Record of the Ophthalmology Advisory Committee Meeting held on 9 August 2024

Ophthalmology Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

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

The Ophthalmology Advisory Committee 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.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

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

Specialist Advisory Committees 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 Specialist Advisory Committees, 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
Chris Pihema
Jim Bartley
Jo Sims
John Mottershead
Logan Robinson
Michelle Wong
Richard Johnson
Sam Kain
Samuel Whittaker

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Voretigene neparvovec for the treatment of *RPE65*-inherited retinal dystrophy, within the context of eye diseases, subject to Special Authority criteria	High Priority
• Access be widened to an anti-VEGF agent, for the second-line treatment of retinal vein occlusion (RVO) within the context of treatment of eye diseases, subject to Special Authority criteria	High Priority
• Dexamethasone implant for the second line treatment of macular oedema due to retinal vein occlusion, within the context of treatment of eye diseases, subject to the following Special Authority criteria	High Priority
• Dexamethasone implant for the treatment non-infectious uveitis and for macular oedema due to non-infectious uveitis, within the context of treatment of eye diseases, subject to Special Authority criteria	High Priority

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Ophthalmology Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021.Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

3.3. The Ophthalmology Advisory Committee is a Specialist Advisory Committee of Pharmac. The Ophthalmology Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Ophthalmology Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for eye diseases 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 eye diseases that differ from the Ophthalmology Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Ophthalmology Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments of eye diseases.

4. Welcome and introduction

4.1. The chair welcomed the committee with a karakia followed by whakawhanaungatanga.

5. Te Pātaka Whaioranga | Pharmac Update

5.1. The Committee noted the Pharmac Update.

6. Record of Ophthalmology Specialist Advisory Committee meeting held Friday, July 23, 2021

6.1. The Committee reviewed the record of the Ophthalmology Subcommittee meeting held on 23 June 2021, and agreed that the record be accepted.

7. Previous action points/recommendations made

7.1. The Committee noted the update provided by Pharmac on the recommendations since the last Ophthalmology Advisory Committee meeting in 2021.

7.2. The Committee noted that Pharmac was previously proposing to decline the application for atropine 0.01% eye drops. However, as a product has recently been approved by Medsafe this application will remain open for Pharmac to progress.

7.3. Members noted that in 2017 the Ophthalmology Subcommittee of PTAC had recommended that chloramphenicol eye ointment be made available on a practitioner's supply order (PSO) with a medium priority. It was considered that there was no longer a need for this as the ability for people to access chloramphenicol eye ointment via pharmacies had improved since this time as many community

pharmacies have increased their operating hours. The Committee considered this action could be closed.

7.4. The Committee did not make any other comments regarding the update on action points since the last Ophthalmology Advisory Committee meeting.

8. Therapeutic Group and NPPA Review

8.1. Review of funding applications

8.1.1. The Committee reviewed the list of funding applications in the Sensory Therapeutic Group that had been received by Pharmac. The Committee noted that a number of items on the list were to be discussed at this meeting.

8.1.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

8.1.3. The Committee noted that Pharmac was proposing to decline a number of currently open funding applications within the Sensory Therapeutic Group, as noted in December 2023 consultation- Proposal to decline inactive funding applications. The Advisory Committee noted that at the time of the meeting a number of the proposals had now been declined.

8.1.4. The Committee noted that the applications were proposed to be declined by Pharmac for a number of reasons including:

- our expert clinical advisors have recommended that the funding application be declined.
- other medicines for the same condition are now funded making the funding application no longer relevant.
- our expert clinical advisors have recommended that the medicine would provide no additional benefits over other treatments we already fund, or it may be harmful.
- no company is willing to supply the medicine in New Zealand.

8.1.5. Members noted that an application for verteporfin (Visudyne) for small subfoveal choroidal neovascularisation due to age-related macular degeneration had recently been declined by Pharmac.

8.1.6. Members considered that verteporfin is no longer used in the treatment of age-related macular degeneration, which is what the recently declined funding application was for. However, members considered it would be helpful to have access to verteporfin for the treatment of central serous retinopathy. The Committee noted that Pharmac has not received a funding application for this indication. Members noted that access to verteporfin was subject to frequent supply issues and was not available in all regions.

8.1.7. The Committee discussed that verteporfin is used in the treatment of central serous retinopathy in combination with a non-thermal laser. The Committee noted that the lasers required for this therapy were not available through the public health system. However, people were funded to access treatment privately if required. The Committee noted it was uncertain how verteporfin was funded by the public system for use in these procedures.

8.1.8. The Committee noted that a small number of requests for funded verteporfin had been made via Pharmac's Named Patient Pharmaceutical Assessment (NPPA) framework. However, these had not been progressed as they did not meet the principles of the NPPA policy.

8.1.9. The Committee noted that an application for loteprednol for eye inflammation with intraocular pressure rise had been declined by Pharmac in 2023 due to no Medsafe approved product. Members noted that access to loteprednol would be beneficial for a small group of people who are known steroid responders, who are at risk of significant increases in ocular pressure from other currently funded corticosteroid eye drops.

8.1.10. The Committee discussed that there were a number of low risk, low cost, and low volume ophthalmology products which would be helpful to have access to, but could not be secured, as a Medsafe approved product could not be sourced.

8.1.11. Members asked whether it would be possible for products used in comparable jurisdictions such as Australia to be sourced.

8.1.12. The Committee noted that supply of funded pharmaceuticals, and listing on the Pharmaceutical Schedule, particularly to the community, can be challenging where a supplier is not able or willing to receive regulatory approval as it means medicines must be prescribed and supplied as unapproved medications in accordance with Section 25 and Section 29 of the Medicines Act 1981. This places additional obligations on suppliers, wholesalers, and prescribers. Members noted supply under Section 29 of the Medicines Act may be an option for some low cost, low volume pharmaceuticals.

8.1.13. The Committee noted there were a number of reasons a particular pharmaceutical may not be approved for use in New Zealand even if it is available overseas, including the supplier considering that the New Zealand market is not commercially viable, international supply challenges, or suppliers being unable to access the required information about the product to submit for regulatory approval.

8.1.14. The Committee noted that where there is an unmet health need, Pharmac and Medsafe work together to secure supply of an appropriate product if possible. Members noted that this issue may be addressed by changes to the Medicines Act 1981 or possible changes to New Zealand's pharmaceutical approval process and timeframes that are currently being considered by the Government.

8.2. Expenditure Summary - Community

8.2.1. The Committee noted the information provided by Pharmac on the net expenditure on pharmaceuticals in the Sensory Therapeutic Group in the community.

8.2.2. The Committee noted that expenditure across the therapeutic group had continued to increase in recent years. The Committee noted that the top ten pharmaceuticals in terms of expenditure in the sensory therapeutic group was largely unchanged compared to previous years. The biggest change was expenditure on olopatadine that had significantly reduced compared to previous years due to price decreases through Pharmac's annual tender process.

8.2.3. The Committee noted that there are a number of new treatments that are expected to be available for ophthalmic conditions in future including new treatments for age related macular degeneration, a range of gene therapies, antisense therapies for corneal recovery, and new treatments for diabetic macular oedema.

Anti-vascular endothelial growth factor (VEGF) agents

8.2.4. The Committee noted that the usage and expenditure information presented in the Therapeutic Group Review did not include usage by Health New Zealand – Te Whatu Ora hospitals via the Hospital Medicines List as this information is self-reported by Health New Zealand hospitals and is not regularly audited by Pharmac. The Committee noted that usage data for anti-VEGF agents funded for use in Health New Zealand hospitals, including (aflibercept, bevacizumab and ranibizumab) had been

collated by Pharmac staff. The Committee noted that the data is provided directly by hospitals and may be inaccurate. The Committee noted that information had also been provided regarding units of anti-VEGF agents distributed in different regions, which had been requested by the Committee in 2021.

8.2.5. The Committee noted that expenditure on anti-VEGF agents had continued to increase in recent years and contributed significant expenditure to the Combined Pharmaceuticals Budget. The Committee noted that on a per unit basis, aflibercept was the most frequently prescribed anti-VEGF agent for ocular use. The Committee noted that multiple people could be treated with a single unit of bevacizumab, therefore while on a per unit basis use of bevacizumab was lower than aflibercept, the number of people treated was significantly higher. The Committee noted that bevacizumab was the most widely used anti-VEGF agent for ocular use as it is funded in a first line setting. Members noted that use of anti-VEGF agents was approximately two quarters to two thirds bevacizumab, with the remaining quarter to one third of use being aflibercept, and a very small amount of ranibizumab.

8.2.6. Members considered that the bevacizumab data provided by Pharmac did not appear to capture all bevacizumab use, as they were aware of higher use in Health New Zealand hospitals where they worked.

8.2.7. The Committee noted that in 2021 the Ophthalmology Advisory Subcommittee had made comments that it would have expected the usage and expenditure growth to have reduced with the Special Authority criteria in place. At the time, the Subcommittee considered an additional criterion requiring a fluorescein angiogram for indications other than diabetic macular oedema (DMO) could be appropriate.

8.2.8. The Committee noted that it was uncertain why use would be expected to decline as these are long term treatments for many people. The Committee considered that there was still a significant unmet health need for those needing anti-VEGF agents in New Zealand and current use of anti-VEGF agents appeared appropriate. Members considered that requiring a fluorescein angiogram would act as a barrier to treatment and could limit access to anti-VEGF agents. The Committee considered that a retrial of bevacizumab following 12 months of consecutive treatment with a second line anti-VEGF provides no health benefit to a person with DMO and very seldom results in continued use of bevacizumab. The Committee recommended the Special Authority criteria be amended to reflect this.

8.2.9. The Committee noted their preferences for anti-VEGF treatment options for wet age related macular degeneration (wAMD), DMO and retinal vein occlusion (RVO) would be first-line treatment with aflibercept (or bioequivalent suitable for ocular use) and second-line treatment with faricimab.

8.2.10. The Committee discussed the timeliness of administering anti-VEGF injections across the country. The Committee considered that across the country, the timeliness of people receiving their anti-VEGF injections was good and it was rare for someone not to receive their injection when it was required. The Committee considered that the challenge remained the capacity and availability of people to access specialists and clinicians for reviews. Members noted that this was being addressed via offering telehealth services and support from optometrists and allied health where possible.

8.2.11. Members noted that the focus on ensuring people received timely anti-VEGF injections could come at the expense of other services being provided by healthcare professionals.

Biosimilar bevacizumab

8.2.12. The Committee noted that Pharmac was planning a procurement activity for bevacizumab, which could result in bevacizumab being funded for a range of

oncological conditions and the funded brand of bevacizumab being changed to a biosimilar. The Committee noted that Pharmac was seeking advice on whether and/or how people currently receiving bevacizumab could be transitioned to a biosimilar bevacizumab if this was the outcome of a procurement activity.

8.2.13. The Committee noted that a biosimilar is a biologic medicine that has been assessed by a regulatory agency as being similar to another biological (reference) medicine. The Committee noted that to be approved, the biosimilar would be required to show equivalency to the biological reference product in terms of efficacy and safety.

8.2.14. The Committee noted that the currently available brand of bevacizumab (Avastin) was not approved globally or in New Zealand for ocular use and was used off label in these indications. Therefore, the Committee considered it was unlikely biosimilar suppliers would undertake their own studies to demonstrate safety and efficacy in ocular use. However, other groups or institutions may undertake these studies.

8.2.15. The Committee considered that product data and information specific to ocular use would be helpful to support any brand change to a biosimilar ocular bevacizumab.

8.2.16. The Committee considered that people with monocular vision with age related macular oedema who are currently stable on treatment would not be considered appropriate to change to a biosimilar ocular bevacizumab.

8.2.17. The Committee considered that people whose condition is close to meeting the exit criteria of the Special Authority would also generally not be considered appropriate for trailing a biosimilar ocular bevacizumab.

8.2.18. The Committee noted that the group of people not appropriate to trial to a biosimilar ocular bevacizumab would likely equate to 5% of people currently receiving bevacizumab for age related macular oedema.

8.2.19. The Committee considered that the exit criteria for anti-vascular endothelial growth factor treatment for people with monocular vision be reviewed to enable longer use for this group.

8.2.20. Members considered that the majority of the cost for bevacizumab is associated with its administration to patients, rather than the cost of bevacizumab itself. Therefore, any savings associated with currently funded indications being awarded to a biosimilar supplier are likely to be minimal.

8.2.21. The Committee considered that if a procurement activity is progressed, there could be an advantage to having a single supplier of bevacizumab for all funded indications.

8.2.22. The Committee considered that rather than having bevacizumab as the first line agent it would have a preference for aflibercept or a similar agent to be available in the first line setting, which is common overseas.

Ear preparations

8.2.23. The Committee noted the usage and expenditure data on ear preparations. The Committee considered that due to supply issues and delistings in recent years, trend information was difficult to interpret.

