

Ophthalmology Subcommittee of PTAC

Meeting held 24 February 2016

(minutes for web publishing)

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

The Ophthalmology Subcommittee may:

- a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 5 & 6 May 2016, a record of which will be available in due course.

**Record of the Ophthalmology Subcommittee of the Pharmacology and Therapeutics
Committee (PTAC) meeting held at PHARMAC on 24 February 2016**

1 Matters arising

Aciclovir eye ointment

- 1.1 The Subcommittee noted that ganciclovir 0.15% eye ointment was currently being supplied under Section 29 of the Medicines Act 1981 (S29) medicine as a temporary substitute for aciclovir eye ointment 3% (Zovirax) which was globally out of stock. Members noted that as a result, optometrists were unable to prescribe ganciclovir due to the regulatory barrier that only allows medical practitioners to prescribe S29 medicines.
- 1.2 The Subcommittee noted that after the 2015/16 tender, it was expected that a registered aciclovir eye 3% ointment would return to the market in late 2016 and replace the temporarily listed ganciclovir 0.15% eye ointment. The Subcommittee considered there would be no clinical risk switching current patients back to aciclovir eye 3% ointment.
- 1.3 The Subcommittee considered that of the two agents, ganciclovir was less toxic to the cornea, better tolerated, easier for patients to use, and evidence showed it to be non-inferior. Members considered that due to those factors, ganciclovir 0.15% eye ointment would be the preferred agent, but noted that it was not registered in New Zealand which was a significant barrier to listing it on the Pharmaceutical Schedule.
- 1.4 The Subcommittee **recommended** that PHARMAC investigate the possibility of a supplier registering ganciclovir 0.15% eye ointment in New Zealand, and funding it only if it was cost neutral to aciclovir, and to keep this as an ongoing action point for the Subcommittee's review.

Olopatadine expenditure

- 1.5 The Subcommittee noted the increasing expenditure of olopatadine 0.1% eye drops in comparison with other anti-inflammatory eye preparations. Members noted that olopatadine had been listed on the Pharmaceutical Schedule from 1 July 2013 for use in ocular allergy without restrictions, and expenditure had risen to over \$900,000 for the financial year ending 30 June 2015 and is projected to continue growing.
- 1.6 The Subcommittee noted it had expected olopatadine use to plateau, and that its use would see a reduction in ophthalmic corticosteroid use. Members noted that, contrary to earlier predictions, current data showed that both olopatadine and ophthalmic corticosteroid usage to be increasing. The Subcommittee considered that it would be useful to have access to the prescriber data on all highlighted pharmaceuticals such as olopatadine to determine if scripts were primarily written by specialists or general practitioners. Members considered that olopatadine could be popular in general practice, and supply-side growth could also be partly induced by free samples provided by the company to clinicians.
- 1.7 The Subcommittee noted that PHARMAC requested advice on the best means of containing the expanding cost of olopatadine. Members noted that approximately 10% of

current patients on olopatadine are chronic users, and that due to its significant price differential olopatadine should be reserved for patients with severe or chronic allergic conjunctivitis. Members noted most patients with these conditions would gain relief from sodium cromoglycate, lodoxamide or levocabastine.

- 1.8 The Subcommittee considered it would be appropriate to instigate Special Authority criteria for olopatadine. Members advised it would be clinically appropriate to place sodium cromoglycate, lodoxamide or levocabastine ahead of olopatadine in sequential treatment pathways in any Special Authority. Members also noted the Special Authority should be prescriber-targeted to ophthalmologists and optometrists for initiation, and renewals could be done by all relevant practitioners. Members noted that a sequential process of prescribing a less expensive drug before prescribing a more expensive drug was appropriate, reasonable and established practice.
- 1.9 The Subcommittee noted that sodium cromoglycate may not give immediate relief in some patients and may take up to 14 days for the full effect to take place, but considered the significant price differential to all other products made it an appropriate first line agent. Members noted that lodoxamide or levocabastine had a faster onset of effect than sodium cromoglycate, has a considerably lower price than olopatadine, and considered these agents should also be included in the Special Authority criteria sequenced before olopatadine, to give clinicians more flexibility in prescribing. Members noted there was a significant inflammatory role in allergic conjunctivitis, and therapy could include sodium cromoglycate, lodoxamide or levocabastine with short-term ophthalmic corticosteroids to gain early control of the condition.
- 1.10 The Subcommittee considered the initial Special Authority should last 4 months, as data reflects this is how long chronic patients continued treatment. Members considered it appropriate that renewal approvals be for 2 years due to the perennial nature of the disease.
- 1.11 The Subcommittee **recommended** the following Special Authority to be applied to olopatadine :

Initial Special Authority

Initial application only from an ophthalmologist or optometrist. Approvals valid for 4 months for applications meeting the following criteria:

1. Patient has chronic allergic conjunctivitis; and
2. Patient has tried a 2 week trial of either regular sodium cromoglycate, lodoxamide or levocabastine ophthalmic preparations and received insufficient benefit.

Renewal Authority:

From any relevant practitioner. Approvals valid for 24 months where the treatment remains appropriate and the patient is benefiting from treatment.

