REQUEST FOR REINSTATEMENT OF EQUINE RABIES IMMUNE GLOBULIN TO THE EML and EMLc

1. Summary statement of the proposal for inclusion

Rabies immune globulin (RIG) products are used for WHO 'category 3' exposed individuals (i.e., bites, scratches and mucosal exposures to rabies virus) during post-exposure prophylaxis (PEP) to neutralize rabies virus locally at the wound site, while an active response to rabies vaccine is mounting. The RIG is derived from the plasma either of horses (eRIG) or humans (hRIG). Both products are safe and effective, but several limitations relate to supply and cost (i.e., for hRIG). During October 2017, the Strategic Advisory Group of Experts (SAGE) reviewed recommendations regarding rabies vaccines and RIG. Among other issues, RIG use was reviewed, and the critical nature of these biologics during PEP was again stressed. Furthermore, SAGE did not state any preference to the use of hRIG over eRIG. Thereafter, the updated WHO position paper on rabies vaccines was published (WHO, 2018b).

Despite the extensive data that demonstrate both safety and efficacy, eRIG is not always used, even when available, due in part to prior medical concerns over the historical use of crude horse serum or unpurified eRIG. Evidence supports the strengthening of current WHO recommendations by the re-inclusion of the critical use for eRIG as an essential medicine, based upon: the evidence in support for its safety and efficacy; the abandonment of the historical practice of skin testing before eRIG administration; current medical promotion as an economical alternative to hRIG; and continued education and awareness for use as a life- and cost-saving option during human PEP.

The latest WHO EML (2019) only includes hRIG. Rabies immunoglobulin (without specification as human or equine) has been included within the EML since 1992. In 2013, the listing changed to specify the biologic as human RIG. Considering that hRIG is in short supply globally and far more expensive than eRIG, we request a consideration to re-instate the equine product within the EML and EMLc.

2. Relevant WHO technical department and focal point

Bernadette Abela-Ridder, Neglected Tropical Diseases, WHO.

Erin Sparrow, Immunization, Vaccines and Biologicals, WHO.

3. Name of organization(s) consulted and/or supporting the application

N/A (beyond the support of the WHO SAGE Working Group and the WHO Expert Consultations, no other organizations have been consulted in relation to this application).

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

Currently, the INN does not exist, hence we suggest use of the term Equine RIG. The ATC code is J06BB05

5. Dose forms(s) and strength(s) proposed for inclusion

We propose the following formulation and strength for the use in both pediatric and adult patients in any available markets:

Equine rabies immune globulin local Injection: 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL in vial

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

We suggest adding a square box to the current hRIG listing, indicating that eRIG was an accepted alternative. Logistically, this would keep the two RIG products together. However, as it is not a human blood derivative, the eRIG individually would probably need to be listed in section 19.2, under sera and immune globulin.

7. Treatment details (including requirements for diagnosis, treatment and monitoring)

Current WHO recommendations on the use of RIG during PEP were updated recently (WHO, 2018b). Changes were based upon functional use, mainly in that the dose of RIG is now based on the anatomical localization of the affected area, instead of the patient's total body weight. Maximum infiltration of RIG into and around the wound is highly effective. Additional benefit from IM administration of any remaining RIG volume at a site distant to the wound appears limited. The amount of administered RIG is therefore in almost all cases based on the location and extent of the lesions, where rabies virus is localized after exposure. Only the maximum dose of RIG is still assessed by body weight (e.g., 20 IU/kg for hRIG; 40 IU/kg for eRIG). Since the introduction of current recommendations, the amount of RIG is estimated to be on average 40% of the quantity that was previously required based on body weight alone (Bharti et al., 2016; 2017; 2019). Hence, these recommendations are expected to have a net positive effect on the costs of human rabies prophylaxis for patients and governments.