8.2.24. Members noted that previously the funded acetic acid ear drops had been useful to provide to individuals, as an alternative to antibiotic ear drops. Members recommended it would be helpful if a funded option of acetic acid with and without hydrocortisone could be sourced so that a preventative treatment and a non-antibiotic treatment for infection remained available. Members noted that over the counter options were currently available.

8.2.25. Members noted that antibiotic ear preparations were frequently requested from GPs by private ear clinics.

Eye/Ear Preparations

8.2.26. The Committee noted that use and expenditure on eye/ear preparations had been relatively stable in recent years. The Committee noted that dexamethasone with framycetin and gramicidin is the key pharmaceutical within this group contributing to usage and expenditure.

8.2.27. The Committee noted that dexamethasone with framycetin and gramicidin and framycetin sulphate are funded for use in the community subject to a manufacturer's surcharge, which have been in place since these pharmaceuticals were first listed on the Pharmaceutical Schedule (1995 and 1994, respectively). This means individuals are required to pay the difference between the amount subsidised by Pharmac and the supplier's selling price and any pharmacy mark-up.

Anti-infective Eye Preparations

8.2.28. The Committee noted that the unit volume for anti-infective preparations has remained relatively stable from 2018 to 2024, with seasonal patterns in dispensing evident. The Committee noted that the main contributors to expenditure in this group are chloramphenicol eye ointment 1% and fusidic acid eye drops. The Committee noted that there had been a significant increase in expenditure in 2023 due to a price increase for 0.5% chloramphenicol eye drops. This price has subsequently decreased via Pharmac's annual tender process.

8.2.29. The Committee noted that many child day care centres do not permit children to attend if they have inflamed/runny appearing eyes until they have had treatment with antibiotic eye drops such as chloramphenicol. Members noted these were frequently accessed over the counter via pharmacy and that these requirements from day care centres could result in inappropriate prescribing of antibiotic eye drops and overuse in the community.

8.2.30. Members noted that a Primary Health Organisation and infectious diseases physician in the South Island had written to local day care centres about the appropriateness of mandating antibiotic eye drops before being able to return to day care. Online resources had also been developed to support this. Members noted that policies at many day care centres were improving regarding this. Members noted that high rates of seasonal winter respiratory illnesses could also increase rates of conjunctivitis and other symptoms that may appear similar to bacterial conjunctivitis in children. Members considered it was likely that many parents were requesting antibacterial eye drops as this would allow then to return to work sooner.

8.2.31. Members noted that use of chloramphenicol eye drops after cataract surgery had decreased as people were now receiving intracameral antibiotics instead.

8.2.32. Members considered that Pharmac's recent decision to fund tacrolimus for atopic dermatitis on eyelids was likely to reduce prescribing of antibacterial eye drops and antihistamines.

Eye corticosteroids and other anti-inflammatory preparations

8.2.33. The Committee noted the usage and expenditure data on eye corticosteroids and other anti-inflammatory preparations. Members noted there was increased emphasis on prescribing prednisolone acetate eye drops following cataract surgery, which may account for the increased dispensing over the last year. The Committee noted that expenditure on eye corticosteroids and other anti-inflammatory preparations continued to increase.

8.2.34. The Committee considered the appropriateness of tendering for supply of a single brand of prednisolone acetate eye drops. Members recalled the 2017 experience when the AFT Pharmaceuticals brand of eye drops had been awarded sole supply

status by Pharmac, which later had to be revoked due to significant tolerability and efficacy concerns. This resulted in the Pred Forte brand continuing to be funded alongside the AFT Pharmaceuticals brand. Pred Forte currently accounted for approximately 97% of prednisolone acetate eye drops in the community.

8.2.35. Members noted that they would have significant concerns if Principal Supply Status of prednisolone acetate eye drops was to be awarded to the AFT Pharmaceuticals brand, particularly for people with significant ocular inflammation.

8.2.36. The Committee considered that it may be appropriate to award Principal Supply Status to an alternative brand of prednisolone acetate eye drops. However, it would be important to test the appropriateness of any preferred brand with clinicians and end users before any final decisions are made.

Glaucoma Preparations – Beta Blockers

8.2.37. The Committee noted the usage and expenditure data for glaucoma preparations – beta blockers.

8.2.38. The Committee noted that Pharmac had been advised by the supplier that the currently funded brands of betaxolol eye drops (0.25% and 0.5%) were being discontinued, and betaxolol was scheduled to be delisted from the Pharmaceutical Schedule from 1 July 2025.

8.2.39. The Committee considered it did not have any concerns about betaxolol being delisted from the Pharmaceutical Schedule. Members noted that betaxolol was very rarely used and considered all people currently receiving betaxolol could be managed using timolol eye drops.

Glaucoma Preparations - Carbonic Anhydrase Inhibitors

8.2.40. The Committee noted the usage and expenditure data for glaucoma preparations - carbonic anhydrase inhibitors.

8.2.41. The Committee noted that the main contributors to expenditure in this group were dorzolamide 2% with timolol 0.5% and brinzolamide 1%, accounting for approximately 85% of the total spend.

Glaucoma Preparations - Prostaglandin Analogues

8.2.42. The Committee noted that usage of glaucoma preparations - prostaglandin analogues had been relatively stable in recent years.

8.2.43. The Committee considered that the general upward trend across glaucoma preparations was likely driven by New Zealand's ageing population. Members considered that while there were new technologies that were likely to reduce demand for eyedrops for the treatment of glaucoma, increasing demand from the aging population would be expected to more than offset this.

Glaucoma Preparations – Other

8.2.44. The Committee noted that usage and expenditure in the glaucoma preparations – other group had been steadily increasing in recent years, particularly following the introduction of latanoprost with timolol in 2021.

8.2.45. The Committee considered there was a growing trend in glaucoma preparations for preservative free options. Members noted they would expect Pharmac to receive funding requests for these.

8.2.46. The Committee noted that it expected preservative free glaucoma preparations would be more expensive than glaucoma preparations with preservatives. Members noted that it would be preferable to have glaucoma preparations without preservatives available subject to the same criteria as preservative containing preparations.

Members acknowledged that this may not be possible and considered that criteria similar to preservative free ocular lubricants would be appropriate to manage this if required.

8.2.47. The Committee noted that when eye drops are tendered Pharmac notes a preference for preservative free options and reserves the right to fund a preservative free alternative if one becomes available.

Mydriatics Cycloplegics

8.2.48. The Committee noted the usage and expenditure data for mydriatics cycloplegics.

Preparations for Tear Deficiency

8.2.49. The Committee noted that usage and expenditure for preparations for tear deficiency has continued to increase.

8.2.50. Members discussed that following injections of anti-VEGF agents, it is common for hypermellose with dextran to be provided to help with the management of dry eye.

Preservative free ocular lubricants

8.2.51. The Committee noted that usage and expenditure of preservative free ocular lubricants had continued to increase in recent years.

8.2.52. Optometrist members noted that they had previously been declined when applying for Special Authorities for preservative free ocular lubricants. Pharmac staff noted they would look into this.

8.2.53. The Committee considered that allowing optometrists to prescribe preservative free ocular lubricants would be appropriate and could reduce the number of people who need to be seen by specialists at clinic.

8.2.54. Members noted that increasing the number of specialties that could prescribe ocular lubricants would likely increase use and expenditure.

Other Eye Preparations

8.2.55. The Committee noted that usage and expenditure of other eye preparations has remained stable in recent years.

Other points discussed

8.2.56. The Committee considered the current access criteria for aflibercept in the treatment of diabetic macular oedema. Members considered that the visual acuity score for diabetic macular oedema should be changed from 6/9 – 6/36 to 6/9 –6/48. Members considered that the revised visual acuity score of 6/9 – 6/48 should also apply to the renewal criteria for aflibercept in the treatment of both diabetic macular oedema and wet age-related macular oedema. Members considered that this would address currently unmet health needs.

8.2.57. The Committee noted from 1 June 2021 to 17 June 2024, a total of 288 applications were received via Pharmac's Named Patient Pharmaceutical Assessment (NPPA) Pathway for the sensory organs therapeutic group, including 146 initial applications, and 142 renewal applications. The Committee noted the majority of applications received in the sensory therapeutic group were for ciclosporin eye drops for severe dry eye and keratoconjunctivitis.

8.2.58. Members noted that Pharmac had a funding application for a ciclosporin eye preparation for severe keratoconjunctivitis which it would like to fund and is in ongoing discussions with a supplier.

8.2.59. Members noted that they most frequently submitted NPPA applications for biologic medicines such as tocilizumab and rituximab and ciclosporin eye drops.

8.2.60. The Committee considered it would also be helpful to see NPPA data for immunosuppressants used in the eye.

8.2.61. Members noted that the need for disease-modifying antirheumatic drugs (DMARDs) in ophthalmology was increasing but numbers were likely low and access via NPPA application would be appropriate.

8.2.62. Members discussed that it would be useful to have a Special Authority criterion for rituximab for peripheral ulcerative keratitis and necrotising scleritis. Members considered there would be fewer than ten people in these groups in New Zealand.

8.3. Horizon Scanning

Aeon eyedrop applications

8.3.1. The Committee noted that Pharmac had received applications for a range of Aeon brand eye drops including Aeon Protect, Aeon Protect Plus, Aeon Repair and, Aeon sodium chloride 5%.

8.3.2. The Committee noted that one brand of currently funded preservative free ocular lubricants was supplied as single use ampoules, which could be challenging for people with dexterity issues, such as older people. The Aeon products may provide a suitability advantage as they come in multi-use bottles.

8.3.3. The Committee considered that it would be reasonable to consider Aeon Protect, Aeon Protect Plus and Aeon Repair as alternatives for currently funded preservative free eye drops when these items are included in Pharmac's annual tender process.

Aeon Sodium Chloride 5%.

8.3.4. The Committee recommended that a sodium chloride 5% hypertonic solution be funded for corneal oedema.

8.3.5. The Committee noted that Aeon sodium chloride 5% is a hypertonic solution indicated for the reduction of symptoms associated with corneal oedema and contains contain sodium chloride 5%, 0.30% sodium hyaluronate and polyethylene glycol (PEG) 400.

8.3.6. The Committee considered that there was an unmet health need for a sodium chloride 5% hypertonic solution and there were no currently funded alternatives for this.

8.3.7. Members noted that sodium chloride 5% was available privately for the treatment of corneal oedema, such as the Muro 128 brand.

8.3.8. The Committee considered that sodium chloride 5% hypertonic solution would be used to delay the need for a corneal transplant or be used while someone is waiting for a corneal transplant. Members noted that the waiting list for a corneal transplant could be 1-2 years.

8.3.9. The Committee considered that the group requiring treatment with sodium chloride 5% hypertonic solution would be approximately 100 people, not all of whom would require long term treatment.

Summary for assessment

8.3.10. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for sodium chloride 5% hypertonic solution if it were to be funded in New Zealand for the treatment of corneal oedema. 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 Committee'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	People with mild unilateral or bilateral corneal oedema
Intervention	Sodium Chloride 5% eye drops • 1 or 2 drops into the pouch of the affected eye(s) 3 times daily May be used alone or alongside topical antibiotics and other treatments.
Comparator(s) (NZ context)	• Best supportive care • Corneal transplant
Outcome(s)	• Improve, maintain or restore visual function
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

Benzocaine and Phenazone ear drops

8.3.11. The Committee recommended that benzocaine and phenazone ear drops be funded with a low priority for people with otitis media/otalgia.

8.3.12. The Committee considered that there was reasonable quality evidence supporting the use of benzocaine and phenazone ear drops for the reduction of pain associated with otitis media and a reduction in antibiotic use.

8.3.13. The Committee noted that lidocaine oral gel solution 2% is currently open listed on the Pharmaceutical Schedule and is intended for use in throats but may be used in the ear. Members considered that a gel consistency may create challenges for external auditory canal ear use.

8.3.14. The Committee considered that the availability of benzocaine and phenazone ear drops would reduce antibiotic prescribing for ear pain as it would provide an option for topical anaesthesia.

8.3.15. The Committee noted that evidence from a Cochrane Review (Foxlee et al. Cochrane Library. 2006; 3; 1-32) reported that use of anaesthetic ear drops in children was associated with a statistically significant proportion of children achieving a 50% reduction in pain at 10 minutes and 30 minutes, but not 20 minutes compared to herbal ear drops.

8.3.16. The Committee considered that this demonstrates that benzocaine and phenazone ear drops may help to treat acute ear pain but would not provide long term pain relief.

8.3.17. Members considered it would be helpful to have an alternative to provide people other than antibiotics.

8.3.18. Members considered if it was funded, prescribing of benzocaine and phenazone ear drops would be high. Members noted that based on the evidence reviewed Foxlee et al. 2006, regardless of the intervention, the majority of ear pain in children would resolve in three to seven days.

