weeks after the end of a primary series of three injections of CHIRORAB when given according to the recommended schedule by the intramuscular and the intradermal route.

Persistence of adequate immune response (RNVAs ≥ 0,5 IU/ml) for up to 2 years after immunisation with CHIRORAB without additional booster has been found in clinical studies. As antibody concentrations slowly decrease, booster doses may be required to maintain antibody levels above 0,5 IU/ml.

The need for and timing of boosting should be assessed on a case by case basis, taking into account official guidance (see section 4.2).

In a clinical trial, a booster dose of CHIRORAB administered 1 year after primary immunisation elicited a 10-fold or higher increase in Geometric Mean Concentrations (GMCs) by day 30.

It has also been demonstrated that individuals who had previously been immunised with Human Diploid Cell Vaccine (HDCV) developed a rapid anamnestic response when boosted

with CHIRORAB.

5.2 Pharmacokinetic properties

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Disodium edetate

Polygeline

Potassium-L-glutamate

Sodium chloride

Sucrose

TRIS-(hydroxymethyl)-aminomethane

Solvent

Water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, CHIRORAB must not be mixed in the same syringe with other medicines.

6.3 Shelf life

48 months.

After reconstitution CHIRORAB is to be used immediately.

6.4 Special precautions for storage

CHIRORAB should be stored protected from light at 2 °C to 8 °C. Do not freeze.

The vaccine may not be used after the expiration date given on package and container.

6.5 Nature and contents of container

Package with 1 clear vial (type I glass) of freeze-dried vaccine with stopper (chlorobutyl) 1 clear glass ampoule (type I glass) Sterile Water for Injection (1,0 ml) for a single dose of 1,0 ml with or without injection syringe (polypropylene with polyethylene plunger) with or without reconstitution needle and with or without needle for IM injection.

6.6 Special precautions for disposal and other handling

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd.

106 16th Road,

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1686,

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8 REGISTRATION NUMBER

33/30.1/0251

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 June 2016

10 DATE OF REVISION OF THE TEXT

10 December 2021