Record of the Ophthalmology Subcommittee of PTAC Meeting held on 23 June 2021

Ophthalmology Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the Ophthalmology Subcommittee meeting; only the relevant portions of the meeting record relating to Ophthalmology Subcommittee discussions about an Application or Pharmac staff proposal that contain a recommendation are generally published.

The Ophthalmology Subcommittee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at an upcoming meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present

Stephen Munn (Chair)
Jo Sims
Lisa Stamp
Malcolm McKellar
Marius Rademaker
Peter Grimmer
Samuel Whittaker

2. Summary of recommendations

2.1. The following recommendation summary is an order of the discussions held at the meeting.

Pharmaceutical and Indication	Recommendation
• 6.2 Atropine 0.01% eye drops to control the progression of myopia	Medium Priority
• 7.2 Cefuroxime 1 mg in 0.1 ml for intracameral injection following cataract surgery, for prophylaxis of endophthalmitis	High Priority
• 7.3 Moxifloxacin 0.5% for intracameral injection following cataract surgery, for prophylaxis of endophthalmitis	High Priority

3. The role of PTAC Subcommittees and records of meetings

3.1. This meeting record of the Ophthalmology Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the Pharmac website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

3.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

3.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

3.4. The Ophthalmology Subcommittee is a Subcommittee of PTAC. The Ophthalmology Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Ophthalmology Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for Ophthalmology that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Ophthalmology that differ from the Ophthalmology Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

Pharmac considers the recommendations provided by both the Ophthalmology Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for Ophthalmology.

4. Record of Subcommittee meeting held Friday, September 2017

4.1. The Subcommittee reviewed the minutes of the Subcommittee meeting held on September 2017, and agreed that the minutes be accepted.

5. Therapeutic Group Review

Anti-VEGF agents

5.1. The Subcommittee noted that expenditure on anti-VEGF agents had increased markedly since the listing of aflibercept, and expenditure has not yet plateaued. The Subcommittee considered that it expected the expenditure growth to have reduced with the special authority criteria in place. An additional criterion requiring a fluorescein angiogram for indications other than DMO could be appropriate. The Subcommittee considered it would like to review patient numbers across DHBs compared to DHB populations, to assess trends in usage. The Subcommittee considered it could review this data by email discussion before its next meeting.

Anti-infective eye preparations

5.2. The Subcommittee noted that the unit volume for anti-infective eye drops has remained stable from 2013 to 2019, but declined in 2020. Members noted that the main contributors to expenditure in this group are chloramphenicol eye ointment 1% and fusidic acid eye drops. The Subcommittee considered that fusidic acid eye drops are also used in the management of dry eye as it has mild anti-inflammatory properties.

5.3. The Subcommittee were made aware that in April 2021, the Royal College of Ophthalmologists issued a safety alert about boron additives in chloramphenicol eye drops, which was based on a European Medicines Agency recommendation of an upper limit on exposure to boric acid and borate used as excipients (1 mg per day for children under 2 years and 3 mg per day for children aged 2 to 12 years, expressed as equivalent doses of elemental boron). The Subcommittee

was also made aware of a recent review article (Bolt et al. Arch. Toxicol. 2020;94:717-24). The Subcommittee considered that the evidence base is largely animal data with very high doses, which are not achieved in humans at therapeutic doses. The Subcommittee noted that boron content of medicines had been referred to Medsafe's Medicines Adverse Reactions Committee (MARC) and that it would like to consider Medsafe's advice on this matter.

5.4. The Subcommittee considered that many patients prefer chloramphenicol ointment over eye drops, but many child day care centres do not permit children to return following conjunctivitis until they have had treatment with antibiotic eye drops, which may lead to inappropriate prescribing.

Eye / ear preparations

5.5. The Subcommittee noted that both framycetin sulphate (Soframycin) and dexamethasone with framycetin and gramicidin (Sofradex) ear and eye drops would be used primarily in the ear, and considered that their use in the eye is uncommon.

Eye corticosteroids and other anti-inflammatory preparations

5.6. The Subcommittee noted that while usage in this group has been relatively stable, expenditure is increasing. Members noted that the main contributors to increased expenditure since 2017 have been diclofenac sodium and prednisolone acetate. The Subcommittee noted that there had been supply issues with diclofenac sodium eye drops, managed with the temporary listing of nepafenac 0.3% eye drops.

Glaucoma preparations - beta blockers

5.7. The Subcommittee noted that usage has been very stable over recent years, apart from a marked decrease from March to June 2020. The Subcommittee considered that this was due to COVID-19 restrictions and resulting missed appointments. Members considered that it was likely that some patients would have been lost to follow up as a result of the COVID-19 disruption.

Glaucoma preparations - carbonic anhydrase inhibitors

5.8. The Subcommittee noted that this group has shown a gradual increase in cost and usage, apart from a marked decrease from March to June 2020, due to the national COVID-19 Alert Level 4/3 circumstances. The Subcommittee noted that acetazolamide usage is relatively high, and noted that usage was mainly short term while awaiting glaucoma surgery.