8.3.19. Members noted that there was a significant amount of pressure on General Practitioners to prescribe antibiotics.

Summary for assessment

8.3.20. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for benzocaine and phenazone ear drops solution if it were to be funded in New

Zealand for the treatment of ear pain associated with otitis media. 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 Committee'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	People with Otitis media/otalgia
Intervention	Benzocaine and Phenazone ear drops: • Two drops to affected ear every two hours
Comparator(s) (NZ context)	• Best supportive care • Analgesia • Antibiotics • Surgery-ventilation tubes
Outcome(s)	• Reduction in pain • Reduction in use of antibiotics
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

Triamcinolone acetonide – intravitreal injection

8.3.21. The Committee noted that Pharmac currently funds two presentations of triamcinolone acetonide injections:

- Inj 10 mg per ml, 1 ml ampoule
- Inj 40 mg per ml, 1 ml ampoule

8.3.22. The Committee noted that the currently funded Kenacort-A 10 and 40 brands contain preservatives and are funded under Principal Supply Status arrangements until 30 June 2026.

8.3.23. Members noted that the preservative in the Kenacort-A 10 and 40 can be associated with increased incidence of sterile endophthalmitis in intravitreal use.

8.3.24. Members noted that this risk was previously avoided via the use of the Triesence brand of preservative free triamcinolone acetonide Inj 40 mg per ml. However, the Triesence brand had not been able to be sourced for two years, which had resulted in a significant unmet health need for a small number of people.

8.3.25. Members noted that there were two other preservative free alternatives available (brand names Vitreal S and Intracinol) which were designed for intraoperative use and are not intended to be used as a therapeutic. When used in the eye these options do not appear to have the duration of efficacy as the Triesence brand.

8.3.26. Members considered that a treatment was required for these people, but currently available options did not appear suitable.

8.3.27. Members noted that the currently funded Kenacort brand was suitable for peri-ocular injections, but for injections into the eye, preservative free products were preferred due to the lower risk of sterile endophthalmitis.

9. Matters arising: Faricimab for the second-line treatment of (wet) neovascular age related degeneration and diabetic macular oedema

Application

9.1. The Committee reviewed the applications for faricimab for the treatment of neovascular (wet) aged-related macular degeneration and diabetic macular oedema.

9.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Discussion

9.3. The Committee noted that faricimab for the treatment of neovascular (wet) aged-related macular degeneration (wAMD) and diabetic macular oedema (DMO) were assessed by PTAC at its February 2024 meeting, in which faricimab for wAMD and DMO was recommended to be listed as cost neutral to aflibercept for second-line treatment.

9.4. The Committee noted that to understand the current situation in New Zealand for anti-vascular endothelial growth factor (VEGF) treatments, PTAC requested Pharmac staff seek advice from the Ophthalmology Advisory Committee on:

9.4.1. the treatment paradigm, including dosing schedule, for aflibercept and faricimab.

9.4.2. whether 12-or 16-week faricimab dosing intervals would be used and the impact this would have for people currently being treated, waiting to receive treatment and the health system.

9.4.3. whether the funding of faricimab would alleviate some of the burden on Ophthalmology services.

9.4.4. estimated likely uptake of treatment.

9.5. The Committee noted that Pharmac recieved correspondence from the supplier following publication of the PTAC record. The correspondence requested that faricimab be considered as a third-line option i.e allowing people to switch from aflibercept to faricimab, so long as the person continues to meet the eligibility criteria and continues to benefit from either treatment.

9.6. The Committee noted that bevacizumab is used first-line for the treatment of wAMD, DMO and retinal vein occlusion (RVO). If people with wAMD or DMO do not receive sufficient health benefit from bevacizumab they can be treated with aflibercept.

9.7. The Committee noted there is no second-line anti-VEGF treatment for people with RVO, and considered there to be an unmet health need for these people that should be addressed if access was widened.

9.8. The Committee noted that ranibizumab is not commonly used in the treatment of wAMD or DMO. The Committee considered a third-line treatment option would be beneficial for some people who have not received appropriate health benefit with bevacizumab or aflibercept.

9.9. The Committee considered that due to the progressive nature of wAMD, it is important to have a third-line option. The Committee considered that some people who do not respond adequately to aflibercept may still continue to get aflibercept injections due to a lack of further lines of therapy.

9.10. The Committee noted that when a person commences an anti-VEGF treatment, they will need to go through an initiation phase which usually involves receiving an injection every month for 6 months. The Committee considered that in the first 6-months, people would usually receive 5 or 6 injections. Following the initiation period, it is common to use a "treat and extend" approach, where the dosing interval is

extended in two week increments to determine how long a person can go between treatments without symptoms.

9.11. The Committee considered that the frequency of injections required to control the symptoms of the disease is variable between people.

9.12. The Committee noted the following studies reporting time between aflibercept treatment intervals when a treat and extend protocol is used:

9.12.1. The Committee noted Ohji et al. Adv Ther. 2020;37:1173-1187 that reported the results of the ALTAIR trial in which people with wAMD were treated with aflibercept. Following initiation, a treat and extend protocol was initiated with dosing intervals increasing by 2 or 4 weeks. From baseline, mean change in best corrected visual acuity (BCVA) was + 9.0 and + 8.4 letters (week 52) and + 7.6 and + 6.1 letters (week 96); mean change in central retinal thickness was − 134.4 µm and − 126.1 µm (week 52) and − 130.5 µm and − 125.3 µm (week 96). Last injection interval before week 52 was at least 12 weeks in 42.3% and 49.6% of people and 56.9% and 60.2% before week 96.

9.12.2. The Committee noted Kim et al. Sci Rep. 2020;10:22030 that reported the results of the VIBIM study, in which people with DMO were treated with aflibercept. Following treatment initiation, a treat and extend protocol was initiated. Compared to baseline, BCVA improved by + 9.1 letters at 52 weeks and was maintained with + 9.4-letter gain at 104 weeks ($P < 0.001$). Between baseline and 104 weeks, central subfield macular thickness (CSMT) decreased from 489 to 298 µm ($P < 0.001$) and eyes with vision ≥ 20/40 increased from 17.4 to 43.5% ($P = 0.007$). The mean number of injections decreased from 8.5 in year one to 3.9 in year two. The injection interval was extended to ≥ 12 weeks in 56.5% of people. The treat-and-extend regimen of aflibercept in DMO showed 2-year efficacy comparable to that of fixed dosing regimens.

9.13. The Committee noted the following studies reporting time between faricimab treatment intervals when a treat and extend protocol is used:

9.13.1. The Committee noted Heier et al. Lancet. 2022; 399:729-740 and Khanani et al. Ophthalmology. 2024;131:914-926, which reported the results of the TENAYA and LUCERNE trials in which people with wAMD, who had not previously received anti-VEGF treatment, received faricimab or aflibercept. Following treatment initiation, the faricimab arm were able to enter a treat and extend protocol. At the end of week 112, in the TENAYA trial (n=315) 25.8% received treatment every 8 weeks, 15.1% every 12 weeks and 59% every 16 weeks. In the LUCERE trial (n=316) 18.8% received treatment every 8, 14.3% every 12 weeks and 66.9% every 16 weeks.

9.13.2. The Committee noted Wykoff et al. Lancet. 2022;399:741-55 and Wong et al. Ophthalmology. 2023: S0161-6420(23)00933-8, which reported the results of the YOSEMITE and RHINE trials, in which people with DMO who had not previously received an anti-VEGF or had not received anti-VEGF in at least 3-months, received faricimab or aflibercept. Following treatment initiation, the faricimab arm were able to enter a treat and extend protocol. At the end of week 96, in the YOSEMITE trial (n=286) 7% received treatment every 4 weeks, 14.8% every 8 weeks, 18% every 12 weeks and 60% every 16 weeks. In the RHINE trial (n=308) 10.1% received treatment every 4 weeks, 11.8% every 8 weeks, 13.6% every 12 weeks and 64.5% every 16 weeks.

9.13.3. The Committee noted the BALATON and COMINO trials, which people with branch retinal vein occlusion (BRVO) and hemiretinal/central RVO (H/CRVO) received faricimab or aflibercept. Following treatment initiation, the faricimab arm were able to enter a treat and extend protocol. In the BALATON trial (BRVO, n=248) 23% received treatment every 4 weeks, 13% every 8 weeks, 12% every 12 weeks and 52% every 16 weeks. In the COMINO trial (H/CRVO, n=330) 35% received treatment every 4 weeks, 20% every 8 weeks, 8% every 12 weeks and 37% every 16 weeks (Ghanchi et al, Presented at the Association for Research in Vision and Ophthalmology Annual Meeting, 2024, poster available here).

9.14. The Committee noted that faricimab is non-inferior to aflibercept regarding improvement in vision measured in BCVA, disease control and safety. The Committee considered the therapeutic benefit of faricimab is likely to last longer than aflibercept, resulting in less injections required. The Committee considered the response to aflibercept and faricimab to be comparable among people with RVO.

9.15. The Committee considered that the number of injections in the first year of treatment is likely to be comparable between aflibercept and faricimab. The Committee considered the proportion of people who are able to extend treatment to ≥12 weeks to be 55-60% with aflibercept and 74-80% with faricimab after 2 years of treatment for people with DMO and wAMD (Wykoff et al. Lancet. 2022;399:741-55, Wong et al. Ophthalmology. 2023: S0161-6420(23)00933-8, Heier et al. Lancet. 2022; 399:729-740,Khanani et al. Ophthalmology. 2024;131:914-926). The Committee considered that a person who is receiving faricimab is likely to receive 20-30% fewer injections per year when compared to aflibercept.

9.16. The Committee considered that fewer injections and visits to the clinic for the same level of health improvement was meaningful for those receiving treatment, particularly those who experience greater barriers to access. The Committee considered the increase in intervals between treatments to positively impact family, who may need to take time off work to help with attending appointments.

9.17. The Committee considered that if faricimab was available as a second line treatment, the majority of people will receive faricimab after bevacizumab.

9.18. The Committee considered that if the ability to switch between second-line anti-VEGF treatments was available, it would be uncommon for people currently receiving aflibercept to change to faricimab if the symptoms of their disease are stable and they were receiving treatment at 8-week or 12-week intervals. However, some people may want to try and extend their treatment intervals. The Committee considered people who have monocular vision and were stable are unlikely to switch treatments.

9.19. The Committee considered that if that if the ability to switch between second-line anti-VEGF treatments was available, people receiving treatment at 4-week intervals, not experiencing appropriate health benefit or experiencing significant difficulty accessing treatment, would likely switch between treatments. The Committee considered this to be 10-20% of the population currently receiving aflibercept.

9.20. The Committee considered that due to the progressive nature of wAMD, it is important to have a third line option and faricimab would be appropriate for wAMD, DMO and RVO.

9.21. The Committee noted high dose aflibercept is being used in some countries and considered that the durability of this treatment may be similar to that of faricimab.

9.22. The Committee noted that treatment may be managed by a multi-disciplinary team, including an ophthalmologist and may include nurse injectors, nurse practitioners and/or optometrists. The management team varies around the country. The

Committee considered that the delivery cost per injection would be the same between treatment regimens, however the frequency of injections with faricimab may reduce the cost to the healthcare system through reduction in nurse injector appointments.

9.23. The Committee considered that following stabilisation on an anti-VEGF agent, the frequency of assessments by the ophthalmologist varies between clinics. These may occur every injection, every 3-4 injections, or once a year. The Committee considered that currently largest constraint of the healthcare system are the assessments with the ophthalmologist and considered that in some centres this would be unchanged if faricimab was funded, in centres where ophthalmologist appointments are aligned to injections there may be some decrease.

9.24. The Committee considered that fewer injections will result in fewer appointments required for a person who is receiving faricimab. The Committee considered the logistics of providing the current number of injections was problematic and fewer follow-up and treatment appointments would be beneficial. The Committee also considered that fewer appointments may improve adherence to treatment.

Funding criteria

9.25. The Committee noted that Pharmac should consider widening the eligibility criteria of anti-VEGF agents to people with 6/60 Snellen vision scale. The Committee considered the improvement in vision to be a significant benefit for these people.

9.26. The Committee noted that Pharmac should consider lowering the Snellen criteria for people who are monocular, as there is a greater need to preserve vision.

9.27. The Committee noted that Pharmac should remove the obligation to rechallenge with bevacizumab every 12 months. The Committee considered there to be no health benefit associated with this and that few, if any, individuals remained on bevacizumab following the retrial.

