A.12	Equine rabies immunoglobulin – post-exposure prophylaxis
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: 1. More than 150 countries affected 2. Almost 100% case fatality rate (CFR) 3. 95% deaths in in Asia and Africa 4. 40% of people bitten by suspect rabid animals are children under 15 years of age. 5. Rough estimate of death 60-70,000/year 6. Asia, 3 billion people are affected with dog rabies and more than 30,000 deaths 7. India about 20,000 deaths annually 8. Sri Lanka about 30 deaths annually 9. WHO leads the collective “United Against Rabies” to drive progress towards "Zero human deaths from dog-mediated rabies by 2030” Source: WHO
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	1. Since CFR is almost 100%, prevention becomes very important 2. Post Exposure Prophylaxis(PEP) is the best mode of prevention 3. PEP involves wound care, vaccine and rabies immunoglobulin 4. Exposure is categorized into three 5. RIG administration is recommended after category III exposures of individuals who have not previously been vaccinated against rabies (in addition to thorough wound care and vaccine) a. Category III - single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (severe exposure) b. Category III contributes to a sizable portion of exposure because it excludes only {touching or feeding animals, animal licks on intact skin (no exposure) and nibbling of uncovered skin, minor scratches or abrasions without bleeding (exposure)} 6. Rabies Immunoglobulin is derived either from Human (hRIG) or equine (eRIG). WHO position paper on rabies (2018) has not differentiated between these two 7. Currently available eRIG is a purified form with minimal serious allergic reactions like anaphylaxis or serum sickness 8. Current recommendation for eRIG include: a. Maximum possible infiltration around the wound/s b. No need to follow this up with IM injection (balance Ig) c. No need of skin test d. Dose is 40 IU/Kg (hRIG is 20 IU/Kg) 9. WHO – EML has listed as Rabies Immunoglobulin until 2011, but in 2013 it has been changed to human RIG 10. Reason for such change is not reported in the relevant TRS 11. Last EML RIG is listed under human immunoglobulin 11. 2.1 (Section 11: Blood products of human origin and plasma substitutes) 12. Application is to list the eRIG under section 19.2 (Sera and Immunoglobulin) (Section 19 is Immunological)

Have all important studies and all relevant evidence been included in the application?	☐ Yes ☐ No ☒ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: Problems 1. Rabies is a neglected tropical diseases 2. Its prevalence is high in resource limited countries 3. Conducting rigorous clinical trials in PEP for prophylaxis will have both ethical as well as financial constrains 4. Application is for reinstatement of eRIG 5. Key reason for the application is to increase the access to RIG
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☒ No ☐ Not applicable See my comments above (point number 3) Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? No Evidence of use is documented in all special groups
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Since safety data mainly comes from observational and post marketing studies, safety data is given more than the efficacy data. In addition, safety is a concern when it comes to equine RIG. However with introduction of purified eRIG, safety of this product has improved
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Recipients have to be monitored for anaphylaxis and other form of allergic reactions. Since this is well documented, rabies management centres are expected to be ready with emergency treatment for anaphylaxis. But with recent purified preparations, risk of anaphylaxis is considerably low

Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable I have assessed this to be favourable though benefit is not supported by hard evidence from well conducted RCTs because of the following reasons 1. Almost 100% case fatality rate 2. Constrains in conducting rigorous RCTs 3. eRIG is used by many countries without any issues in benefits or risks 4. WHO's position on RIG 5. Risks are "well documented" 6. Risks are less with purified preparations
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Low (see my comments above)
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: 1. Management of anaphylaxis 2. Availability of vaccines as well 3. Injection skills (ID, IM for vaccines and local infiltration for eRIG)
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: But it is recommended in the WHO'S position paper (approved by SAGE (Strategic Advisory Group of Experts on Immunization)
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	1. Equine Rabies Immunoglobulin is listed in the national EMLs of many countries such as India, Sri Lanka, China, Thailand, Philippines…. Some countries such as Ghana, Bangladesh, Pakistan have listed as rabies immunoglobulin without specifying the source (human/equine) (I did not do a complete search) 2. However, there are problem in production (which is more with the alternative, hRIG) 3. Cost and affordability (Cost of human RIG is very much higher than that of equine RIG 4. In Sri Lanka, rabies vaccine, eRIG and hRIG had been in the top 10 items purchased (cost wise) – Old data, unpublished, in 2011, 295915, 104134, 8352 vials of ARV, ARS and hRIG have been procured incurring a cost of 230.4, 42.35 and 50.80 million Sri Lanka rupees respectively (unit cost of 300 U vial of hRIG was about 12-13 time higher than that of eRIG (1000- 1500 IU) 5. Application to reinstate eRIG is submitted to compensate the problems in availability and affordability of having one RIG in the EML

Any additional comments	None
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	RECOMMEND reinstating equine RIG into EML and EMLc under section 19.2 Good to have a range of strengths as production is difficult and there can be batch to batch variation Reasons for the recommendation 1. Rabies has no treatment 2. Case fatality of symptomatic treatment is almost 100% 3. Annually about 60,000 people die of rabies 4. Cases and deaths are common in RLCs in Asia and Africa 5. WHO targets "that the deaths caused by dog transmitted rabies to zero in 2030" 6. Pre exposure prophylaxis of susceptible population post exposure prophylaxis (PEP) of people after exposure are the two pharmacological preventive strategies 7. Annually about 3 million receive PEP 8. PEP involves wound care, vaccine and rabies immunoglobulin 9. WHO recommendation: Category III exposure (severe exposure) needs all 3 modalities of PEP 10. RIG can be equine or human derived 11. Clinical trials comparing these products are limited 12. Observational studies have reported no difference in efficacy 13. Being of equine origin, eRIG is expected to have more adverse effects including anaphylaxis 14. However, with recent purified forms, frequency of anaphylaxis is considerably low 15. Since PEP is provided in a hospital setting recognizing and treating anaphylaxis is feasible 16. Rabies is considered under neglected tropical disease with many resource rich countries have eradicated rabies from their countries with rabies cases limited to only a handful (bat more than dogs) and to travellers 17. Though hRIG is preferred over equine due to relative safety aspects, hRIG is more expensive then equine 18. Hence availability of hRIG in countries where rabies is still prevalent is low and restricts the success prevention of rabies after exposure 19. Considering the CFR of 100% and problems in affordability and production of hRIG, I personally believe that whatever the risk associated with eRIG is negligible and benefits are favourable 20. Application is requesting to reinstate eRIG in EML and EMLc

	21. Up to 2013, EML had rabies immunoglobulin with square box, but in 2013, it has been changed to human RIG (I looked for discussion in the TRS, I could not find) 22. Having hRIG in the EML should not be considered as an impediment for having eRIG also in EML
References (if required)	1. https://www.who.int/news-room/fact-sheets/detail/rabies 2. Harischandra PAL, Gunesekera A, Janakan N, Gongal G, Abela-Ridder B. Sri Lanka takes action towards a target of zero rabies death by 2020. WHO South- East Asia J Public Health 2016; 5(2): 113–116. 3. https://www.who.int/rabies/resources/who_wer9316/en/(Weekly Epidemiological Report: 20 APRIL 2018, 93th YEAR / No 16, 2018, 93, 201–220 http://www.who.int/wer 4. https://www.who.int/selection_medicines/country_lists/en/