Glaucoma preparations - prostaglandin analogues

5.9. The Subcommittee noted that expenditure in this group decreased from 2019 to 2020 as a result of a tender brand change to travoprost. Members noted that due to a global discontinuation, the Travopt brand is no longer available, so expenditure has increased again following the listing of the Travatan brand. The Subcommittee noted that expenditure on travoprost was expected to decrease again following the 2020/21 Invitation to Tender.

Glaucoma preparations - other

5.10. The Subcommittee noted that usage and expenditure in this group have been stable until 2020. Members noted that brimonidine accounted for the increase in expenditure from January 2021.

Mydriatics cycloplegics

5.11. The Subcommittee noted that mydriatics and cycloplegics are used to dilate the pupil during eye examinations and intraocular surgery. The Subcommittee considered that there is a need for the continued availability of a short-acting mydriatic, such as tropicamide. Members considered that cyclopentolate was a possible replacement but has a longer duration of action than tropicamide, which can be inconvenient for patients. The Subcommittee considered that while reversible eye drops such as pilocarpine can be used, they can cause discomfort and severe miosis. The Subcommittee considered that Māori and people with diabetes would be particularly affected by supply issues for mydriatics and cycloplegics.

Preparations for tear deficiency

5.12. The Subcommittee noted that usage and expenditure on preparations for tear deficiency have been increasing yearly. The Subcommittee noted that polyvinyl alcohol (Vistil) was discontinued in early 2020 and that hypromellose with dextran (Poly-Tears) accounted for most of the usage in this category.

5.13. The Subcommittee considered that there were many lubricant products available, although many contain preservative. Members noted that preservatives in eye drops may start to cause issues if they are used more than six times per day, although patients with dry eye tend to have increased flora in their eyes and the preservative can have a role in supressing the flora which may in fact be of benefit.

5.14. Members considered that, in general, there are limited options for products which are easy to use for people with dexterity issues. Members noted that single-use dropper ampoules are the easiest to use for people with dexterity issues, however also recognised that this packaging creates greater plastic waste.

Preservative free ocular lubricants

5.15. The Subcommittee noted that usage and expenditure has continued to increase in the preservative free ocular lubricant group. Members considered that the increase in usage likely reflected the previously unmet health need, hence usage grows as more people who do not tolerate preserved eye drops continue to access preservative free options.

5.16. The Subcommittee noted that the current eligibility criteria for preservative free eye drops require confirmation of diagnosis of severe dry eye by slit lamp. The Subcommittee considered that the criteria could be amended to include diagnosis by slit lamp OR Schirmer test. The Subcommittee considered that rheumatologists see patients with Sjogren Syndrome and would be able to perform the Schirmer test without requiring specialised equipment. The Subcommittee requested that Pharmac seek members' input into some revised eligibility criteria that included the Schirmer test as an alternative to diagnosis by slit lamp.

5.17. The Subcommittee considered that it would be useful to have more funded options for preservative-free lubricant eye drops and considered that carmellose would be

a suitable additional option. Members noted that carmellose is supplied in single dose plastic vials, which creates plastic waste. It would be preferable to have individual vials that can be capped for the day. Members considered that most patients would use one vial per day.

Other eye preparations

5.18. The Subcommittee noted that olopatadine accounted for the majority of usage and expenditure in the other eye preparations group. The Subcommittee noted the seasonal nature of olopatadine use. The Subcommittee noted that there is a ciclosporin 0.9% eye drop currently under assessment by Medsafe. The Subcommittee considered that if ciclosporin eye drops were listed in the future for atopic or vernal keratoconjunctivitis, it would be unlikely to reduce olopatadine usage, but would be expected to reduce ophthalmic steroid and ocular lubricant usage.

Horizon scanning

5.19. The Subcommittee considered that it would be useful to have a ganciclovir product available and noted that at its February 2016 meeting it had recommended the listing of ganciclovir 0.15% eye ointment if cost neutral to acyclovir. The Subcommittee noted that there are currently no Medsafe approved ganciclovir eye products available in New Zealand. Members noted that the Virgan brand of ganciclovir is supplied by Thea Pharmaceuticals in the UK.

5.20. The Subcommittee noted that there were promising developments with gene therapy for treating retinitis pigmentosa, with outcome data now covering up to four years. The Subcommittee noted that it was only effective in a particular genotype. The Subcommittee considered that any future funding application for this product should be considered by both the Ophthalmology Subcommittee and the Rare Disorders Subcommittee, possibly with further input from ocular geneticists.

5.21. The Subcommittee considered that dexamethasone implants could be used for macular oedemas that are not related to diabetes.

5.22. The Subcommittee noted that the ant-VEGF brolicizumab has a longer half-life than currently funded agents for wet age-related macular degeneration. The Subcommittee noted that brolicizumab was approved by the TGA in April 2020 and was very recently approved by Medsafe. The Subcommittee considered it would like to review any funding application that might be received for brolicizumab.

