I.4 (item number)	**Antibacterials – Ocular infections** (application title)
Does the application adequately address the issue of the public health need for the medicine?	■ Yes ☐ No ☐ Not applicable Comments: *The WHO Essential Medicine List (EML) lists the most efficacious and safe medicines to treat illnesses that are considered high priority, including antibiotics. However, most antibiotics were listed decades ago and a comprehensive review of all the antibiotics listed over the past 40 years has never been done. Given increasing concerns about overuse of antibiotics, the emergence of antimicrobial resistance and the need to guarantee prompt access to highly beneficial treatments, revising and updating the list is an important priority*

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.	*The following antibiotics with ophthalmological preparations are already included in the 21st WHO Model List of Essential Medicines (2019, pg 45): azithromycin erythromycin, gentamicin, natamycin, ofloxacin and tetracycline.*
	Azithromycin for trachoma is already covered in 21st WHO Model List of Essential Medicines (2019, pg 12)
	The applicant suggests the following for EML:
	• *Conjunctivitis and keratitis: fluoroquinolone-containing topical antibiotics (e.g. ofloxacin 3mg/ml) - already covered in EML list (pg 45)*
	• *Trachoma: Azithromycin (oral) for paediatric and adult patients with trachoma (20mg/kg body weight up to 1000mg) - already covered in EML list (pg 12)*
	• *Endophthalmitis:*
	  • *Vancomycin plus ceftazidime for intravitreal administration.*
	  • *For systemic treatment, IV ceftriaxone (2g daily) plus IV vancomycin 15-20mg/kg twice daily).*

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:

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).
	
	(1) Conjuntivitis
	• *Bacterial:*
	  ○ *azithromycin, polymyxin, bacitracin, moxifloxacin, besifloxacin, ciprofloxacin, norfloxacin, fusidic acid, and chloramphenicol showed a benefit for early clinical resolution (day 2-5) (RR 1.36; 95% CI, 1.15-1.61) and late resolution (day 6-10) (RR 1.21; I95% CI 1.10-1.33) when compared to placebo (11 RCTs; 2116 patients). There were no serious outcomes in either arm [Sheikh 2019].*
	  ○ *chloramphenicol and fusidic acid showed higher cure rate at day 7 (risk difference 0.08; 95% CI 0.01-0.04; 3 RCTs; 626 patients), and in particular, for those with purulent discharge and mild severity of eye redness in subgroup analysis [Jefferis 2011].*
	  ○ *No studies of head-to-head comparison was identified, therefore there is no systematic review data to guide the choice of antibiotics*
	• *Trachoma:*
	  ○ *topic antibiotics showed a benefit for cure at 3 months (RR 0.78, 0.69-0.89), but no effect on a benefit at 12 months (RR 0.74, 0.55-1.0) [Evans 2019].*
	  ○ *systemic azithromycin showed benefit when compared with topical tetracycline (RR 0.76, 0.59-0.99) at 12 months outcome of active trachoma, while there was no difference at the 3 months (no effect size was reported) [Evans 2019].*
	
	(2) Keratitis
	• *Different topical antibiotics: no significant difference between groups. was found for treatment success, time to cure, or serious complications (including corneal perforation) (16 RCTs; 1823 participants) [McDonald 2014].*
	• *Fluoroquinolones were better tolerated in terms of ocular discomfort and chemical conjunctivitis than aminoglycoside-cephalosporin combinations (RR 0.20, 0.10-0.41).*
	• *Fluoroquinolones increased the risk of corneal precipitates compared to the aminoglycoside-cephalosporin combinations (RR 24.4, 4.68-126.89).*
	
	(3) Endophthalmitis
	• *No data from primary or secondary studies was provided.*
	
	Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?
	• *No diverse setting was explored in the studies presented by the applicant.*

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	■ Yes ☐ No ☐ Not applicable Comments:
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ■ No ☐ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	*The applicant does not provided evidence for head-to-head comparison of different antibiotics for ocular infections, the overall benefit to risk ratio is uncertain.*
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	*The overall quality for head-to-head comparison of different antibiotics for ocular infections is unknown.*
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:
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: *Trachoma: WHO webpage recommends azithromycin for treating trachoma (https://www.who.int/health-topics/trachoma#tab=tab_3).*
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	*The applicant did not present any cost or cost-effectiveness data.* *It is reasonable to expect that newer antibiotics are relatively more expensive than other alternatives already incorporated on EML with heterogeneous accessibility and affordability in different countries.*
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.	*The antibiotics suggested by the applicant for conjunctivitis (including trachoma) and keratitis are already covered in EML.* *Regarding the antibiotics proposed for endophthalmitis (vancomycin plus ceftazidime for intravitreal administration and ceftriaxone plus IV vancomycin for systemic treatment, the lack of comparative data and the uncertainties regarding the incremental cost of newer antibiotics prevents a favourable recommendation to incorporate further antibiotics on the EML.* *Therefore, the proposed recommendation to the Expert Committee is t**o not incorporate further antibiotics for ocular infections on the EML**.*
References (if required)	*Evans, J.R., et al., Antibiotics for trachoma. Cochrane Database Syst Rev, 2019. 9: p. CD001860.* *Jefferis, J., et al., Acute infective conjunctivitis in primary care: who needs antibiotics? An individual patient data meta-analysis. Br J Gen Pract, 2011. 61(590): p. e542-8.* *Sheikh, A., et al., Antibiotics versus placebo for acute bacterial conjunctivitis. Cochrane Database Syst Rev, 2012(9): p. CD001211.*