9.28. The Committee noted Pharmac should widen access to include RVO in all current and future anti-VEGF treatments.

Summary for assessment

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

	wAMD	DMO
Population	People with wAMD who have tried and have not experienced a satisfactory response with bevacizumab, or who have developed severe endophthalmitis or severe posterior uveitis following treatment with bevacizumab. People who are receiving aflibercept or ranibizumab	People with DMO who do not experience therapeutic response to treatment with bevacizumab. People who are receiving aflibercept for wAMD but experience an unsatisfactory response to treatment.

	for wAMD but experience an unsatisfactory response to treatment.	
Intervention	Faricimab 6 mg (0.05 ml solution) every 4 weeks (monthly) for the first four doses. Thereafter, a treat-and-extend approach is used. The dosing interval may be extended up to every 16 weeks (4 months), in increments of 4 weeks.	Faricimab 6 mg (0.05 ml solution) every 4 weeks (monthly) for the first four doses. Thereafter, a treat-and-extend approach is used. The dosing interval may be extended up to every 16 weeks (4 months), in increments of 4 weeks.
Comparator(s) (NZ context)	Aflibercept injection once per eye every 4 weeks for 3 consecutive months. Thereafter, a treat-and-extend approach is used. The dosing interval may be extended up to every 16 weeks (4 months), in increments of 4 weeks. Ranibizumab injection once every 4 weeks until maximum visual acuity is achieved and/or there are no signs of disease activity. Treatment is usually given for 3-6 months and extended if needed.	Aflibercept 2 mg every 4 weeks (monthly) for five months, followed by one injection every 8 weeks (two months). After the first 12 months, the treatment interval may be adjusted based on visual and/or anatomic outcomes. Bevacizumab to be retried every 12 months as required in the current Special Authority criteria.
Outcome(s)	Non-inferiority to other anti-VGEF treatments in maintaining or improving clearness or sharpness of vision in people with wAMD. Extended treatment interval compared to other anti-VEGF treatments.	Non-inferiority to other anti-VGEF treatments in maintaining or improving clearness or sharpness of vision in people with DMO. Extended treatment interval compared to other anti-VEGF treatments.

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 target 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.

10. Voretigene neparvovec for the treatment of inherited retinal dystrophy due to pathological biallelic *RPE65* mutations

Application

10.1. The Committee reviewed the application for voretigene neparvovec for the treatment of *RPE65*-inherited retinal dystrophy.

10.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

10.3. The Committee **recommended** that voretigene neparvovec be listed with **high priority** for the treatment of *RPE65*-inherited retinal dystrophy within the context of eye diseases subject to the following Special Authority criteria:

> **Initial application – inherited retinal dystrophy**
> Applications from any relevant practitioner
> 1. All of the following:
> 1.1. Patient has inherited retinal dystrophy; and
> 1.2. Patient has documented biallelic *RPE65* mutations as determined by a validated test; and
> 1.3. Patient has sufficient viable retinal cells as determined by a relevant specialist; and
> 1.4. Treatment is to be limited to one treatment per eye per patient lifetime.

10.4. When making the recommendation the Committee considered the following:

- Biallelic *RPE65*-inherited retinal dystrophy has a significant negative impact on a person's health-related quality of life due to poor visual function and the progressive nature of the disease leading to blindness.
- There is good evidence that voretigene neparvovec provides meaningful improvement of visual acuity and general visual function in people with *RPE65*-IRD for at least 7.5 years.
- The lack of other available treatments.

Discussion

Māori impact

10.5. The Committee discussed the impact of funding voretigene neparvovec for the treatment of *RPE65*-inherited retinal dystrophy on Māori health areas of focus and Māori health outcomes. The Committee considered as it was a rare condition there was no data to suggest if Māori were more disproportionally affected. The Committee considered that theoretically disease severity would be similar across different ethnicities.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

10.6. The Committee considered people who were in rural areas or from higher socioeconomic deprivation quintiles may experience barriers to accessing low vision services and ability to purchase or access low vision aids.

Background

10.7. The Committee noted that voretigene neparvovec was considered by PTAC in February 2023 that deferred making a recommendation until further evidence regarding the longevity of the therapeutic benefits becomes available.

Health need

10.8. The Committee noted inherited retinal dystrophies (IRDs) are a group of genetically and phenotypically heterogenous diseases. The Committee noted that both retinitis

pigmentosa and Leber congenital amaurosis were linked with mutations in the *RPE65* gene. The Committee noted that the phenotype to be treated was similar in severe early childhood onset retinal dystrophy, and early onset severe retinal dystrophy and degeneration, as well as Leber congenital amaurosis.

10.9. The Committee noted that in New Zealand there are three people with genetic confirmation of early onset severe bi-allelic *RPE65*--mediated IRDs. No later onset bi-allelic disease due to *RPE65* has been identified in New Zealand.

10.10. The Committee considered it unlikely that there would be children or adolescents with *RPE65*-mediated IRDs who had not already been identified, due to routine screening programmes for vision impairment during B4School checks and in school settings, which are very likely to pick up IRDs.

10.11. The Committee considered that among older adults who have been diagnosed with IRD for some time and or are already blind, the uptake of genetic testing for IRDs is variable across the country. The Committee considered that among children and young adults the uptake of genetic testing is high and considered it to be unlikely for there to be a significant number of people with undiagnosed *RPE65*-IRD.The Committee considered that at most, there may be two to three adults in New Zealand with RPE65-mediated IRD who have not already been identified. The Committee considered that in recent years, uptake of genetic testing may have increased due to awareness of the future availability of gene therapies.

10.12. The Committee considered that in recent years, uptake of genetic testing may have increased due to awareness of the future availability of gene therapies. The Committee considered that at most, there may be two to three adults in New Zealand with RPE65-mediated IRD who have not already been identified.

10.13. The Committee noted that people with inherited retinal dystrophies are reported to experience a reduced health-related quality of life, and they experience high rates of anxiety, depression, social isolation, financial stress, fear, stress, and fatigue. Furthermore, impaired vision is associated with an inability to work, low socioeconomic status, loss of independence, limitations in performing activities associated with daily life, and an increased risk of falls and injuries (Galvin et al. Clin Ophth. 2020; 14:707-19, Cumberland et al. JAMA Ophth. 2016;134:959-66, Garcia et al. Clin Ophth. 2017; 22:417-27).

10.14. The Committee noted that there is no treatment for *RPE65*-IRD, and people are limited to low vision support including glasses and low vision aids. The Committee considered this would not improve vision and they would have severe visual disability.

Health benefit

10.15. The Committee noted the phase three randomised controlled trial that treated 20 individuals with voretigene neparvovec and nine people in a control arm (Russell et al. Lancet. 2017;390:849-60, Maguire et al. Ophthalmology. 2021; 128:1460-1468).

10.16. The Committee considered that the disease was rare and therefore the number of people enrolled in the trials was small. The Committee noted that no New Zealanders were included in the trials, however there was no reason to suggest the results were not generalisable to the New Zealand population.

10.17. The Committee considered that full field light sensitivity threshold (FST) has been validated to correlate well with the multi-luminance mobility test (MLMT), the primary endpoint of the clinical trial. The Committee considered this test evaluated the person's ability to navigate in low light, which is a good test of functional vision, The Committee considered FST was a more objective test, as these individuals have low

levels of vision that can fluctuate visit to visit, and it is harder to ascertain their visual acuity.

10.18. The Committee noted the two-year results from the PERCIEVE study (Fischer et al. Biomolecules. 2024;14:122) reported similar safety and efficacy results between trial data and people treated outside of the studies. The Committee considered there was some data that may suggest the earlier treatment of individuals is beneficial, as these individuals have a higher number of viable retinal cells and more preserved vision compared to those untreated for longer. The Committee considered several studies reported the greatest improvements in visual acuity and FST were in individuals who were less than 18 years of age in comparison to over 18 years of age.

10.19. The Committee noted the following publications:

- Maguire et al. Lancet. 2009;374:1597-605
- Testa et al. Ophthalmology. 2013; 120:1283-91
- Bennet et al. Lancet. 2016; 388:661-72
- Leroy et al. Ophthalmic Res. 2023;66:179-196
- Chung et al. ARVO Annual Meeting Abstract. 2019
- Bennet et al. ARVO Annual Meeting Abstract. 2021
- Leroy et al. ADC. 2021.
- Bommakanti et al. Ophthalmol Retina. 2024;8:42-48.
- Sengillo et al. Ophthalmol Retina. 2022;6:273-283
- Gange et al. Ophthal Retina. 2022; 6:58-64

10.20. The Committee considered that a key uncertainty in the benefit derived from voretigene neparvovec treatment was the duration of treatment effect, which refers to the period over which an individual accrues some, or all, of the potential benefit from treatment.

10.21. The Committee considered that, based on the available trial evidence, it was reasonable to assume a treatment effect of at least 7.5 years with no obvious waning up until this point. The Committee noted that this 7.5-year duration corresponded to the longest available follow-up duration for a trial of voretigene neparvovec available at the time of the meeting.

10.22. The Committee noted that evidence to support an assumption of treatment effects beyond seven years duration in humans was not yet available, but this was biologically plausible.

10.23. The Committee considered that experiencing at least 7.5 years of benefit would have a large impact on the health-related quality of health of individuals, especially those less than 18 years of age where it may support engagement in formal education etc.

10.24. The Committee noted that retinal cells are a terminally differentiated, non-replicating, cell type which could reasonably be expected to retain episomes of copies of *RPE65* after successful delivery via voretigene neparvovec for the remainder of the cells' lives.

10.25. The Committee noted evidence that in animal studies of voretigene neparvovec, episomes with functional copies of the *RPE65* gene were found in the target cell types as long as 10 years after injection (Leroy et al. Ophthalmic Res. 2022 [preprint]). The Committee considered however that persistence of episomes was not in itself evidence of expression of the functional copies of *RPE65* although there was

no obvious reason to assume that expression of the genes within episomes would decrease over time.

Suitability

10.26. The Committee considered that as many individuals with *RPE65* mutations would be receiving care in Auckland currently, and that as most of the infrastructure and specialists for this treatment would be based there, delivery of care in this location would not represent an additional burden to the individual receiving treatment.

Cost and savings

10.27. The Committee noted that to date, three individuals with RPE65-mediated IRDs have been identified in New Zealand through testing. The Committee considered this to comprise most, if not all, people in New Zealand who would be eligible for voretigene neparvovec if it were to be funded. The Committee considered based on epidemiological data there was 1.4 new diagnosis of Leber congenital amaurosis every two years, of which 10% would have biallelic *RPE65* disease, who might also be eligible for treatment.

10.28. The Committee noted the treatment requires vitrectomy surgery, with each eye treated one to two weeks apart.

10.29. The Committee considered the consequences for the health system if voretigene neparvovec were to be funded. The Committee considered it reasonable to assume there would be a single treatment centre in New Zealand with an ophthalmologist with expertise in IRDs, and a retinal surgeon experienced in sub-retinal surgery and capable of administrating voretigene neparvovec. The Committee considered anecdotal evidence that there was a trained surgeon in New Zealand and the necessary infrastructure for the treatment may exist.

10.30. The Committee noted that in Australia, where voretigene neparvovec had been funded since 2020, 10 people had received treatment as of December 2023 (Retina Australia. Gene Therapy. 2024 [Accessed 9 August 2024 at https://retinaaustralia.com.au/research/gene-therapy/]).

10.31. The Committee was made aware that in Australia, the Medical Services Advisory Committee (MSAC) recommended that a 0.3 log unit change on the FST, 60 days after administration, be used as the threshold to define 'successful treatment' with voretigene neparvovec to inform a 'pay-for-performance' arrangement (Medical Services Advisory Committee. Public Summary Document – Luxturna [voretigene neparvovec]. 2020).

10.32. The Committee noted that the supplier estimated that 55% of individuals with RPE65-mediated IRDs in New Zealand would have sufficient viable retinal cells to be eligible for voretigene neparvovec. The Committee considered that there was no specific test or established threshold to determine 'sufficient viable cells', and as such, this estimate appeared to be highly uncertain.

10.33. The Committee noted the FST was an appropriate endpoint for defining health outcomes and was consistent with how other funding jurisdictions assessed treatment success for purposes of determining levels of public reimbursement.

10.34. The Committee considered that a reasonable base case would be to assume a duration of treatment effect of 20 years for the purposes of economic assessment, as a balance between maturity of the evidence base and biological plausibility, and it was reasonable to consider scenarios with a treatment effect of 40 years.

10.35. The Committee considered that the number of people in the untested prevalent pool was uncertain, and that genetic testing would increase if treatment for the disease became funded. The Committee considered that it would not be a large increase.

10.36. The Committee noted that prednisone immunosuppression would be required in the two-week peri-operative period.

Funding criteria

10.37. The Committee considered that in practice, determining whether someone had 'sufficient viable retinal cells' would involve performing visual acuity tests and an optical coherence tomography (OCT) to ensure there was enough active retina to treat. The Committee considered it is difficult to attain an exact percentage of residual viable photoreceptor cells. The Committee considered that in very young children this sort of testing may be unnecessary, and or difficult to carry out, in recently diagnosed young people, who could generally be assumed to have sufficient retinal cells.