5.23. The Subcommittee considered that it would like to review any funding application that might be received for vitamin supplements used in the prevention of macular degeneration in high risk patients.

6. Atropine 0.01% for myopia

Application

6.1. The Subcommittee reviewed a clinician application for the use of atropine 0.01% eye drops to control the progression of myopia, reducing the risk of ocular conditions

(such as cataracts, glaucoma, retinal detachment and myopic maculopathy) secondary to myopia.

Recommendation

6.2. The Subcommittee **recommended** that atropine 0.01% eye drops to control the progression of myopia be funded with a **medium priority** within the context of treatment of eye diseases, subject to the following Special Authority criteria:

> **ATROPINE 0.01% EYE DROPS**
> **Initial application** from any optometrist or ophthalmologist.
> All:
> 1. Patient is a child 6 to 18 years of age inclusive; and
> 2. Patient has myopia; and
> 3. Patient's refractive error has changed by -0.5 dioptres (D) in the past six months.

6.2.1. In making this recommendation, the Subcommittee noted:

- the natural history of myopia and the unmet health need in this population;
- the equity issues in current access to atropine and other treatments to slow the progression of myopia;
- the absence of funded pharmaceutical treatments to slow the progression of myopia; and
- the high-quality evidence of some benefit from treatment with atropine 0.01% eye drops; and
- the possibility that funding a pharmaceutical treatment for myopia may help to reduce inequities.

Discussion

6.3. The Subcommittee noted that myopia, also known as short-sightedness or near-sightedness, is a refractive error affecting a person's vision due to an image inaccurately focusing on the retina of the eye. Myopia usually results from increased axial length of the eyeball, although some cases may be due to increased curvature of the cornea, a lens with increased optical power, or occasionally due to other disease (eg arising secondary to corneal disease). The Subcommittee noted that myopia is quantitatively defined by a spherical equivalent objective refractive error of ≤ −0.50 dioptres (D) in either eye and that high myopia is defined by a spherical equivalent objective refractive error of ≤ −5.00 D in either eye (Flitcroft et al. Invest Ophthalmol Vis Sci. 2019:60;M20-M30).

6.4. The Subcommittee noted that the prevalence of myopia worldwide is varied and rising, with estimates that half of the world population will be affected by 2050. The Subcommittee noted there is particularly high prevalence in East and Southeast Asian populations (60-97%) compared with the rest of the world (31-35%) and that about 20% of patients have high myopia (Holden et al. Ophthalmology. 2016:123;1036-42). The Subcommittee noted that myopia progresses at a faster rate at younger ages and in those with a myopic parent or myopic parents. Members noted that myopia progression after age 17 is minimal and considered that after age 21 a patient with myopia is considered to be stable with no further

growth in axial length expected and no benefit to be gained from treatments intended to slow the progression of myopia.

6.5. The Subcommittee was made aware of evidence that reported axial lengths of ≥26 mm and refractive errors of ≤ −6 D were significantly associated with an increased lifetime risk of visual impairment (Tideman et al. JAMA Ophthalmol. 2016;134:1355-63). The Subcommittee noted that high myopia increases the risk of eye diseases including myopic macular degeneration, retinal detachment, glaucoma and cataracts. Of these, the Subcommittee noted that myopia of ≥ -7 D substantially increases the incidence of retinal detachment [odds ratio (OR) 44.2] and myopic maculopathy (OR 126.8), the latter of which is a permanent problem (Flitcroft DI. Prog Retin Eye Res. 2012;31:622-60).

6.6. The Subcommittee considered that ideally diagnostic criteria should include a reduction in axial length progression after a baseline measurement, however, access to ophthalmology services could present a barrier if axial length measurement is required in order to access a funded treatment. The Subcommittee considered there was substantial variation in the degree of myopia screening around the country. Members considered that a meaningful change in refraction of -0.5 D after six months from the previous assessment would be a reasonable threshold for consideration of treatment for a young patient to slow the progression of their myopia; however, the Subcommittee considered that requiring multiple visits to assess myopia progression could be challenging for some patients. Members noted that reallocation of heath resource in response to COVID-19 has meant that age 4 years eye checks are not currently performed in some regions, although members considered that this would be an appropriate time point to identify myopia in children.

6.7. The Subcommittee noted that there are no funded pharmaceutical or other interventions for myopia. The Subcommittee considered that approximately 1,000 children in New Zealand would be receiving treatment for myopia consisting of either bifocal or Hoya MiyoSmart spectacle lenses, soft disposable multifocal contact lenses, orthokeratology or self-funded atropine eye drops. The Subcommittee noted that these interventions can be prohibitively expensive to patients due to the need for regular optometry and ophthalmology appointments and optical prescription changes. Members noted that laser eye surgery is not used for treatment of myopia in children and does not change the risk of complications such as retinal detachment, however, it may be used to correct refractive error in patients over 20 years of age.

