



**health**

Department:  
Health  
REPUBLIC OF SOUTH AFRICA



**NATIONAL INSTITUTE FOR  
COMMUNICABLE DISEASES**

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## **NOTICE: RECOMMENDED THERAPEUTIC ALTERNATIVE FOR HUMAN RABIES IMMUNOGLOBULIN**

The supply of human rabies immunoglobulin (HRIG) presently being used in South Africa is in critical short supply. The current supplier of HRIG, has indicated that there will not be any stock available for the period May to August 2016. An alternative source of HRIG is available internationally, but is almost twice the price as the currently available product. Equine rabies immunoglobulin (ERIG) 300 IU/5mL, is however available at a cheaper price.

This aim of the circular is to guide health personnel in the administration of ERIG and management of patients requiring rabies post-exposure prophylaxis (PEP).

ERIG is produced in horses. It has been widely used for PEP over many decades in countries with high rates of canine rabies such as India where it has been found to be safe and effective. However, compared with HRIG, the use of ERIG does carry a low risk (1 in 150,000 doses administered) of adverse drug reactions, specifically anaphylaxis.<sup>1</sup> Therefore ERIG should only be administered in facilities that are equipped to respond appropriately to anaphylactic shock. ERIG also has a different dosing schedule to HRIG (refer to Section 2.1 in the notice).

### **1. Management of humans exposed to rabies**

All patients who are exposed to a suspected rabid animal should be managed according to the current Standard Treatment Guidelines (STGs) and Essential Medicines List (EML).<sup>2, 3</sup> These are accessible online at: <http://www.health.gov.za/index.php/component/phocadownload/category/197>.

#### **1.1 Wound management**

Since the rabies virus enters the human body through a bite or scratch, all bite wounds should be copiously flushed as soon as possible. Wounds can be flushed for 5 to 10 minutes with water or soap and water. Deep puncture wounds should be irrigated using a syringe. Wounds should not be sutured and local anaesthetic should not be given. Anti-tetanus treatment and antibiotics may be administered if indicated.<sup>4</sup>

<sup>1</sup> National Rabies Control Programme: National Guidelines on Rabies Prophylaxis. Delhi: 2015.

<sup>2</sup> National Department of Health, Affordable Medicines: Hospital Level Adults Standard Treatment Guidelines and Essential Medicine List, 2015 Edition.

<sup>3</sup> National Department of Health, Affordable Medicines: Hospital Level Paediatrics Standard Treatment Guidelines and Essential Medicine List, 2013 Edition.

<sup>4</sup> Bishop GC, Durrheim DN, Kloock PE, et al. Rabies: Guide for the Medical, Veterinary and Allied Professions. Second Edition. Pretoria: Government Printer; 2010.



## 1.2 Animal health

Following exposure of a person to a suspected rabid domestic animal, the state veterinarian should be informed. After an assessment by the veterinarian, the animal should either be euthanised, and its brain submitted for rabies diagnosis, or the suspected rabid animal should be kept in quarantine under observation for a period determined by the state veterinarian.<sup>4</sup>

## 1.3 Post-exposure prophylaxis (PEP)

PEP is required if a risk assessment indicates the possibility of rabies exposure. The risk assessment should be based on the behaviour of the animal, the animal species, the vaccination status of animal, the local and provincial rates of canine rabies, and the bite wound category. Table 1 describes the categories of exposure and patient management following exposure to a suspected rabid animal. PEP includes rabies vaccine with or without rabies immunoglobulin (RIG). **As with HRIG, administration of ERIG MUST BE ADMINISTERED in category III wounds (Table 1) to effect an immediate neutralisation of the virus as the vaccine will only lead to an immune response after 7- 10 days.** For further information regarding risk assessment, please consult the national rabies guidelines.<sup>4</sup>