Summary for assessment

10.38. The Committee considered that the table below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for voretigene neparvovec if it were to be funded in New Zealand for *RPE65*-mediated IRDs. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with inherited retinal dystrophy due to pathological biallelic mutations of the *RPE65* gene, with sufficient viable retinal cells.
Intervention	Voretigene neparvovec, administered once as a subretinal injection in each eye in combination with peri-procedural treatment with prednisone.
Comparator(s)	Best supportive care
Outcome(s)	Improved visual acuity. • Russell et al. Lancet. 2017;390: 849-860 reported that voretigene neparvovec treatment is associated with an improvement in LogMAR score compared to placebo at 1-year post-treatment (mean difference -0.16, 95% CI = -0.41 to 0.08). • The long-term duration of such benefits is uncertain. • Reduced vision impairment (i.e., improved LogMAR score) is associated with improvements in health-related quality of life (Lloyd et al. BMJ. 2019;103: 1610-1614) Improved full field light sensitivity threshold test averaged over both eyes. • Russell et al (2017) reported that voretigene neparvovec treatment is associated with an average change of 2 log units for VN group compared to control group (difference between groups -2.11; 95% CI -3.9, -1.04; p=0·0004)
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

11. Considerations for aflibercept biosimilars

Application

11.1. The Committee reviewed the application for ziv-aflibercept in the treatment of ocular neovascularisation and considered the possible funding of a biosimilar aflibercept.

11.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

11.3. The Committee **did not recommend** the listing of ziv-aflibercept in place of, or as an alternative to aflibercept (or an aflibercept biosimilar) for currently funded indications based on insufficient evidence that it is therapeutically equivalent.

11.4. The Committee **recommended** that Pharmac should consider the funding of a biosimilar aflibercept either as an alternative to or alongside the currently funded brand if this would allow access to aflibercept to be widened to additional ophthalmology indications.

11.5. The Committee **recommended** that access be widened to an anti- vascular endothelial growth factor (VEGF) agent, with a **high priority** for the second-line treatment of retinal vein occlusion (RVO) within the context of treatment for ophthalmology, subject to the following Special Authority criteria:

> **Initiation** (Macular oedema - retinal vein occlusion) only from an ophthalmologist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has retinal vein occlusion; and
> 2. Patient has reduced visual acuity of between 6/12 – 6/60 with functional awareness of reduction in vision; and
> 3. Either:
>   3.1. Patient has not received adequate benefit from at least 3 injections with one anti-VEGF agent; or
>   3.2. Anti-VEGF treatment is unsuitable or contraindicated.
>
> **Renewal** (Macular oedema - retinal vein occlusion) only from an ophthalmologist. Approvals valid for 12 months
> 1. Patient's vision is stable or has improved (prescriber determined).

11.6. The Committee noted the high health need, lack of alternative anti-vascular endothelial growth factor (anti-VEGF) options for people with RVO, and benefit of combined anti-VEGF and corticosteroid treatment.

Discussion

Background

11.7. The Committee noted that off-label bevacizumab is currently funded as the first-line treatment of ocular neovascularisation and exudative ocular angiopathy, which includes wet aged related macular degeneration (wAMD), diabetic macular oedema (DMO) and RVO.

11.8. The Committee noted bevacizumab is listed on the Hospital Medicines List for a number of indications and is registered with Medsafe for intravenous treatment of different cancer indications. Bevacizumab is compounded (3.75mg/0.15mL) for intravitreal use. Bevacizumab was recommended by the Ophthalmology Subcommittee at its May 2012 meeting to be listed on the National Hospital Preferred Medicines List (PML) to treat ocular neovascularisation and exudative ocular angiopathy as it was already funded by some District Health Board hospitals at the time.

11.9. The Committee noted that the currently funded brand of aflibercept (Eylea) has been listed on the Pharmaceutical Schedule since 1 June 2018 and is funded for the second-line treatment of wAMD and DMO) subject to Special Authority access criteria.

Ziv-aflibercept considerations

11.10. The Committee noted that Pharmac had received an application for the listing of ziv-aflibercept (Zaltrap) for second-line treatment of wAMD, DMO and RVO.

11.11. The Committee noted that the applicant considered that funding ziv-aflibercept may provide an opportunity for savings to New Zealand Health sector and/or enable the widening of aflibercept eligibility to include people with other ophthalmic conditions such as RVO without incurring additional expenditure to the pharmaceutical budget.

11.12. The Committee noted that Medsafe approval of ziv-aflibercept for the treatment of metastatic colorectal cancer lapsed in 2019. The Committee noted that ziv-aflibercept is being supplied under Section 29 of the Medicines Act 1981.

11.13. The Committee noted that there is some international off-label use of ziv-aflibercept for the treatment of ophthalmic conditions, Members considered that ziv-aflibercept is used in ophthalmic conditions due to its low cost compared to aflibercept.

11.14. The Committee noted that ziv-aflibercept is used to treat ophthalmic conditions in New Zealand's private healthcare sector. The Committee noted that any use of ziv-aflibercept by Health New Zealand (Te Whatu Ora) hospitals for indications where the Eylea brand is funded does not comply with the Pharmaceutical Schedule rules and is not supported by Pharmac.

11.15. The Committee noted that the net price for the Eylea brand of aflibercept is subject to a confidential rebate and the Pharmaceutical Schedule list price is not representative of what Pharmac pays for aflibercept.

Health need for a second line treatment for RVO

11.16. The Committee noted that there is no currently funded anti-VEGF agent for second line treatment of macular oedema secondary to RVO. As a result, people who do not receive appropriate visual health benefit or are intolerant following treatment with bevacizumab are considered for treatment with corticosteroid agents.

11.17. The Committee noted Spooner et al., BMJ Open Ophthalmol. 2019;4:e000249 a retrospective review conducted in Sydney, Australia, reported that approximately 40% of people with RVO move to a second-line anti-VEGF agent. The Committee considered that in many overseas countries it is common for people with macular swelling in RVO to have access to a second-line anti-VEGF agent.

11.18. The Committee noted Zhang et al. BMC Ophthalmol. 2022;22:472 a systemic review and meta-analysis which reported:

11.18.1. Anti-VEGF with steroid combination therapy had a better effect on improvements to best corrected visual acuity outcomes (BCVA) compared to anti-VEGF monotherapy (pooled standardised mean difference [SMD], 95% CI, -0.16 [-0.28, -0.04], P = 0.01) or steroid monotherapy (pooled SMD, 95% CI, -0.56 [-0.73, -0.40], P < 0.00001).

11.18.2. Anti-VEGF with steroid combination therapy has a better effect on improvements to central macular thickness (CMT) compared to anti-VEGF monotherapy (pooled SMD 5% CI, -9.62 [-17.31, -1.93], P = 0.01).

11.19. The Committee considered that combination treatment with anti-VEGF and corticosteroids may provide superior health outcomes for people with macular

oedema secondary to RVO and there is an unmet health need for people requiring second line anti-VEGF treatment.

Health benefit

11.20. The Committee noted the molecular structure of ziv-aflibercept is identical to reference aflibercept. However, ziv-aflibercept undergoes a different purification process and contains a different buffer solution and therefore has a higher osmolarity (1000 versus 300 mOsmol/L), and lower drug concentration (25 mg/ml versus 40 mg/ml) compared to reference aflibercept.

11.21. The Committee noted Singh et al. Br J Ophthalmol. 2019;103:805-810 a retrospective review of medical records including a total of 1704 eyes of 1562 patients received 5914 intravitreal ziv-aflibercept injections (mean ± SD= 3.73 ±3.94) over a 2.5 years period. The study reported that ziv-aflibercept has an acceptable ocular and systemic safety profile with incidences of adverse events similar to those of other anti-VGEF's.

11.22. The Committee noted the Kanadani T, et al. Int J Retina Vitreous. 2024 Feb 2;10(1):13 prospective, observational, case series study. Using a treat and extend protocol efficacy of ranibizumab (n=33), aflibercept (n=33), bevacizumab (n=32) and ziv-aflibercept (n=33) in the first line treatment of wAMD over two years was evaluated. The study reported a statistically significant difference ($p< 0.05$) between pre- and post-treatment in the distribution of BCVA measurements by drug used where the distribution of BCVA measurements after treatment was significantly lower than before treatment. Intravitreal aflibercept provided better visual and anatomical improvements when compared to other drugs used in this study, including ziv-aflibercept. During the treat-and-extend protocol the study reported jndividuals treated with aflibercept had significantly fewer injections than people using the other drugs (mean = 9.03; $p<0.01$). However, the Committee considered that differences in baseline individual characteristics in the different treatment groups may have confounded the results.

11.23. The Committee noted the D'Souza et al. Semin Ophthalmol. 2021;36:28-34 study (ZEBRA) which was a prospective randomised control trial in those with wAMD being treated with ziv-aflibercept (n=29) or their existing anti-VEGF (n=27). At 24 months mean change in BCVA was 0.01 LogMAR (95% CI −0.146, 1.66) for ziv-aflibercept and 0.11 logMAR (95% CI −0.103, 0.321) for existing anti-VEGF treatment (treatment arm difference p=0.48). Mean change in central foveal thickness was −5 µm (95% CI −36 to 25.6; p = .24) for ziv-aflibercept and 26 µm (95%CI −12.4 to 64.4) for existing anti-VEGF treatments. The nature of the study precluded any comparison of changes to a new agent since the only individual receiving a change in medication were those switched to ziv-aflibercept.

The Committee noted Ayachit et al. Asia Pac J Ophthalmol (Phila). 2020;9:144-148 retrospective comparative review of medical records in those with wAMD receiving first line treatment with ziv-aflibercept (n=12 eyes) or aflibercept (n=11 eyes). At 3 months, mean change in BCVA was 0.51±0.12 LogMAR ($p<0.01$) for ziv-aflibercept and 0.029± 0.12 LogMAR for aflibercept. The Committee considered the differences in the baseline BCVA (ziv-aflibercept =1 ± 0.39, aflibercept 0.52 ± 0.30) confounded the outcome of results following three months of treatment (ziv-aflibercept = 0.49 ± 0.26, aflibercept 0.5 ± 0.32).

11.24. The Committee noted Sinawat et al. Clin Ophthalmol. 2023:17:2719-2728 a randomised non-inferiority study, in those with macular oedema secondary to RVO being treated as required with bevacizumab (n=12) or ziv-aflibercept (n=12). The 6-month interim analysis reported mean change in BCVA of 0.48 ± 0.42 LogMAR (95% CI 0.21, 0.74; $p<0.01$) in bevacizumab and 0.59 ± 0.53 LogMAR (95% CI 0.25, 0.93; $p<0.01$) in ziv-aflibercept. Mean change in CMT was 402.5 ± 293.6 µm (95% CI

216.3, 588.7; p<0.001) in bevacizumab and 405.3 ± 263.3 µm (95% CI 238.0, 572.7; p<0.001) in ziv-aflibercept. Ziv-aflibercept was non-inferior to bevacizumab regarding central subfield thickness (CST) reduction but inconclusive for BCVA.

11.25. The Committee noted Braimah et al. Indian J Ophthalmol. 2019;67:1109-1113 a retrospective interventional study, treating macular oedema secondary to branch-RVO as required with bevacizumab (n=32 eyes) or ziv-aflibercept (n=17 eyes). At 12 months the mean change in BCVA was 0.36 ± 0.3 logMAR for bevacizumab and 0.27 ± 0.3 logMAR for ziv-aflibercept. The mean change in CMT was 178.9 ± 180.9 for bevacizumab and 173.5 ± 344.4 ziv-aflibercept. The mean injections were 4.0 ± 1.8 for bevacizmab and 1.82 ± 0.8 for ziv-aflibercept.

11.26. The Committee noted Ashraf et al. Acta Ophthalmol. 2017;95:e803-e804 a prospective non-randomised study in which DMO was treated in the first line with ziv-aflibercept (n=27) or bevacizumab (n=23). The mean change in BCVA was 0.27 ± 0.28 logMAR for ziv-aflibercept and 0.39 ± 0.37 logMAR for bevacizumab. The mean change in CMT was 76.3 ± 125.6 µm for ziv-aflibercept and 97.9 ± 99.08 µm for bevacizumab (difference p<0.001). The baseline mean CMT was significantly different between treatment arms (ziv-aflibercept= 390.8 ± 90.28; bevacizumab473.2 ± 153.04; p<0.05).

11.27. The Committee considered that the most reliable evidence regarding the health benefit of ziv-aflibercept is two small randomised control trials of reasonable quality reported by D'Souza et al. 2021 and Sinawat et al. 2023. In which the Sinawat et al. 2023 was unable to conclude ziv-aflibercept was non-inferior to bevacizumab following 6-months of treament. The Committee considered that in the cohort studies the treatment arms are not well matched.

11.28. The Committee noted the following studies:

11.28.1. Braimah et al. Int Ophthal.2021:41;2445-53

11.28.2. Braimah et al. Br J Ophthalmol. 2018;10:91-96

11.28.3. Mansour et al. Br J Ophthalmo. 2018;102:1387-1390.

11.28.4. Singh et al. Semin Ophthalmol. 2019;34:420-435.

11.28.5. De Oliveira Dias et al. Retina. 2017;37:1499-1507

11.28.6. De Oliveira Dias et al. Retina. 2019;39:648-655

11.29. The Committee considered there is insufficient high-quality evidence to confidently assert that ziv-aflibercept is therapeutically equivalent to aflibercept in the treatment of wAMD, DMO and macular oedema secondary to RVO.