6.8. The Subcommittee noted that atropine is an anticholinergic agent which blocks muscarinic acetylcholine receptors. The Subcommittee noted that topical atropine 0.01% as a compounded eye drop is thought to interact with receptors in the eye which control growth of the eye and through this action, may slow the progression of myopia. The Subcommittee noted that atropine 0.01% eye drops are proposed to be used at a dose of one drop per eye, per day.

6.9. The Subcommittee noted that two presentations of atropine 1% eye drops (Atropt and Minims Atropine Sulfate) have current Medsafe approval with no specific listed indications, however, atropine 0.01% eye drops are not approved by Medsafe for any indication.

6.10. The Subcommittee noted evidence for atropine 1.0% eye drops that came from the phase II, parallel-group, placebo-controlled, randomised (1:1), double-masked ATOM 1 study of 400 children with refractive error of spherical equivalent -1.00 to

-6.00 D and astigmatism of -1.50 D or less (Chua et al. Ophthalmology. 2006;113:2285-91). The Subcommittee noted that participants received atropine sulfate 1% eye drops or placebo (vehicle eye drops containing 0.5% hydroxypropyl methylcellulose and 1:10,000 benzalkonium chloride) once nightly for 24 months in ATOM 1.

6.11. The Subcommittee noted that ~94% of ATOM 1 participants were of ethnic Chinese origin and that all participants were aged 6 to 12 years, with a mean age of 9.2 years. The Subcommittee noted that mean myopia in the treated eye at baseline was -3.36 (+/-1.38) D in patients who received atropine vs -3.58 (+/-1.17) D in patients who received placebo, and that the mean axial length in the treated eye at baseline was 24.80 mm in both groups.

6.12. The Subcommittee noted that after two years mean myopia progression was -0.28 (+/-0.92) D with atropine vs -1.20 (+/-0.69) D with placebo (P<0.001) and that the axial length was -0.02 (+/-0.35) mm with atropine vs elongation of 0.38 (+/-0.38) mm with placebo (P<0.001) in ATOM 1. The Subcommittee considered that in the atropine group, growth in axial length was essentially stopped and that the refractive error slowed to the point where progression in refractive error was very little.

6.13. The Subcommittee noted that phase II of the ATOM 1 trial provided a further 12 months follow up of the 400 children who previously received either atropine 1% or vehicle eye drops (placebo) for two years in ATOM 1 (Tong et al. Ophthalmology. 2009;116:572-9) and noted that there was an additional analysis out to 3 years in this trial population (Kumaran et al. Invest Ophthalmol Vis Sci. 2015;56:5650-5). The Subcommittee noted that in the 12 months after cessation of atropine, a rebound effect was seen in myopia progression and axial length.

6.14. The Subcommittee noted evidence from the ATOM 2 single centre, double-masked, randomised (2:2:1) study of 400 children aged 6 to 12 years with refractive error of spherical equivalent -1.00 to -6.00 D and astigmatism of -1.50 D or less who received either atropine 0.5%, atropine 0.1% or atropine 0.01% once nightly to both eyes for two years (Chia et al. Ophthalmology. 2012;119:347-354). The Subcommittee noted that untreated patients were mean 9 years of age and atropine-treated patients mean 10 years of age; the sample size was small given the three trial groups; and the trial did not include a placebo control group. The Subcommittee noted that after two years in the patients who received atropine 0.01% in ATOM 2, the mean myopia progression was -0.49 D (+/- 0.63) and the mean increase in axial length was 0.41 mm (+/- 0.32).

6.15. The Subcommittee was made aware of evidence from ATOM 2 reporting outcomes after three years, in which the authors conclude that the myopic rebound one year after stopping treatment was less with atropine 0.01% compared with atropine 0.5% and 0.1% (Chia et al. Am J Ophthalmol. 2014;157:451-7.e1).

6.16. The Subcommittee noted evidence from phase III of the ATOM 2 trial reporting outcomes for 345 children who previously received atropine 0.01% and were followed up to five years, including 192 patients who experienced myopia progression and restarted atropine 0.01% for 24 months (Chia et al. Ophthalmology. 2016;123:391-9). The Subcommittee noted that the mean spherical equivalent at baseline and five years was -4.07 D and -6.20 D in retreated children, respectively, and -4.80 D and -5.86 D in untreated children, respectively. The Subcommittee noted that ATOM 2 patients who restarted

treatment with atropine following prior atropine treatment experienced a delay in myopia progression of about 2.5 years compared with patients who received treatment with placebo. Members considered that treatment and re-treatment with myopia resulted in a lesser degree of myopia in ATOM 2 patients in their teenage years, however, the Subcommittee considered that it remained unclear whether atropine would prevent complications of myopia after five years and over a patient's lifetime due to the absence of long term follow-up studies. The Subcommittee noted the authors conclude that atropine 0.01% was more effective over five years than atropine 0.5% or 0.1% at slowing the progression of myopia.