**Table 1: Categories of exposure and appropriate management following exposure to suspected rabid animals<sup>5</sup>**

Category	Type of exposure	Management
1	<ul style="list-style-type: none"><li>• Touching/feeding of animal.</li><li>• Licking of intact skin.</li></ul>	<ul style="list-style-type: none"><li>• No treatment if history is reliable.</li><li>• If history not reliable, treat as category 2.</li></ul>
2	<ul style="list-style-type: none"><li>• Nibbling of uncovered skin.</li><li>• Superficial scratch without bleeding.</li></ul>	<ul style="list-style-type: none"><li>• Wound management.</li><li>• Administer full course vaccine. Only stop if animal tested negative for rabies or is still healthy after 10 days observation.</li><li>• Do not give immunoglobulin, except in immune-compromised patients.</li></ul>
3	<ul style="list-style-type: none"><li>• Bites/scratches that penetrate the skin and with any visible blood.</li><li>• Licking of broken skin or mucous membranes e.g. eyes and mouth.</li><li>• Bat bites:<ul style="list-style-type: none"><li>– Any close contact with a bat: single or multiple bites or scratches and bruising (even with minor bites or unapparent skin penetration).</li><li>– Direct physical contact with bat saliva or neural tissue; contact with mucous membranes with bat saliva, droppings or urine.</li></ul></li></ul>	<ul style="list-style-type: none"><li>• Wound management.</li><li>• Administer full course vaccine.</li><li>• Only stop vaccine if animal tested negative for rabies or is still healthy after 10 days observation.</li><li>• Administer HRIG or ERIG.</li><li>• Administer tetanus vaccine.</li><li>• Prescribe antibiotics.</li></ul>

## 2. Administration of ERIG

### 2.1 Dosage and administration<sup>1</sup>

The dose of ERIG is twice as high as the dose needed for HRIG. The recommended dose of ERIG is 40 IU/kg:

- Infiltrate as much as possible in and around the wound and inject the rest intramuscularly into the deltoid (not buttock, unless the wound is on the buttock).
- The patient must be observed for 30 minutes.

<sup>5</sup> National Department of Health, Affordable Medicines: Primary Health Care Level Standard Treatment Guidelines and Essential Medicine List, 2014 Edition.



- Follow with a complete course of vaccine as per national rabies guidelines.<sup>1</sup>

## 2.2 Test dose

Due to the potential for anaphylactic reactions with the administration of ERIG, it is recommended by some ERIG manufacturers to perform a skin test (test dose).<sup>6,7</sup>

- The skin test is an intradermal injection with a 1:10 dilution of ERIG (0.1ml) on the ventral aspect of the forearm.
- An equivalent intradermal injection of normal saline solution should be used as a control.
- Observation of the injection site should be done 15 minutes after administration.
- The observation is considered positive if erythema (>6 mm), local oedema, or a systemic reaction is observed and the control site shows no such dermal reaction. A positive test result is not a formal contraindication for use, however it should be considered a warning, and in such cases ERIG should be administered only after ensuring the facility can treat anaphylactic shock.
- A negative test will not guarantee the absence of an immediate allergic type reaction.

According to recent recommendations from the World Health Organization (WHO), there are no scientific grounds for performing a skin test prior to administering ERIG. The test dose does not predict reactions and therefore ERIG should be given whatever the result.<sup>1</sup>

## 2.3 Adverse effects of ERIG

The main adverse effect of ERIG is an anaphylactic reaction. The incidence of this, however, is low occurring in 1 in 150 000 people.<sup>1</sup> Other adverse effects include pain, swelling, redness and itching at the site of administration. Serum sickness can also occur and may be more common than anaphylaxis.

Anaphylactic reactions can be identified by symptoms of tiredness and a tight chest that progresses into difficulty breathing, hypotension and collapse. Anaphylaxis usually occurs within 30 minutes after administration. In cases of severe anaphylactic reactions, adrenaline should be injected intramuscularly at a dose of 0.5 ml of 0.1 percent solution (1 in 1000, 1mg/ml) for adults and 0.01ml/kg body weight of the same solution for children. Other emergency medicines such as hydrocortisone, dopamine, and supportive treatment (intravenous fluids and oxygen) should also be administered.<sup>1, 2, 3</sup>

Serum sickness occurs in 1% to 6% of patients usually 7 to 10 days after injection of ERIG.<sup>8</sup> The symptoms of serum sickness include a pruritic rash (urticaria), fever, headache and arthralgia. Important components of management are to exclude infection at the wound site and to reassure the patient that serum sickness is not rabies.