8. Information supporting the public health relevance

Rabies is a preventable viral zoonotic and NTD, responsible annually for tens of thousands of global human fatalities (Hampson et al., 2015). Most human rabies cases result from dog bites, and following the onset of symptoms, the disease is almost always fatal. While control heavily depends on prevention of canine rabies by mass vaccination, postexposure prophylaxis (PEP) of bitten humans is a highly effective preventive intervention. After a bite exposure, PEP involves the combined use of extensive wound washing, infiltration of rabies immune globulin (RIG) and administration of modern tissue culture vaccines (WHO, 2018a).

9. Review of benefits: summary of evidence of comparative effectiveness

In addition to increased safety, purified eRIG is highly efficacious, as evident after decades of use (WHO 2018a). One study (Madhusudana et al., 2013) compared the neutralization effectiveness of reduced eRIG and hRIG in cell culture and in mice: *in vitro*, neutralization of rabies virus by eRIG and hRIG were identical, while *in vivo*, full protection was conferred by both (Madhusudana et al., 2013). Moreover, no vaccine was administered to those animals that received RIG, yet the experimental groups that received at least 0.025 IU/100 µl of either eRIG or hRIG had a 100% survival rate, compared to 100% morality in the control group.

Although antigen-binding IG fragments (F(ab')2) may have a shorter half-life *in vivo* than intact IG, the F(ab')2 fragments have a higher specificity and instances of antigen-binding reactions, and therefore efficacy is preserved (Quiambo et al., 2009). In a similar manner to the issue of safety, the relative efficacy of eRIG is strongly supported, especially considering the price and scarcity of hRIG and the 100% case-fatality of rabies.

10. Review of harms and toxicity: summary of evidence of safety

Longstanding biomedical data support the relative safety of eRIG in human PEP (Wilde & Chutivongse, 1990). In the past, crude horse serum and unpurified eRIG were associated with serum sickness, anaphylaxis and other severe adverse reactions (Madhusudana et al, 2013). Today, modern eRIG is highly purified and enzyme-refined and contains over 85% antigen-binding Ig fragments (F(ab')2) (Lang et al., 1998; Shantavasinkul & Wilde, 2011; Quiambao et al., 2008). Through techniques such as heat treatment, pepsin digestion and enzyme refinement, the IG crystallizable/constant (Fc) fragment is removed and the nonspecific protein content of the purified serum is decreased to less than 3% (Behera et al., 2011). As the Fc fragment in unpurified eRIG is responsible for direct complement activation and anaphylactic reactions, the high F(ab')2 content and low Fc proteins allow for increased safety and specific activity (Madhusudana et al., 2013; Quiambao et al., 2008). This eRIG treatment has even been shown to be safe for pregnant women, as the F(ab')2 IG fragments do cross the placenta (Dixit et al., 2016). Studies to date suggest that severe adverse reactions, such as serum sickness and anaphylaxis, are infrequent (Satpathy et al., 2005). Other adverse events tend to be mild, not life-threatening, and easily resolved, such as local pain, redness, induration, fever and pruritus. Clinical studies show that adverse reaction rates for eRIG are similar to the use of penicillin (Wilde, 2012).

Table 10.1 Relative safety of eRIG

LOCATION	NUMBER OF PATIENTS	OBSERVATION PERIOD	SERUM SICKNESS	ANAPHYLAXIS	OTHER ADVERSE EVENTS	REFERENCE
Thailand	27 adults	15 days	0	0		Lang et al., 1998
India	286	90 days		0	82.9% reported pain; 6.3% reported fever	Satpathy et al., 2005
Thailand	42,965		0.05% (under 10 years of age)	1/42,965		Suwansrinon et al., 2006
India	168	30 days	0	0	31.5% of patients experienced local reactions, including pain, swelling, pruritis, induration or erythema	Chawan et al., 2007