6.17. The Subcommittee noted evidence from the Low-Concentration Atropine for Myopia Progression (LAMP) Study, which was a randomised (1:1:1:1), double-blinded, placebo-controlled trial of 438 children aged 4 to 12 years with myopia of at least -1.0 D and astigmatism of -2.5 D or less who received either atropine 0.05%, atropine 0.025%, atropine 0.01% eye drops or placebo for 12 months (Yam et al. Ophthalmology. 2019;126:113-124).

6.18. The Subcommittee was made aware of the following evidence on health utility values for myopic patients:

- Lim et al. Clin Exp Ophthalmol 2005;33: 598-603
- Saw et al. Br J Ophthlamol 2003;87: 341-5
- Li et al. Optom Vis Sci 2014;91: 723-9

6.19. The Subcommittee noted that there was no difference in any of the dimensions of the vision-related quality of life scores between groups at the end of the LAMP study, as measured by the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ). The Subcommittee considered the relationship between disease specific quality of life questionnaires (such as the NEI-VFQ) and generic quality of life questionnaires was uncertain but considered that the quality of life gain would primarily be through a reduction in long-term complications associated with myopia. The Subcommittee considered there was insufficient evidence to suggest atropine would be associated with shorter-term quality of life gains.

6.20. The Subcommittee was made aware of evidence from the beginning of the second year of follow-up in LAMP, in which children who received placebo were switched to receive 0.05% atropine whereas those receiving atropine 0.05%, 0.025%, and 0.01% continued with the same regimen (Yam et al. Ophthalmology. 2020;127:910-9). The Subcommittee noted that after two years, the mean spherical equivalent was -1.12 D (+/-0.85), and the mean axial length change was 0.59 mm (+/- 0.38) with atropine 0.01%. Members considered that while all concentrations provided greater benefit than placebo, greater reductions in axial length were seen with atropine 0.05% in particular.

6.21. The Subcommittee also noted the following evidence:

- Kinoshita et al. Jpn J Ophthalmol, 2018;62:544-53
- Wang et al. Medicine (Baltimore). 2017;96:e7371
- Walline et al. Cochrane Database Syst Rev. 2020;1:CD004916
- Gong et al. JAMA Ophthalmol. 2017;135:624-30

- Huang et al. Ophthalmology. 2016;123:697-708
- The impact of myopia and high myopia: report of the Joint World Health Organization–Brien Holden Vision Institute Global Scientific Meeting on Myopia. Geneva: World Health Organization; 2017 [Internet]
- Leo SW. Curr Opin Ophthalmol. 2017;28:267-75

6.22. The Subcommittee considered that atropine 0.01% was generally well tolerated in the ATOM 1, ATOM 2 and LAMP trials, although noted cases of cycloplegia, mydriasis, photosensitivity and systemic effects in a small number of cases proportional to atropine concentrations.

6.23. Overall, the Subcommittee considered that ATOM 1, ATOM 2 and LAMP provided good quality, short-term, evidence from randomised trials for a benefit from atropine 0.01% in reducing the progression of myopia in dioptres (D). The Subcommittee considered these trials provided slightly weaker evidence of the benefit of atropine in reducing the progression of myopia in axial length. However, the Subcommittee noted that the trial populations did not represent the range of ethnicities in New Zealand and were older than the New Zealand population who would be targeted for treatment if atropine 0.01% were funded. The Subcommittee considered that while it was plausible that a benefit from atropine could be maintained beyond five years, the available evidence was not able to confirm this or inform the incidence of long-term effects (eg macular degeneration, glaucoma, cataract). The Subcommittee considered that long-term outcomes are associated more closely with axial length than with the refractive index.

6.24. The Subcommittee considered that it was not possible to identify and predict which patients would do well with atropine 0.01% treatment for myopia because outcomes vary between individuals with some patients receiving greater benefits, therefore renewal criteria for funded treatment with specific outcomes or thresholds for treatment continuation or retreatment may not be appropriate. The Subcommittee considered that a funded duration of two years of treatment, followed by a period of monitoring post-treatment cessation and the ability to again access funded treatment upon progression for a further two years would be appropriate.

6.25. The Subcommittee considered that, if atropine 0.01% eye drops were funded for the treatment of myopia, it would be reasonable to estimate that similar proportions of children with myopia would opt to use atropine, orthokeratology, and either soft disposable contact lenses or multifocal lenses (ie one third usage of each). However, members considered that dual therapy with atropine 0.01% eye drops and another intervention may occur eg in patients with rapidly progressing myopia. Members considered some children and their parents would not be willing to use daily eye drops, and that it would be reasonable to assume uptake of approximately 70% in patients with myopia and for whom atropine is considered a suitable treatment.

6.26. The Subcommittee considered that, ideally, patients would undergo axial length measurement annually to assess progression, and that the funding of atropine would be unlikely to change the ideal frequency of measurements or specialist visits. However, the Subcommittee considered that many patients would not be able to undergo regular axial length measurements as there are significant barriers to accessing specialist treatment specifically for this. The Subcommittee considered that while the funding of atropine would provide treatment to some

patients from populations facing health disparities, the overall impact on health equity and the demographics of patients who would benefit from the funding of atropine are uncertain.