Antihistamines may be used for the pruritic rash and analgesics such as ibuprofen and paracetamol can be given for the fever, headache and arthralgia. In severe cases with high fevers and significant arthralgia or arthritis, corticosteroids such as prednisone can be considered. In most cases, symptoms and signs characteristic of serum sickness resolve within 7 days.<sup>1</sup>

<sup>6</sup> Periodic Safety Update Report: Equirab (Rabies Antiserum - Equine). Bharat Serums and Vaccines Ltd. Report No.: BSV/PSUR-EQUIRAB, Version V8. 2015.

<sup>7</sup> Bharat Serums and Vaccines Limited. Package insert: 1500 IU/5mL Equirab (Rabies Antiserum - Equine), 23 March 2015.

<sup>8</sup> WHO Recommendations on Rabies Post-Exposure Treatment and the Correct Technique of Intradermal immunization against Rabies. Available at:

[http://www.who.int/rabies/en/WHO\\_recommendation\\_post\\_exp\\_treatment.pdf](http://www.who.int/rabies/en/WHO_recommendation_post_exp_treatment.pdf).



Certain persons are at higher risk of anaphylactic shock. These include persons with a known hypersensitivity to horse serum, those with a history of anaphylaxis, or those with known history of allergy to penicillin or sulphur drugs. In these patients, the need for ERIG should be carefully evaluated, and the risk-assessment repeated. If possible, HRIG should be preferentially administered to these persons.

### 2.3.1 Adverse events reporting

The National Adverse Drug Event Monitoring Centre (NADEMC) is a unit of the Medicines Control Council. Its core activity is the collection and evaluation of adverse drug reaction reports submitted by health care professionals in the country.

Adverse events following administration of ERIG should be reported directly to the Provincial Communicable Disease Control Coordinator and NADEMC, using the form in Appendix 1. The reporting form should be completed in as much detail as possible.

**National Adverse Drug Event Monitoring Centre**  
c/o Division of Clinical Pharmacology  
Faculty of Health Sciences  
University of Cape Town  
Observatory, 7925  
Facsimile 021 448 6181  
Telephone 021 447 1618,

## **3. Procurement of ERIG for governmental institutions**

ERIG will be purchased by the National Department of Health, for public institutions, through the Section 21 authorisation route.

## **4. Placement of ERIG within health facilities**

Due to the risk of anaphylactic reaction, ERIG should be administered in healthcare facilities that are equipped to manage anaphylactic reactions. The appropriate level of care to place ERIG should be guided by Pharmaceutical and Therapeutics Committees. Where access to rabies vaccine and immunoglobulin is not immediately available, urgent referral to facilities where ERIG is available will be required.<sup>5</sup> It is important to strengthen referral systems to ensure that patients are not lost to follow up and that they receive the necessary care.

## **5. Training on administration of ERIG**

Training will be conducted by Communicable Diseases, together with NICD, to the provincial Communicable Disease Control Coordinators, prior to introduction of ERIG at healthcare facilities in South Africa. Training will include indication for ERIG, administration and dosage, adverse effects and management of this, reporting of adverse effects and referral systems where ERIG is not available, in the form of a standard operating procedure.

## **6. Additional Information**

For all rabies related advice, contact the NICD hotline on **082 883 9920**.



Comments may be submitted via e-mail to:

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Kind regards



**MR G STEEL**  
**CLUSTER MANAGER: SECTOR WIDE**  
**PROCUREMENT**  
DATE: 31/05/2016



**DR F BENSON**  
**CLUSTER MANAGER: COMMUNICABLE**  
**DISEASES**  
DATE: 1/6/2016