A.26	Rabies monoclonal antibodies – post-exposure prophylaxis
Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☒ No ☐ Not applicable While totally accepting the public health importance of rabies, adequate evidence was not available in the application for the claim "The inclusion of ARV MAbs into human PEP represents an opportunity for large scale production of safe, effective, well-characterized, dependable, and uniform biologics, with anticipated lower long term manufacturing costs (Sparrow et al., 2019) found in the application. The referenced publication (Sparrow et al., 2019) is a review article and it also did not provide evidence for the claim. First and last author of this cited publication are the contacts in the relevant WHO Technical department and focal point for this application
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.	Application to reinstate eRIG into EML and EMLc is also submitted. If this application is recommended, we will have two options for passive immunization (PEP) in the EML. These two are time tested intervention in PEP and countries have to take immediate steps to ensure universal access to these two products. I did not see adequate evidence to add monoclonal antibodies as well to this list at this juncture Application claims that Rabies MAB will overcome the issues related to low production of eRIG and hRIG: Of the studies listed in Table 9.1, only 2 are beyond Phase I and recruited patients (N= around 250). With COVID-19 pandemic, the process will be further delayed. Hence, I am unable to recommend Rabies MAB to be added to EML at this juncture. It is too early
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: Limited studies. Inadequate evidence Six trials (testing 3 different products) have been presented. Only 2 of these trials are beyond Phase II. SAGE background paper published in 2017 has recommended post marketing surveillance (PMV) data as one product was registered in India at that time. No evidence from PMV as well.

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☒ No ☐ Not applicable 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). Six trials (testing 3 different products) have been presented. Only 2 of these trials are beyond Phase II. These 2 trials tested two products 1. 17C7/SII RAB1 (Homologous (single human MAb) 2. M777-16-3 & 62-71-3 (Heterologous (cocktail of 2 murine MAbs) Hence we cannot pool the results **Product 1**: Day 14 MAb GMC, 24.9 IU/mL (95% CI, 18.9–32.7); RIG GMC 5.9 IU/mL (95% CI, 4.1–8.4) {surrogate outcome}. Not statistically different in day 28, 42 and 84 (101 and 98 patients, respectively) **Product 2:** 130 (90.3%) patients in the MAb arm and 134 (94·4%) patients in the RIG arm had an antibody titer ≥0·5 IU/ml by Day 14, with a GMT of ***4.4 and 4.9 IU/ml,*** respectively (MAbs found to be non-inferior to RIG) Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? No, of the 6 studies, only 2 are beyond Phase II. Both have been conducted in India. No evidence for children , elderly or pregnant patients Note: 40% of exposure in children < 15 years
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: Application provide adverse effects data from 6 premarketing studies; Of them only 2 are Phase III with about 250 patients. Inadequate number to provide evidence of safety data No post marketing data for the product which was registered in India in 2017 (though SAGE has recommended to monitor and report)
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☐ No ☐ Not applicable Comments: No post marketing surveillance data. Pre-marketing clinical trials with 250 patients is hardly adequate to provide any adverse effects data. Hence unable to comment about AEs of concern

Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Uncertain 1. Inadequate data on efficacy of the product 2. Inadequate data on adverse effects
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 for the question about evidence of efficacy
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: Should be as it is a parenteral preparation
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: Heterologous (cocktail of 2 murine MAbs) – Registered only in India Homologous (single human MAb) – Registered in India and few more RLCs. Not registered with FDA, EMEA, TGA, etc. Not sure whether this could come under WHO pre-qualification programme
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 given in the background paper of SAGE as "*mAb should be used as part of PEP. The currently available single mAb and its use in selected geographic and epidemiological settings will serve as an important learning process for future mAb products. Post-marketing surveillance and close monitoring of adverse events, including in depth investigations on suspected PEP failures associated should be conducted. The uptake of mAb will also depend on pricing*"
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	1. Set back in clinical trials due to COVID-19 Pandemic 2. Only two products are so far registered 3. Not registered in many countries 4. Non familiarity with the products 5. Cost is higher than the alternative options

Any additional comments	
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.	NOT RECOMMENDED REASONS 1. Inadequate evidence on efficacy, safety, effectiveness, cost and access 2. Though started to market in India in 2017, no data from post marketing surveillance 3. Two products (one is cocktail of two murine antibodies and the other is one MAB). Former is registered only in India, latter in few more countries. 4. Not sure about the actual cost /exposure with MAB 5. Countries have been familiar with the use of hRIG and eRIG – We should strengthen these two products at this juncture 6. Too early to recommend RMAB to be added to EML now
References (if required)	1. WHO. Rabies Working Group Report, SAGE meeting, October 2017. Available at http://www.who.int/immunization/sage/meetings/2017/october/1_Background_paper_WG_RABIES_final.pdf?ua=1. 2. World Health Organization. Rabies vaccines: WHO position paper, April 2018 – Recommendations. Vaccine. 2018a;36(37):5500-3. 3. Gogtay NJ, Munshi R, Ashwath Narayana DH, Mahendra BJ, Kshirsagar V, et al. Comparison of a Novel Human Rabies Monoclonal Antibody to Human Rabies Immunoglobulin for Postexposure Prophylaxis: A Phase 2/3, Randomized, Single-Blind, Noninferiority, Controlled Study. Clin Infect Dis. 2018;66(3):387-39.