6.27. The Subcommittee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for atropine 0.01% eye drops if it were to be funded in New Zealand for myopia. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	All children with ≤ -0.50D myopia (often starting at around the age of school initiation); likely to be a small prevalent pool of children with myopia starting at a slightly later age
Intervention	Atropine 0.01% one drop per eye per day for a duration of two years, followed by observation; if further progression occurs after a year of observation, atropine treatment is re-commenced for another two years.
Comparator(s) (NZ context)	Placebo (no funded treatments)
Outcome(s)	Slowed progression in axial length and myopic refractive error. No direct evidence to inform long-term outcomes (e.g. glaucoma, cataracts, macular degeneration); would require extrapolation from axial length changes to inform these longer-term outcomes

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

6.28. The Subcommittee considered that the evidence suggested a concentration-dependent benefit from atropine 0.025% and 0.05% eye drops and considered that Pharmac could seek advice regarding these formulations for slowing the progression of myopia at a future meeting of the Subcommittee.

7. Cefuroxime for post-cataract surgery endophthalmitis prophylaxis and moxifloxacin for post intra-ocular surgery endophthalmitis prophylaxis

Application

7.1. The Subcommittee noted two clinician applications for endophthalmitis prophylaxis:

7.1.1. the use of cefuroxime 1 mg in 0.1 ml for intracameral injection following cataract surgery, for endophthalmitis prophylaxis; and

7.1.2. the use of moxifloxacin 0.5% solution for intracameral injection following routine or trauma related intra-ocular surgery for endophthalmitis prophylaxis.

Recommendation

7.2. The Subcommittee **recommended** that cefuroxime 1 mg in 0.1 ml for intracameral injection following cataract surgery, for prophylaxis of endophthalmitis, be listed with a **high priority** within the context of treatment of eye diseases, subject to the following Special Authority criteria:

CEFUROXIME
INITIATION – Cataract surgery
Ophthalmologist.

1. Single dose for prophylaxis of endophthalmitis following cataract surgery

7.3. The Subcommittee **recommended** that moxifloxacin 0.5% for intracameral injection following cataract surgery, for prophylaxis of endophthalmitis, be listed with a **high priority** within the context of treatment of eye diseases, subject to the following Special Authority criteria:

MOXIFLOXACIN
INITIATION – Cataract surgery
Ophthalmologist.

1. Single dose for prophylaxis of endophthalmitis following cataract surgery

7.4. The Subcommittee made these recommendations based on the high health need of patients with endophthalmitis (noting that the risk of developing it is low), and the severe patient and health system consequences and costs of endophthalmitis.

Discussion

7.5. The Subcommittee noted that there are an estimated 45,000 eye surgeries per year in New Zealand, 30,000 of which are cataract surgeries. The average age of patients receiving cataract surgeries is 73 years and the surgery may involve the administration of intracameral or topical/ subconjunctival antibiotics. The Subcommittee also estimated that 50% of these surgeries are publicly funded, the threshold for which is failing a New Zealand driver licence test. The most likely need for cataract surgery occurs in those who have diabetes, are overweight, or have hypertension. The Subcommittee considered that people with diabetes undergo cataract surgery at a younger age, and generally have poorer outcomes. The Subcommittee noted that this data is not complete and that it primarily comes from clinician surveys from the private sector.

7.6. The Subcommittee noted that intracameral therapy involves depositing therapies into the anterior chamber of the eye, whereas subconjunctival therapy leaves a

'blister' of therapeutic agent injected in the conjunctival space. The Subcommittee considered that intracameral therapy for antibiotic treatment following cataract surgery is usually more effective, as the concentration of antibiotic can be up to three times greater compared to subconjunctival techniques.

7.7. The Subcommittee noted that post-cataract endophthalmitis, involving bacterial or fungal infection, is a well-recognised complication of cataract surgery. This results in severe inflammation of the anterior and/or posterior chambers of the eye and is most commonly caused by gram-positive bacteria, particularly coagulase-negative staphylococci, with the most severe outcomes a result of streptococcal infection (approximately 9% of cases) (Durand et al. Up to Date. 2017). The Subcommittee noted that symptoms of post-cataract endophthalmitis usually present within a few days following surgery and can include pain, swelling, decreased visual activity, redness (of eyelids and/or conjunctiva) and haziness of the cornea. It can have a significant long-term and often irreversible effect on a patient's vision and quality of life. The severity of visual loss is associated with the pathogen (pseudomonal infections having the worst outcomes), presenting visual acuity and the promptness of appropriate treatment. The Subcommittee noted that the risk of developing post-cataract endophthalmitis is significantly greater when the cataract surgeries are complex, such as in the case of posterior capsule tears.

7.8. The Subcommittee noted that post-cataract endophthalmitis is rare, with a worldwide incidence of between 0.1 and 4 per 1,000 surgeries. The Subcommittee noted that incidence data for New Zealand is incomplete with literature reporting anywhere from 3 to 120 cases a year, and numbers vary based on type of surgery, geographical location, surgeon experience. The Subcommittee considered that, though rare, post-cataract endophthalmitis can result in significant healthcare costs borne by both patients and the public health system.