The Philippines	7,660 (4 months to 98 years of age)	35 days to 29 months			0.46% experienced local and 1.36% reported systemic reactions (including pain, pruritis, rash, dizziness, or drowsiness)	Quiambao et al., 2008
India	2,008	26 months			1.5 % reported at least 1 adverse event (mild to moderate but no severe events)	Sudarshan et al., 2011
India	1,494 children, < 15 years old	28 days	3%	0	91.8% induration; 43.1% erythema; 29.8% local pruritis; 19.9% pain; 34.8% fever; 29.5% malaise; 6.8% general pruritis	Behera et al., 2011
Thailand	150,000			2/150,000		Shantavasinkul & Wilde, 2011
India	195 children		1.53%	0	49.7% local (pain, induration, pruritis); 12.3% systemic (low grade fever)	Behera et al., 2012

India	269	9 months	0	0	40% reported local redness; 60: reported focal pain	Bharti et al., 2016
Thailand	70,000		0.72%	0	1.83% reported at least 1 adverse event	Dixit et al., 2016

11. Summary of available data on comparative cost and cost-effectiveness of the medicine

In view of many more years of experience in countries and additional data available, the use of eRIG is supported to be a safe and efficacious alternative in the many areas where hRIG is unavailable or unaffordable (Quiambao et al., 2009; Wilde et al., 2016). In general, all RIGs are both expensive and scarcely available. For example, in Cambodia, eRIG (which is consistently less expensive than its sole alternative, hRIG) costs between US$20 and US$30 per dose, while in comparison, a Cambodian farmer's monthly salary is between US$60 and US$80 (Tarantola et al., 2015). Thus, a dose of RIG can drain up to half of one's monthly salary. Similar discrepancies between income and RIG price exist throughout Asia and Africa (Madhusudana et al., 2013; Tarantola et al., 2015; Tenzin et al., 2012). The disparity of cost and availability are even more prominent for hRIG, and thus it is impractical for use in areas with limited monetary resources (Anderson, 2007). Therefore, the data regarding eRIG safety and efficacy are relevant to most rabies virus-exposed individuals.

12. Summary of regulatory status and market availability

Currently, eRIG is registered primarily in LDC of Asia, Africa and Central/South America, including Brazil, China, India, and Thailand, among others. Availability is unpredictable, based in part upon equine stocks, local animal welfare concerns and production limitations.

Table 12.1 Global availability of eRIG products

PRODUCT	FORMULATION	VIAL	PRODUCER	COUNTRY
Anti-rabies serum	200 IU/mL	5 mL	Butantan Institute	Brazil
Rabies Anti-serum	400 IU/mL	2 mL	Shanghai Serum Bio-technology Co., Ltd.	China
Rabix-IG	200 IU/mL	5 mL	Incepta Pharmacueticals	India
VINRIG 1500 IU	300 IU/mL	5 mL	Vins Bioproducts Ltd	India
VINRAB 1000 IU	200 IU/mL	5 mL	Vins Bioproducts Ltd	India

Abhay-RIG	300 IU/mL	5 mL	Indian Immunological	India
Anti-rabies serum	300 IU/mL	5 mL	Haffkine	India
EquiRab	300 IU/mL	5 mL	Bharat Serums and Vaccines	India
EquiRab	200 IU/mL*	5 mL	Bharat Serums and Vaccines	India
Anti-rabies serum	300 IU/mL	5 mL	Serum Institute of India	India
Anti-rabies serum	300 IU/mL	5 mL	Central Research Institute Kasauli HP	India
Plasmarab	300 IU/mL	5 mL	Premium Serums	India
PremiRab (Rabies antiserum I.P)	300 IU/mL	5 mL	Kings Global Biotech Limited	India
PremiRab	300 IU/mL	5 mL	Premium Serums	India
PremiRab	200 IU/mL*	5 mL	Premium Serums	India
Vinrig	300 IU/mL	5 mL	Vins Bioproducts	India
Vinrab	200 IU/mL*	5 mL	Vins Bioproducts	India
TRCS eRIG	200 IU/mL	5 mL	Queen Saovabha Memorial Institute	Thailand
Anti-rabies Immuneglobulin	150 IU/mL	5 mL, 3 mL or 1 mL	Pharmstandard-Biolik	Ukraine

*This formulation is used for export to other countries

13. Availability of Pharmacopoeia standards

Currently, no pharmacopeial standards exist for eRIG.

14. References

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