(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☒ No ☐

Please provide brief details: The annual incidence of microbial keratitis varies with geographical location. In tropical regions approximately half of all microbial keratitis cases (all causes) are widely reported to be caused by fungal infections. Fungal keratitis is associated with low Gross National Income countries. The annual incidence of microbial keratitis in contact lens wearers varies: 1.2-1,304/10,000, and the proportion of microbial keratitis cases caused by fungi in contact lens wearers varies from 0.33% to 50% with an occurrence of international outbreak of Fusarium keratitis in contact lens users in 2004-2006.

(2) Have all important studies/evidence of which you are aware been included in the application?

Yes ☒ No ☐

Please provide brief comments on any relevant studies that have not been included:

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☒ No ☐

(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine: Natamycin 5% topical ophthalmic solution has been widely used for more than 40 years in the treatment of fungal keratitis caused by filamentous organisms. Three clinical trials indicate that natamycin 5% topical ophthalmic solution is more effective than voriconazole in the treatment of fungal ulcers. A trial found no significant difference between natamycin 5% topical ophthalmic solution and econazole.

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details: Yes. The evidence of efficacy of Natamycin is based on the results of seven clinical trials performed in India and Bangladesh. Topical natamycin
has been used extensively for the treatment of fungal keratitis in South Asia, South-East Asia and North America. It has recently become the standard of care in the UK. However, the clinical trials of efficacy do not represent diverse populations.

(4) **Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?**

Yes ☒ No ☐

Please provide brief details: Although Experience from carefully reported clinical trials indicate that the possible adverse events connected to natamycin are rare and that topical natamycin is generally well tolerated, the safety and adverse effects of natamycin 5% topical ophthalmic solution require monitoring because the sample size of patients in clinical trials was not large.

(5) **Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).**

The overall benefit to risk ratio of natamycin 5% topical ophthalmic solution is favourable. The benefit largely overweighs the risk of rare adverse events.
ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☒ No ☐

Please provide brief details: Training is needed especially for the appropriate use. Treatment outcome of Natamycin 5% eye drops depends on the timely treatment and the frequency and course of treatment. For treatment of fungal keratitis, natamycin 5% eye drops used hourly initially (day and night). Eye examination every 2 days until the ulcer starts improving. The frequency of treatment is adjusted according to the clinical response. Typically drops are continued at least 3 hourly for at least 2 weeks after healing of the ulcer. Prolonged treatment courses lasting several weeks are usually necessary.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☒

Please provide brief details: Clinical trials have shown the good efficacy and safety of Natamycin 5% eye drops. Topical natamycin has been used extensively for the treatment of fungal keratitis in South Asia, South-East Asia and North America. It has recently become the standard of care in the UK.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☐ No ☒

Please provide brief details:

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

Natamycin 5% topical ophthalmic solution is expensive, and is not widely available in some tropical countries such as Nepal, Ecuador, Chile or Madagascar. In the Philippines and Denmark, it can be specially imported. It is actively sold in India and Myanmar. However, clinical use is necessary for treatment of fungal keratitis.

(10) Any additional comments?
None.

(11) Please frame the decisions and recommendations that the Expert Committee could make.
Natamycin 5% topical ophthalmic solution should be included into the WHO EML despite an expensive cost for a single bottle, in terms of its effect superior to alternative treatment for fungal keratitis. Especially, there are no topical antifungal ophthalmic preparations in the current WHO EML for the treatment of fungal keratitis.

(12) References (if required)

There is a systematic review and Meta-analysis reference should be cited in review.