7.9. The Subcommittee noted an Auckland study (Yoon et al. Clin Exp Ophthalmol. 2016;44:106-13) which indicated that 4.7% of cataract surgery patients were Māori, which is lower than the Māori proportion of the national and DHB population. The Subcommittee noted that Māori who do get cataract surgery present with symptoms up to a decade earlier than non-Māori, which leads to longer quality of life impacts in the case of surgery complications. The Subcommittee noted that data on the rates of cataract surgery in the Pacific population are incomplete. However, it was noted that because the incidence of diabetes in the Pacific population is potentially up to 3-fold greater than in the non-Pacific population, which would likely result in earlier presentation and potentially worse outcomes for Pacific peoples. The Subcommittee noted that, overall, post-cataract endophthalmitis rates have been falling over time, as surgical interventions and therapies have become more targeted and effective, and the standard of care has become more focused on single- compared with multi-use items.

7.10. The Subcommittee noted that the current practice in New Zealand for the prevention of infections following cataract surgery involves the application of povidone antiseptic twice prior to surgery, then the administration of either a subconjunctival antibiotic injection (cefuroxime, cefazolin or gentamicin) or an intracameral antibiotic injection (cefuroxime or cefazolin), followed by the application of post-operative topical antibiotic therapy (chloramphenicol or neomycin/polymyxin) for one week. The Subcommittee considered that the use of povidone pre-operatively currently has the biggest impact on reducing rates of post-cataract surgery infections. The Subcommittee considered that intracameral

antibiotics are already commonly used, and if funded, it is thought likely that most, if not all, ophthalmologists would switch to this route of antibiotic prophylaxis.

7.11. The Subcommittee noted that the main driver for intracameral antibiotic administration is to reduce the incidence of endophthalmitis. Other drivers considered for this route of administration include reduced stinging and discomfort for patients, compared with topical administration; the option of giving a topical (and thus less dense) anaesthetic; removal of the need for patients to wear an eye-patch following surgery; and allows bilateral same-day surgery to be undertaken (which is more convenient for patients who need surgery on both eyes and who may be travelling from out of town, and reduces the carbon footprint associated with multiple surgeries).

7.12. The Subcommittee noted a 2007 prospective trial identifying the risk factors and effects of antibiotic prophylaxis on the incidence of postoperative endophthalmitis after cataract surgery (Endophthalmitis Study Group. J Cataract Refract Surg. 2007;33:978-88). The Subcommittee noted that the study reported an almost five-fold increase in the risk of developing endophthalmitis for patients who did not receive intracameral antibiotic prophylaxis (4.92-fold increase; 95% CI 1.87-12.9). The Subcommittee noted that although the study is widely accepted as justification for intracameral antibiotic prophylaxis, it has received criticism for having high endophthalmitis incidence in the control arm and included a variety of surgical techniques which confounded the results.

7.13. The Subcommittee noted that the results from various other pivotal studies vary significantly. Post-operative infection rates, when using intracameral antibiotics post cataract surgery, of anywhere between 0 and 22-fold reductions have been reported, and there are no head-to-head trials, either comparing intracameral antibiotic treatment with no post-operative antibiotics or comparing subconjunctival injection to intracameral administration. The Subcommittee considered that a 3-5-fold reduction in infection rate was a reasonable estimate. The Subcommittee noted that intracameral antibiotic administration post cataract surgery is the standard of care across Europe and the UK.

7.14. The Subcommittee noted that although intracameral antibiotics are safe and effective, they come at a greater cost compared to current treatments, and there are currently no funded ‘ready to go’ options which do not require reconstitution or serial dilutions. The Subcommittee noted that compounding of pharmaceuticals such as intracameral antibiotics occurs in surgical theatre in private ophthalmological practice, rather than in a hospital pharmacy, which the Subcommittee considered increases the risk of contamination, human error, and toxicity. The Subcommittee considered that if cefuroxime or moxifloxacin were to be funded, vials would not be used for more than one patient, due to the higher risks of contamination associated with vial sharing.

7.15. The Subcommittee noted that cefuroxime (1.0 mg per 0.1 mL powder for injection, reconstituted with saline) is a second-generation cephalosporin and is the most studied regarding post-cataract endophthalmitis. The Subcommittee noted people with penicillin allergy may also react to cephalosporins. The Subcommittee also noted that cefuroxime is less effective than moxifloxacin in the treatment of gram-positive bacteria and discussed the problem of enterococci resistance. The Subcommittee noted that intracameral cefuroxime has a relatively short duration of action (4-5 hours), that adverse events are rare and usually involve accidental overdose leading to toxicity, and is traditionally harder to compound than moxifloxacin.