11.30. The Committee considered there to be sufficient evidence to support ziv-aflibercept to have a comparable safety profile to aflibercept.

11.31. The Committee considered that a second-line anti-VEGF treatment is required for those ophthalmic conditions such as RVO who currently only have access to bevacizumab. The Committee considered that anti-VEGF agents are generally better and safer than corticosteroid monotherapy, and that combination therapy could be better monotherapy for the treatment of macular oedema secondary to RVO (Zhang et al. 2022). The Committee considered that in the absence of widening access to aflibercept for other indications ziv-aflibercept would be a suitable treatment option.

11.32. Members noted that in their experience ziv-aflibercept was being administered in the same volumes as the aflibercept (0.05 ml) resulting in people being treated with a lower dose of ziv-aflibercept compared to aflibercept. The Committee considered that some people's symptoms may not be controlled with the comparatively lower dose of ziv-aflibercept and could risk the loss of disease control. Members noted that in their

private practice experience differences in disease control had not been observed when ziv-aflibercept is used.

11.33. Members considered that the ziv-aflibercept dose would need to be adjusted if the same concentration of aflibercept is to be administered. Members considered this would have logistical implications for the administration of ziv-aflibercept and is likely to mean that ziv-aflibercept would not be able to be administered by nurse injectors due to the larger volume of the injection.

Suitability

11.34. The Committee noted that because it has not been developed specifically for ophthalmic use, compounding is required before ziv-aflibercept can be used in these indications. If ziv-aflibercept was funded, this service would need to be completed by Health New Zealand hospitals or external compounding providers.

11.35. The Committee noted that ziv-aflibercept requires repackaging into a single use syringe containing 1.25mg aflibercept in 0.05ml (25 mg/ml) to be used.

11.36. The Committee noted the following studies:

11.36.1. de Lima Farah et al. Int J Retina Vitreous. 2018:4:39

11.36.2. Juhong et al. Sci Rep. 2022; 12: 2971

11.36.3. Sivertsen et al. Sci Rep. 2018;8:2101

11.37. The Committee considered that when ziv-aflibercept is compounded in sterile conditions and stored in appropriate conditions, the stability and binding-affinity to VEGF measured through enzyme-linked immunosorbent assays may be preserved for up to four weeks.

Commercial Considerations – biosimilar aflibercept

11.38. The Committee noted that ophthalmic aflibercept biosimilars have been approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA). The Committee noted that Medsafe has not received any applications for the registration of an ophthalmic aflibercept biosimilar, however some suppliers have expressed interest in bringing their product to the New Zealand in the future.

11.39. The Committee considered it reasonable for a competitive procurement process to be considered for aflibercept biosimilars. The Committee considered that any aflibercept biosimilar being considered in the competitive procurement process must have sufficient evidence demonstrating its ophthalmic bioequivalence to reference aflibercept.

11.40. The Committee considered that if an aflibercept biosimilar was awarded Principal Supply Status, consideration should be given to ongoing funding of reference aflibercept (Eyelea) for people who are unable to change.

11.40.1. The Committee considered that people who have monocular vision who are receiving appropriate health benefit should not be transitioned due to the significant impact of any vision loss.

11.40.2. The Committee considered that people who experience intolerable adverse events, are contraindicated to, or do not receive appropriate health benefit from treatment with an aflibercept biosimilar should be able to return back to reference aflibercept.

11.40.3. The Committee considered that less than 5% of people currently receiving reference aflibercept would not be able to transition to an aflibercept biosimilar.

11.41. The Committee considered if the preferred product of the competitive process was an aflibercept biosimilar, it would be reasonable to allow a 12-month transition period to the aflibercept biosimilar.

11.42. The Committee recommended an aflibercept biosimilar be listed, or access to aflibercept be widened, for second-line treatment of RVO where there are currently no further anti-VEGF treatment options funded.

11.43. The Committee considered that it would be important for Pharmac to work with support organisations such as Macular Degeneration New Zealand throughout any change to the funded brand of aflibercept.

12. Dexamethasone implant for the treatment of macular oedema due to retinal vein occlusion

Application

12.1. The Committee reviewed the application for dexamethasone implant for the treatment of macular oedema secondary to retinal vein occlusion.

12.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

12.3. The Committee **recommended** that the dexamethasone implant for the second line treatment of macular oedema due to retinal vein occlusion be listed with a **high priority** within the context of treatment of eye diseases subject to the following Special Authority criteria:

> **Initiation** (Macular oedema - retinal vein occlusion) only from an ophthalmologist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has retinal vein occlusion; and
> 2. Patient has reduced visual acuity of between 6/12 – 6/60 with functional awareness of reduction in vision; and
> 3. Either:
> 3.1. Patient has not received adequate benefit from at least 3 injections with one anti-VEGF agent; or
> 3.2. Anti-VEGF treatment is unsuitable or contraindicated; and
> 4. Dexamethasone implants are to be administered not more frequently than once every 4 months into each eye, and up to a maximum of 3 implants per eye per year.
>
> **Renewal** (Macular oedema - retinal vein occlusion) only from an ophthalmologist. Approvals valid for 12 months
> 1. Patient's vision is stable or has improved (prescriber determined); and
> 2. Dexamethasone implants are to be administered not more frequently than once every 4 months into each eye, and up to a maximum of 3 implants per eye per year.

12.4. In making this recommendation, the Committee considered:

- The high unmet health need
- The lack of alternative treatment in second line treatment
- It represented an alternative option for people who are contraindicated to anti-vascular endothelial growth factors including due to pregnancy or childbearing potential where alternatives are not available.

Discussion

Māori impact

12.5. The Committee discussed the impact of funding the dexamethasone implant for the treatment of macular oedema due to retinal vein occlusion on Māori health areas of

focus and Māori health outcomes. The Committee noted the New Zealand Diabetes, Heart and Health Survey 2002/2003 reported that Māori and Pacific peoples had higher average systolic and diastolic blood pressure levels compared with individuals of other ethnicities (Ramachandran et al. BMJ Open. 2021; 11: e054225). In addition, the cardiovascular disease mortality rate for Māori was twice as high compared to non-Māori (Sullivan et al. Qual Life Res. 2023; 32: 2117–26). Metabolic syndrome (defined as a combination of obesity, hypertension, dyslipidaemia and insulin resistance) was statistically significantly higher in rural and urban Māori vs non-Māori populations (Cameron et al. BMJ Open. 2012; 2: e000799). The Committee considered this places Māori and Pacific people at increased risk for ocular disease.

12.6. The Committee considered that there were higher rates of myocardial infarction and cerebral vascular accident in Māori that may restrict access to first line vascular endothelial growth factor inhibitor treatments, and therefore Māori have a higher unmet health need.

12.7. The Committee considered that due to the higher prevalence of aetiological risk factors, it is likely that Māori would have higher rates of treatment of macular oedema due to retinal vein occlusion.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

12.8. The Committee considered Pacific peoples have higher rates of aetiological risk factors and are more likely to have higher rates of treatment of macular oedema due to retinal vein occlusion.

12.9. The Committee considered that there were higher rates of myocardial infarction and cerebral vascular accident in Pacific peoples that may restrict access to first line vascular endothelial growth factor inhibitor treatments, and therefore Pacific peoples have a higher unmet health need.

Background

12.10. The Committee noted that it had not previously considered treatment for retinal vein occlusion (RVO). The Committee noted that dexamethasone implants are funded for diabetic macular oedema in the second line setting post cataract surgery, as well as in second line in pregnant women. It was declined for funding in the first line setting in 2024 following a recommendation to decline by the Committee in 2016.

Health need

12.11. The Committee noted retinal vein occlusion (RVO) is an obstruction of the retinal venous system by thrombus formation and may involve the central, hemi central or branch retinal vein.

12.12. The Committee noted the two main complications of RVO are macular oedema (MO) and retinal ischaemia leading to iris and/or retinal neovascularisation (Nicholas et al. Eye (Lond). 2022;36:909-12). MO is the most common cause of visual impairment in RVO, followed by foveal ischaemia (Nicholas et al. 2022). MO occurs in approximately 75% of people with central retinal vein occlusion (CRVO) and 85% of people with branch retinal vein occlusion (BRVO). Visual impairment due to macular oedema occurs is experienced by 50% of people with BRVO and 100% of people with CRVO (Royal College of Ophthalmologists, RVO clinical guidelines 2022).

12.13. The Committee noted the risk factors for development of RVO include advancing age as well as systemic conditions like hypertension, arteriosclerosis, diabetes mellitus, hyperlipidaemia, vascular cerebral stroke, blood hyperviscosity, and thrombophilia. A strong risk factor for RVO is metabolic syndrome, including end-organ damage

caused by diabetes mellitus and hypertension. In addition, other risks include congenital thrombophilic diseases like factor V Leiden mutation, hyperhomocysteinaemia and anticardiolipin antibodies increase the risk of RVO. Further risk factors including smoking, and systemic inflammatory conditions like vasculitis and Behcet disease. Ophthalmic risk factors for RVO are ocular hypertension and glaucoma, higher ocular perfusion pressure, and changes in the retinal arteries. (Kolar et al. J Ophthalmol. 2014;724780). The Committee noted that hypertension was the strongest risk factor for any RVO with a meta-odds ratio (OR) of 2.82 (95% CI, 2.12- 3.75) (Song et al. J Glob Health. 2019; 9:010427).

12.14. The Committee considered that individuals with retinal vein occlusions have a high health need, and also noted that this group had a high prevalence of co-morbidities. The Committee considered development of MO due to RVO had a large effect on the lives of people who developed it and led to a loss of independence, as well as an inability to work. The Committee also considered it affected their whānau, with the need to support frequent visits to eye specialists, and time away from paid employment to support the individual as well as the effect of the burden on the family.

12.15. The Committee considered that people with central RVO, including people with hemi-RVO have a worse prognosis due to both hemispheric vasculature sides being affected and are more likely to become ischaemic.

12.16. The Committee noted an Australian study that reported the prevalence of any RVO of 0.90% (confidence interval (CI) 0.59,1.3), as well as BRVO of 0.73% (CI 0.46, 1.1) and CRVO of 0.17% (CI 0.05, 0.39) (Keel et al. Clin Exp Ophthalmol. 2018;46:260-5). The Committee considered this would be the equivalent to 38,500 people experiencing any form of RVO, 32,000 experiencing BRVO and 6,500 experiencing CRVO in New Zealand.

12.17. The Committee noted the New Zealand Diabetes, Heart and Health Survey 2002/2003 reported that Māori and Pacific peoples had higher average systolic and diastolic blood pressure levels compared with individuals of other ethnicities (Ramachandran et al. BMJ Open. 2021; 11: e054225). In addition the cardiovascular disease mortality rate for Māori was twice as high compared to non-Māori (Sullivan et al. Qual Life Res. 2023; 32: 2117–26). Metabolic syndrome (defined as a combination of obesity, hypertension, dyslipidaemia and insulin resistance) was statistically significantly higher in rural and urban Māori vs non-Māori populations (Cameron et al. BMJ Open. 2012; 2: e000799). The Committee considered this places Māori and Pacific people at increased risk for ocular disease.

12.18. The Committee noted that the current funded first line treatment for MO secondary to RVO is bevacizumab. The Committee noted that the outcomes of treatment are measured through evaluating central foveal thickness, visual acuity and tolerance to the treatment. The Committee noted that treatment persists until resolution, however if the MO remains unresolved retreatment either monthly, or by treating and extending the review period until the maximal treatment and review period that maintains disease stability for each individual is found. The Committee noted pan-retinal laser photocoagulation is considered an adjunctive treatment if neovascularisation of the retina or the iris occurs.

12.19. The Committee considered intravitreal steroids would be used in second line however there remains challenges with this approach. The Committee considered there were issues with the supply of a preservative free formulation of a triamcinolone acetonide intravitreal injection, whilst the off-label use of a formulation that includes preservatives has a risk of sterile inflammatory endophthalmitis. The Committee considered preservative free intravitreal steroids would be used in second line treatment if available.

12.20. The Committee noted that there are several other vascular endothelial growth factor inhibitors including ranibizumab and aflibercept, however these are not approved for this indication. The Committee noted that some individuals may receive adjunctive sectoral or pan-retinal photocoagulation laser therapy. The Committee noted there are no funded second line treatments currently available.

12.21. The Committee noted anecdotal evidence that approximately 3-5% of individuals receive insufficient response to bevacizumab and this group of individuals have the highest unmet health need. The Committee noted the response rate does not differ depending on the type of vein occlusion causing the macular oedema.