7.16. The Subcommittee noted that moxifloxacin (0.15 mg per 0.1 mL or 0.6 mg in 0.4 mL solution, prepared by mixing with saline for a dose of 600 ug in 0.4 mL) is a fourth-generation fluoroquinolone which is effective against gram-positive and gram-negative bacteria. The Subcommittee noted that moxifloxacin is less well studied in endophthalmitis, but that studies have shown a 2-fold reduction in the rate of endophthalmitis following posterior capsule rupture when moxifloxacin is used as part of the treatment regimen for cataract surgery. The Subcommittee noted that moxifloxacin has a biphasic action with a long duration, contains no preservative, and is possibly less toxic intracamerally than cefuroxime. The Subcommittee also noted that there is a possibility of coagulase negative staphylococci resistance with moxifloxacin but considered that this risk was low. The Subcommittee noted that due to the larger injection volume used for moxifloxacin compared to cefuroxime, there is a higher chance of the therapeutic dose of the antibiotic reaching the desired part of the eye. The Subcommittee also noted that moxifloxacin during surgery can be used to re-form and reconstitute the eye. The Subcommittee considered that moxifloxacin is straightforward to compound and would provide a significant suitability benefit over currently funded options, and a small suitability benefit over cefuroxime.

7.17. The Subcommittee noted that there are only two head-to-head trials of cefuroxime and moxifloxacin. These did not show any difference between the two therapies in effect or adverse events (Malik et al. Ophthalmol Update. 2011;9:42-5; Rathi et al. Indian J Ophthalmol. 2020;68:819-24).

7.18. The Subcommittee reviewed the following evidence for intracameral cefuroxime for endophthalmitis prophylaxis following cataract surgery:

7.18.1. ESCRS Endophthalmitis Study Group. J Cataract Refract Surg. 2007;33:978-988.

7.18.2. Barreau et al. J Cataract Refract Surg. 2012;38:1350-5

7.18.3. Beselga et al. Eur J Opthalmol. 2014;24:516-9.

7.18.4. Friling et al. J Hosp Infec. 2019;101:88-92.

7.18.5. García-Sáenz et al. J Cataract Refract Surg. 2010 Feb;36:203-7.

7.18.6. Jabbarvand et al. Ophthalmology. 2016;123:295-301.

7.18.7. Katz et al. Graefes Arch Clin Ophthalmol.2015;253:1729-1733.

7.18.8. Ng et al. Graefs Arch Clin Exp Ophthalmol. 2016;254:1987-1992.

7.18.9. Rahman et al. Ir J Med Sci. 2005;184:395-398.

7.19. The Subcommittee noted the following evidence for intracameral moxifloxacin for endophthalmitis prophylaxis following intra-ocular surgery:

7.19.1. Haripriya et al. J Cataract Refract Surg. 2019;45:1226-33

7.19.2. Galvis et al. Ophthalmol Eye Dis. 2014;6:1-4

7.19.3. Mitchell et al. Ophthalmol Glaucoma. 2021;4:11-9

8.19.4. Vierira et al. Arq Bras Oftalmol. 2017;80:165-7

7.20. The Subcommittee considered the evidence for cefuroxime and moxifloxacin in the prevention of endophthalmitis to be of good strength and quality. The Subcommittee considered that the strength of evidence was stronger for cefuroxime due to the greater volume of evidence, but that both agents offer similar benefit in this setting.

7.21. The Subcommittee estimated that currently, 50% of patients receive a subconjunctival injection after surgery, while 50% receive intracameral antibiotics (generally cefuroxime, though cefazolin is sometimes used). The Subcommittee estimated that if an easy-to-prepare presentation of moxifloxacin or cefuroxime were to be funded, 95% of patients would receive intracameral antibiotics after surgery.

7.22. The Subcommittee considered that moxifloxacin has a wider spectrum of activity, which could be associated with greater resistance to moxifloxacin. The Subcommittee considered that anti-microbial stewardship is important, and that from a stewardship perspective, cefuroxime would be the more appropriate agent to fund.

7.23. The Subcommittee considered that as therapeutic agents both moxifloxacin and cefuroxime are well tolerated, effective, and equivalent options. The Subcommittee considered that moxifloxacin is the more suitable agent due to greater convenience for healthcare workers, but also considered that cefuroxime would ultimately be the preferred agent due to the greater risks of antibiotic resistance associated with moxifloxacin.

7.24. The Subcommittee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for cefuroxime and moxifloxacin if it were to be funded in New Zealand for endophthalmitis. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	All patients undergoing cataract surgery (~30,000 per year)
Intervention	Cefuroxime 1 mg in 0.1 ml, intracameral (add on to existing antimicrobial precautions at time of surgery). Moxifloxacin 0.4ml of a 1.5mg/ml solution given as a single intracameral injection at conclusion of surgery.
Comparator(s) (NZ context)	Existing antimicrobial precautions at time of surgery (including perioperative iodine and topical antibiotics). 40% of patients currently receiving compounded prophylaxis against endophthalmitis, based on 2016 survey of ophthalmologists

Outcome(s)	Reduction in post-operative endophthalmitis Reduction in pharmacist preparation time, compounding errors, compounding waste.

Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.