12.22. The Committee noted that the proposed treatment paradigm suggests the use of the dexamethasone implant in individuals where three bevacizumab injections have failed to result in adequate outcomes, or in those who are considered contraindicated or unsuitable for bevacizumab treatment including in individuals who have had a myocardial infarction in the last three months. Treatment failure is defined as reduction in vision or worsening of central foveal thickness. The Committee noted that the maximum number of treatments is three implants in one year.

Health benefit

12.23. The Committee noted Haller et al.Ophthalmology. 2011;118:2453-60 and Haller et al. Ophthalmology.2010;117:1134-46.e3 that reported the results of two identical, multicentre prospective phase 3 studies each included a randomized, 6-month, double-masked, sham-controlled phase followed by a 6-month open-label extension in 1265 people with decreased visual acuity as a result of clinically detectable macular oedema associated with CRVO or BRVO. The following results were reported at 12 months:

- In the group receiving two 0.7-mg dexamethasone (DEX) implants (n = 341), a ≥10-mmHg intraocular pressure (IOP) increase from baseline was observed in (12.6% after the first treatment, and 15.4% after the second).
- The IOP increases were usually transient and managed with observation or controlled with medication; an additional 10.3% initiated IOP-lowering medications after the second treatment. A ≥15-letter improvement in best corrected visual acuity (BCVA)from baseline was achieved by 30% and 32% 60 days after the first and second DEX implant, respectively.
- Over 12 months, cataract progression occurred in 90 /302 phakic eyes (29.8%) that received 2 DEX implant 0.7 mg injections vs 5/88 sham-treated phakic eyes (5.7%); cataract surgery was performed in 4/302 (1.3%) and 1/ 88(1.1%) eyes, respectively.
- Single administration: time to achieve a ≥15-letter improvement in BCVA was significantly less in both DEX implant groups compared with sham (P>0.001). The percentage (%) of eyes with a ≥15-letter improvement in BCVA was significantly higher in both DEX implant groups vs sham at days 30 -90 (P>0.001).
- The % of eyes with a ≥15-letter loss in BCVA was significantly lower in the DEX implant 0.7-mg group vs sham at all follow-up visits (P>0.036). Improvement in mean BCVA was greater in both DEX implant groups vs sham at all follow-up visits (P>0.006).
- Improvements in BCVA with DEX implant were seen in BRVO and CRVO, although the patterns of response differed. The % of DEX implant-treated eyes with IOP of ≥25 mmHg peaked at 16% at day 60 (both doses) and was not different from sham by day 180.

- The incidence of serious adverse events (AEs) was similar across all treatment groups and singular or repeated implant treatment.
- The most common AEs were conjunctival haemorrhage associated with the injection and increases in IOP.

12.24. The Committee noted the following publications:

- Capone et al. Retina. 2014;34:342-51
- Eter et al. Graefes Arch Clin Exp Ophthalmol. 2017;255:77-87
- Georgalas et al. Cutan Ocul Toxicol. 2019;38:330-7
- Korobelnik et al. Graefes Arch Clin Exp Ophthalmol. 2016;254:2307-18.
- Singer et al. BMC Ophthalmol. 2015:15:33.
- Ferrini et al. Klin Monbl Augenheilkd. 2013;230:423-6
- Li et al. Graefes Arch Clin Exp Ophthalmol. 2018;256:59-69.
- Gado et al. Clin Exp Ophthalmol. 2014;42:650-5.
- Kuppermann et al. Retina. 2014;34:1743-9
- Yuan et al Front Pharmacol. 2022:13:951666
- Ming et al. BMJ Open. 2020;10:e032128
- Glanville et al. BMC Ophthalmol. 2014:14:7.
- Hu et al. Indian J Ophthalmol. 2019;67:1800-9
- Ji et al. Medicine (Baltimore). 2019;98:e15798
- Gao et al. BMC Ophthalmol. 2019;19:8

12.25. The Committee noted overall there was a good level of high-quality multi-centre randomised controlled trial data and meta-analyses with long term follow up data.

12.26. The Committee noted that there is a risk of active, latent, or suspected ocular or peri ocular infections especially those that are herpetic, mycobacterial, or fungal in nature from dexamethasone implantation treatment. The Committee also noted that approximately 25% of people will experience an intraocular pressure rise, that peaks at 8 weeks post treatment. The Committee considered therefore that it is important for individuals to have regular follow up appointments to measure the intraocular pressures.

12.27. The Committee noted that cataract development occurred within 68% of individuals treated with a dexamethasone implant compared with 21% of individuals provided a sham procedure within 12 months.

12.28. The Committee noted that individuals who have had a posterior capsular tear during cataract surgery are contraindicated due to anterior chamber spillover of the steroid which increases risk of developing a steroid response.

Suitability

12.29. The Committee considered that the dexamethasone implant is given by an ophthalmologist after training in the idiosyncratic delivery technique, and this might affect clinical and costing efficiency, noting many anti- vascular endothelial growth factor injections are administered by nurse injections.

Cost and savings

12.30. The Committee considered at present everyone with a MO due to RVO would receive bevacizumab injections in first line unless contraindicated, or not tolerated due to anxiety, with a series of three injections for induction followed by monthly injections. The Committee considered this would move to *pro re nata* (PRN) or extended monitoring between treatments, dependent on the individual.

12.31. The Committee considered very few people would receive dexamethasone implants in both eyes.

12.32. The Committee noted that while bevacizumab is the only funded vascular endothelial growth factor inhibitor, that more than 3-5% of individuals may swap to dexamethasone implants. If other vascular endothelial growth factor inhibitors were funded, individuals losing efficacy over time could swap to one of these biosimilars, however given the currently funded treatments around 25% may swap from bevacizumab to dexamethasone implants.

12.33. The Committee considered that most receiving dexamethasone implants would receive the maximum dosing frequency allowed by the special authority; 4-monthly.

12.34. The Committee noted that due to the high proportion of people having a rise in IOP, there should be regular IOP follow ups, particularly in the early stages of treatment.

12.35. The Committee considered the cost to the health sector expenditure would be similar to vascular endothelial growth factor inhibitors, however in phakic individuals there is a 68% chance of requiring cataract surgery within 12 months of the treatment initiation. This would equate to a cost in the region of $3500 dollars in phakic individuals.

12.36. The Committee considered most people undergo treatment for between 2-5 years. The Committee noted BRVO 40% of individuals will successfully discontinue treatment within 2 years, in CRVO this rate is 35% (Lo T et al Opthalm Surg Lasers Imaging Retina 2021 Jul; 52(2): 84-92).

Funding criteria

12.37. The Committee considered this treatment was suited to individuals who were pseudophakic or individuals who were able to undergo cataract extraction within 12 months, with no history of a posterior capsule tear during cataract surgery, and who have shown limited or no response to three or more intravitreal vascular endothelial growth factor blockers based on BCVA or central foveal thickness (CFT) measurements, those who are contraindicated to vascular endothelial growth factor treatments, or those who have diminished ability to undergo monthly intravitreal procedures due to adherence or accessibility issues.

12.38. The Committee considered this treatment would be suitable for third line treatment if an alternative VEGF inhibitor becomes available as a second line treatment due to the risk benefit profile.

Summary for assessment

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

Population	People with macular oedema (MO) secondary to retinal vein occlusion (RVO), who have experienced insufficient treatment benefit or intolerable side effects from anti-VEGF treatment.
Intervention	Dexamethasone 0.7mg intravitreal implants: • Administered once every four months into each eye. • Duration of treatment indefinite provided the individual is benefitting from treatment. Implants to be used as an adjunctive treatment to currently funded therapies for MO secondary to RVO.
Comparator(s)	Current therapies for MO secondary to RVO, comprised of topical steroids, intravitreal steroids and certain immunosuppressive therapies
Outcome(s)	Improved visual acuity, as measured by best corrected visual acuity (BCVA) • Among trial participants who received dexamethasone 0.7mg intravitreal implants, 29% experienced an improvement in BCVA of ≥15 letters at 60 days post-administration compared to baseline compared to 11% for those who received sham (Haller et al. Ophthalmolog.2010;117:1134-46) • Treatment benefit wanes rapid and substantially after 60 days post-administration. Improved health-related quality of life • Greater visual acuity is associated with improved health-related quality of life.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

13. Dexamethasone implant for the treatment non-infectious uveitis and for macular oedema due to non-infectious uveitis

Application

13.1. The Committee reviewed the application for dexamethasone implant for the treatment non-infectious uveitis and for macular oedema due to non-infectious uveitis.

13.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

13.3. The Advisory Committee **recommended** that dexamethasone implant for the treatment non-infectious uveitis and for non-infectious inflammatory macular oedema be listed with a **high priority,** within the context of treatment of eye diseases, subject to the following Special Authority criteria:

> **Initiation** (Uveitis). Applications from an ophthalmologist or any practitioner on the recommendation of an ophthalmologist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:

1. Patient has severe uveitis with a risk of moderate or severe vision loss; and
2. Any of the following
   2.1. The condition is not controlled with periocular or intravitreal steroid injection; or
   2.2. Uveitis has persisted or rebounded on a tapering course of systemic steroid; or
   2.3. Patient is contraindicated to immunomodulatory agents, steroids, or immunosuppressants; and
3. Dexamethasone implants are to be administered not more frequently than once every 4 months into each eye, and up to a maximum of 3 implants per eye per year.

Renewal (Uveitis). Applications from an ophthalmologist or any practitioner on the recommendation of an ophthalmologist. Approvals valid for 12 months
Both:
1. Patient has experienced sufficient benefit from treatment with dexamethasone implant (prescriber determined); and
2. Dexamethasone implants are to be administered not more frequently than once every 4 months into each eye, and up to a maximum of 3 implants per eye per year.

Initiation (macular oedema - chronic). Applications from an ophthalmologist or on the recommendation of an ophthalmologist. Approvals valid for 12 months for applications meeting the following criteria:

1. Patient has inflammatory macular oedema; and
2. Patient has tried topical steroid and topical non-steroidal anti-inflammatory combination for four weeks; and
3. Either
   3.1. Patient has experienced relapse of symptoms or the condition is not controlled following periocular or intravitreal steroid injection; or
   3.2. Patient is contraindicated to immunomodulatory agents, steroids, or immunosuppressants; and
4. Dexamethasone implants are to be administered not more frequently than once every 4 months into each eye, and up to a maximum of 3 implants per eye per year

Renewal (macular oedema - chronic). Prescribed by or recommended by an ophthalmologist. Approvals valid for 12 months

1. Patient has experienced sufficient benefit from treatment with dexamethasone implant (prescriber determined); and
2. The chronic macular oedema has relapsed when the implant has worn off; and
3. Dexamethasone implants are to be administered not more frequently than once every 4 months into each eye, and up to a maximum of 3 implants per eye per year.

13.4. In making this recommendation, the Committee considered:

- People with macular oedema and uveitis are currently experiencing unmet health need in New Zealand, as approximately 10% of people experience moderate-severe vision loss despite treatment with currently available therapies.
- Potential benefits that could be gained from dexamethasone implant included less impact on vision due to pellet design, and specific design for intraocular use, more durable responses than to intraocular suspensions, and a lower risk of sterile endophthalmitis.
- A suitability benefit of the treatment is the fewer number of clinic visits required than for the currently funded alternatives (periocular steroids and intravitreal triamcinolone).
- That the need for fewer clinic visits due to the longer duration of action of dexamethasone implant compared to currently available treatments may reduce costs to the health system, as would lower risk of falls and other adverse health issues related to poor vision.

Discussion

Māori impact

13.5. The Committee discussed the impact of funding dexamethasone implant for the treatment non-infectious uveitis and for macular oedema due to non-infectious uveitis on Māori health outcomes. The Committee noted uveitis and macular oedema are not one of Pharmac's five Hauora Arotahi - Māori Health Areas of Focus. The Committee noted the Auckland Uveitis database showed 6.7% of uveitis cases occurred in Māori (although the Committee noted this can vary depending on the subtype/specific uveitis diagnosis). The Committee noted that presentations of HLA B27 uveitis were often more severe in Māori, and Māori were more likely to experience intermediate or panuveitis.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

13.6. The Committee discussed the impact of funding dexamethasone implant for the treatment non-infectious uveitis and for macular oedema due to non-infectious uveitis for people who have been underserved by the health system. The Committee noted the Auckland Uveitis Database showed a slight under-representation of Māori and Pacific people compared to the general population. However, the Committee considered that uveitis can be more severe in these populations.

Background

13.7. The Committee noted adalimumab was funded in September 2019 for chronic or severe uveitis.

13.8. The Committee noted dexamethasone implants were funded in October 2017 for the second-line treatment of diabetic macular oedema post-surgery, and for second-line treatment of diabetic macular oedema in pregnant women.

13.9. The Committee noted that at the time of the meeting, Pharmac was reviewing consultation feedback regarding declining an application for dexamethasone implants for the first-line treatment of diabetic macular oedema.

Health need

13.10. The Committee noted the health need of individuals with uveitis was previously considered by PTAC in August 2017. The Committee noted non-infectious causes of uveitis (ie intraocular inflammation) are commonly autoimmune/autoinflammatory. The Committee noted macular oedema (CMO) is the swelling of the central retina (the part of the eye used for reading). The Committee noted that CMO is the most common complication of non-infectious uveitis (Massa et al. Clin Ophthalmol. 2019; 13: 1761–77).

13.11. The Committee noted symptoms of uveitis and CMO include eye pain, blurred vision, scotomas (patches missing from vision), and floaters; all which the Committee considered impact people's ability to work, drive, function, and remain independent. The Committee noted evidence shows that that uveitis and CMO are associated with lower quality of life, work loss, disability, depression, and anxiety (Hariprasad et al. BMJ Open Ophthalmol. 2021; 6: e000896, Hui et al Ocul Immunol Inflamm. 2017;25:486-91, Choo et al. Curr Opin Ophthalmol. 2023;34:543-49). The Committee noted evidence reporting that children with chronic uveitis have medical, educational, psychological, developmental, and interpersonal challenges (Parker et al. Am J Ophthalmol. 2018; 191: xvi–xxiv). The Committee considered uveitis accounts for 10-15% of all causes of blindness amongst working age individuals, with CMO being an important cause of this blindness. The Committee estimated that approximately 50% of people with non-infective uveitis will have an associated autoimmune/ autoinflammatory issue.

13.12. The Committee noted the Auckland Uveitis Database includes data from 4395 people with uveitis over a 15-year period. The Committee noted the median age at presentation for people included in the database was 45 years. The Committee noted 29% of people experienced a chronic course of uveitis, with 75% of those experiencing non-infectious uveitis. The Committee noted 54% of people were Caucasian, 6.7% were Māori 13.4% Pacific people, and 22.7% Asian. The Committee noted this to show a slight under-representation of Māori and Pacific people compared to the general population. However, the Committee considered that uveitis can be more severe in these populations.

13.13. The Committee noted that of the 4395 people with uveitis included in the Auckland Uveitis database, 7% developed inflammatory macular oedema. The Committee noted this was the most common cause for moderate or severe vision impairment related to uveitis (Ali et al. Ocul Immunol Inflamm. 2024:1-9). The Committee noted development of inflammatory macular oedema was more common in older people, and people with posterior or panuveitis. The Committee noted that approximate 3.7% of people develop macular oedema following cataract surgery (Han et al. Am J Ophthalmol. 2019:197:114-120).

13.14. The Committee noted that the risk of moderate or severe vision loss due to uveitis differs by subtype, with highest rates in New Zealand associated with ischaemic retinal vasculitis (21% moderate or severe vision loss at 5 years) (Yap et al. Br J Opthalmol. 2024:325775), and paediatric uveitis (17% risk of moderate vision loss) (Samalia et al. N Z Med J. 2023;136:56-66), and lower rates associated with anterior uveitis (9.5% risk of moderate vision loss) (Al-Ani et al. Br J Opthalmol. 2020;104:1652-7), and HLA B27 uveitis (1.75 risk of moderate vision loss, and 0.8% risk of severe vision loss) (Al-Ani et al. Eye (Lond). 2023;37:1673-7). The Committee noted that internationally reported rates of vision loss due to uveitis are higher (Tomkins-Netzer at al. Ophthalmology. 2014;121:2387-92) but considered this may be due to the study being older, and published before more effective treatments were introduced.

13.15. The Committee noted that currently funded treatments for uveitis in New Zealand include systemic and local treatments. The Committee noted systemic treatment options include oral steroids, intravenous steroids, non-biologic disease-modifying antirheumatic drugs (DMARDS), and biologic DMARDS (infliximab and adalimumab via Special Authority criteria). The Committee considered the benefit of biologic DMARDs has been notable since they were introduced in recent years. The Committee considered systemic treatment is often favoured in bilateral uveitis, systemic autoimmune disease, and in children (to decrease the risk of cataracts associated with steroid eye drops). The Committee considered that in addition, systemic treatment is appropriate for people whose eye pressure increases to an unacceptably high level with the use of steroid eye drops. The Committee considered systemic treatment is inappropriate for people with post-operative macular oedema.

13.16. The Committee noted currently funded local treatment options for uveitis include steroid eye drops, periocular (around the eye) steroid injections, and intravitreal steroid suspensions. The Committee noted that the currently funded steroid suspension contains preservative, which is associated with increased risk of sterile endophthalmitis. The Committee considered all suspensions are associated with the risk of causing ‘floaters’ in the vision, all wash out quickly, and noted none are approved for uveitis treatment. The Committee noted all local steroid increase the risk of cataracts, increases in intraocular pressure, and glaucoma.

13.17. The Committee considered most people with uveitis will receive sufficient benefit from steroid eye drops and/or a short course of systemic steroids. The Committee noted the Auckland Uveitis database reported that 12% of people with uveitis required

treatment with a non-biologic DMARD, and 5.3% required treatment with a biologic DMARD. The Committee noted younger people were more likely to require DMARD treatment.

13.18. The Committee noted that in New Zealand patients on anti TNF are a severe group who have been treatment resistant to other medications. Only 20-30% may be controlled with combination treatment adalimumab and infliximab.

13.19. The Committee noted that approximately 15% of people with uveitic macular oedema didn't respond to any of the available funded treatments in New Zealand, and approximately one third of people who did receive adequate benefit from treatment experienced disease recurrence, mostly within one year. The Committee noted that at one year, despite treatment, 9.7% experienced moderate vision loss, and 6.9% experienced severe vision loss (Ali et al. Ocul Immunol Inflamm. 2024:1-9).

13.20. The Committee considered people with macular oedema and uveitis are currently experiencing unmet health need in New Zealand, as approximately 10% of people experience moderate-severe vision loss despite treatment with currently available therapies. The Committee considered the currently funded systemic treatments have associated immune-suppression risk, and local treatments are associated with risk of cataracts, increased intraocular pressure, and obscuration of vision from suspensions.

13.21. The Committee considered there may be a health need for other people as a result for caring for individuals with impaired vision, as they may need to provide support for the person with uveitis psychologically, socially, and financially, dependent on the severity of vision loss caused.

13.22. The Committee considered that treatment with steroid injections or implants would be considered for chronic uveitis that can't be managed with low dose topical steroids with/without DMARDs due to patient factors such as in elderly/frail people and people with recent cancers. The Committee considered local treatment is preferred in unilateral uveitis. The Committee considered treatment with steroid injections or implants are often considered as the most appropriate option for uveitic macular oedema as high doses of oral prednisone are often required for a response, and local steroids have a faster onset of action than DMARDs, so are often used in conjunction. The Committee considered steroid injections/ implants are also considered if there is high risk of imminent vision loss and DMARDs and prednisone aren't working well enough (as adjunctive or monotherapy)

Health benefit

13.23. The Committee noted results of a 26-week, prospective, multicentre, masked, randomised, parallel-group, sham-controlled trial (*N* = 229) which compared to efficacy of dexamethasone implant to sham control (Lowder et al. Arch Ophthalmol.2011;129:545-53). The Committee noted dexamethasone implant significant improved vision; a gain of ≥15 letters from baseline best-corrected visual acuity (BCVA) was reported in significantly more eyes in the dexamethasone implant groups than the sham group at all study visits, although the Committee noted dexamethasone implant was also associated with higher rates of cataract.

13.24. The Committee noted results from the MERIT randomised controlled trial which compared the efficacy of the dexamethasone implant to intravitreal methotrexate, an intravitreal ranibizumab (*N* = 225 eligible eyes) (Acharya et al. Ophthalmology. 2023;130:914-23). The Committee noted that at 12 weeks, reduction of macular oedema was significantly greater in the dexamethasone group than for either methotrexate (P < 0.01) or ranibizumab (P = 0.018), and only the dexamethasone group showed a statistically significant improvement in BCVA during follow-up (4.86

letters; P < 0.001). The Committee noted elevated intraocular pressure was more common in the dexamethasone group.

13.25. The Committee noted results from the POINT trial randomised controlled trial which compared periocular triamcinolone, intravitreal triamcinolone and dexamethasone implant for the treatment of uveitic macular oedema (*N* = 235 eyes) (Thorne et al. Ophthalmology. 2019;126:283-295). The Committee noted intravitreal triamcinolone, and the dexamethasone implant had larger resulted in larger reductions in central subfield thickness at 8 weeks and were superior in improving and resolving uveitic macular oedema, than periocular triamcinolone. The Committee considered results from the study showed dexamethasone implant was non-inferior to intravitreal triamcinolone, and the two treatments exhibited similar risk of raised intraocular pressure.

13.26. The Committee noted results from a single-centre, interventional clinical trial which reported the effectiveness of repeated intravitreal dexamethasone (DEX) inserts in people with non-infectious uveitis (*N* = 109 eyes) (Pohlmann et al. Ophthalmology. 2018;125:1088-99). The Committee noted the authors reported significant reductions in macular thickness, 72% of people needed >1 implant in 5 years, and the mean number of implants required was 2.46 at 2 years.

13.27. The Committee considered potential benefits that could be gained from dexamethasone implant included less impact on vision due to pellet design, specific design for intraocular use, a lower risk of sterile endophthalmitis, and more durable responses than to intraocular suspensions.

13.28. The Committee noted a study which included 1076 people with uveitis in UK, resulted in vision loss in 19.2% of eyes (Tomkins-Netzer at al. Ophthalmology. 2014;121:2387-92).

13.29. The Committee noted NZ data which shows out of 248 eyes in 218 patients with uveitic cystoid macular oedema (CMO),, 15% did not respond to any available treatment. Some of this 15% would respond to dexamethasone implants, some of the 85% would also swap it is difficult to say what proportions.

13.30. The Committee noted in the post operative CMO setting most studies show that <1% still have issues at 1 year.

13.31. The Committee considered all intraocular/periocular steroid formulations are associated with risks of increased intraocular pressure and cataract, and considered dexamethasone implant was not likely to increase these risks compared to the currently funded steroid treatment options.

Suitability

13.32. The Committee noted dexamethasone implant would be administered by an ophthalmologist as an outpatient procedure as required, with a maximum frequency of every 4 months.

13.33. The Committee considered a suitability benefit of the treatment is the fewer number of clinic visits required than for the currently funded alternatives (periocular steroids and intravitreal triamcinolone).

Cost and savings

13.34. The Committee considered that if moderate and severe vision loss is reduced, people are more likely to remain in education and/or employment.

13.35. The Committee noted that the prevalence of uveitis is estimated at 21.5 per 100,000 (Hart et al. CEO. 2019: 47; 733-740). The committee noted from the Auckland database; 75% of uveitis cases are non-infectious.

13.36. The Committee noted that the data shows recurrence in 36.5% of patients, most recurrences in the first year and considered that for the purposes of modelling, it could be assumed that two thirds of individuals may only have one dose of dexamethasone implants.

13.37. The Committee noted that less than 1% of people on dexamethasone implants would receive implants in both eyes based on individuals currently receiving intravitreal injections, as bilateral treatment is generally systemic.

1.1. The committee reported 7% of uveitis in the Auckland database resulted in macular oedema, noting this was more common in posterior or panuveitis and more common in older individuals. (Al-Ani et al. Eye (Lond) 2023;37:1673-77, Al-Ani et al. BR J Opthalmol. 2020;104:1652-7, Samalia et al. N Z Med J. 2023;136:56-66)

13.38. The Committee considered that improved vision may be associated with a reduced risk of falls which may reduce costs to the health system, as would the need for fewer clinic visits due to the longer duration of action of dexamethasone implant compared to currently available treatments. The Committee considered funding dexamethasone implants could also result in lower use (and thus costs) of systemic treatments for uveitis.

Summary for assessment

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

Population	• People with uveitis, uncontrolled or contraindicated to treatment with steroids and other immunosuppressants, with a severe risk of vision loss or, • People with non-infective inflammatory macular oedema
Intervention	Single-use intravitreal dexamethasone implant, 700 µg per eye (entire contents of a single-use OZURDEX device). Used in conjunction with topical steroids and possibly systemic immunosuppression.
Comparator(s) (NZ context)	Dexamethasone implant might replace some or all of the following: • Topical steroid or NSAID • Periocular and intravitreal steroid injections • Systemic steroid and DMARDs

Outcome(s)	Improved visual acuity, as measured by best corrected acuity (BCVA) - The proportion of individuals with at least 15 letters improvement from baseline BCVA in the study eye at week 8 was more than 6-fold higher with OZURDEX® (42.9%) compared to sham (6.6%), p < 0.001. Statistical superiority was achieved at week 3 and maintained up to and including week 26 (p < 0.001) (Lowder et al. Arch Ophthalmol.2011;129:545-53). - Structural improvement: - Reduction in macular oedema (OCT scan) - Reduction in severity of intermediate or posterior uveitis (SUN criteria) Improved health-related quality of life - Greater visual acuity is associated with improved health-related quality of life.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	