- 1.12 The Subcommittee **recommended** that PHARMAC arrange for the management of allergic conjunctivitis to be included into a BPAC article outlining appropriate use of anti-inflammatory eye preparations.

Olopatadine minute signed off 16 March 2016

Pred Mild eye drops discontinuation

- 1.13 The Subcommittee noted that PHARMAC had been notified by Allergan that it had issued a discontinuation notice for Pred Mild (prednisolone acetate 0.12%) eye drops and that the current stock was likely to be exhausted by the end of April 2016. Members noted that Allergan had not given sufficient advanced notice to PHARMAC and considered this to be clinically irresponsible.
- 1.14 The Subcommittee considered that most patients on Pred Mild were being treated for anterior uveitis and corneal conditions, and there was some niche use in the prevention of post-transplant graft failure. Members considered most patients would be able to be switched to fluorometholone 0.1% or dexamethasone 0.1% drops, which are less potent and more potent, respectively, requiring doses to be titrated up or down. Members further considered that a tightly-defined group of patients could be switched to preservative-free prednisolone to prevent post-transplant graft failure and paediatric uveitis patients who demonstrate intraocular pressure rise with more potent topical steroid.

2 Ciclosporin eye preparations

Application

- 2.1 The Subcommittee reviewed a paper by PHARMAC staff regarding the funding status of topical ciclosporin for ocular conditions. Members noted that the Subcommittee had previously considered topical ciclosporin for funding in May 2010 and again in March 2012 in response to a number of Exceptional Circumstance (EC) clinician applications. Members noted that the inability to source a registered product was a barrier to a schedule listing.
- 2.2 The Subcommittee noted that the paper contained an update on new evidence available since the Subcommittee first considered ciclosporin eye preparation in 2010.

Recommendation

- 2.3 The Subcommittee **recommended** that ciclosporin 0.05% eye preparation be funded on the Pharmaceutical Schedule for the treatment of vernal keratoconjunctivitis (VKC); atopic keratoconjunctivitis (AKC) and the treatment of dry eye disease, secondary to secretory dysfunction, responsive to steroid treatment with medium priority dependent on registration subject to the following restriction criteria:

Severe AKC/VKC:

Initial application only from an Ophthalmologists : Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

Patient has severe Atopic Keratoconjunctivitis/vernal keratoconjunctivitis; and

1. Any of the following:
 - 1.1 Corneal epithelium breakdown; or
 - 1.2 Progressive limbus thickening/hypertrophy; or
 - 1.3 Steroid induced intraocular pressure rise; or

1.4 Requiring longer than 6 weeks of continuous steroid therapy.

Renewal criteria: Ophthalmologists and optometrists valid for 6 months. Requiring reduction in usage of steroids, 75% improvement in symptom measure. Evidence in improvement corneal epithelium measure.

Severe keratoconjunctivitis sicca:

Initial application only from an Ophthalmologists : Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

1. Patient has severe secretive tear deficiency disease, and does not have evaporative tear deficiency;
2. Patient must be responsive to ophthalmic corticosteroids and requires daily treatment with ophthalmic corticosteroids for more than 6 weeks;
3. Patient has developed unbearable side effects (glaucoma or increased intra-ocular pressure) to low dose ophthalmic corticosteroids;

Renewal criteria: Ophthalmologists and optometrists valid for 6 months.

Both:

1. Patient has responded; and
2. Return of intraocular pressure to baseline or acceptable level.

Discussion

- 2.4 The Subcommittee noted that PHARMAC had received a considerable number of Exceptional Circumstances (EC) and Named Patient Pharmaceutical Assessment (NPPA) applications for ciclosporin eye preparations. Members considered that VKC, and AKC could be clinically considered the same group of patients. Members noted a significant number of NPPA/EC applications had been received for dry eye syndrome and suggested there was a clinical need for the most severe of these patients. Members considered that, due to the low patient numbers for other indications, such as corneal transplants, that these circumstances were best assessed through the NPPA process.
- 2.5 The Subcommittee noted ciclosporin works through inhibit the proliferation and differentiation of T cells and decrease the production of cytokines such as interleukins (IL-2, 4 and 5) and interferon gamma through inhibition of calcineurin activation in cytoplasm.
- 2.6 The Subcommittee considered the new body of evidence for AKC and keratoconjunctivitis sicca (dry eye disease) since the Subcommittee last reviewed ciclosporin eye preparation at its 2010 meeting. Members considered the evidence supplied was of reasonable efficacy, but the quality was poor due to the variability of comparators, subjective measures, and restriction of participants in trials.
- 2.7 The Subcommittee noted a number of reviews and clinical trials including a Cochrane Review for AKC; and studies by Chen et al, Baiza-Dura'n et al, and Rao for keratoconjunctivitis sicca.
- 2.8 Members noted the Cochrane review for AKC (Cochrane Database Syst Rev. 2012 Sep 12;9:CD009078) suggested that topical ciclosporin may provide clinical and symptomatic

relief in AKC and may help to reduce topical steroid use in patients with steroid-dependent or steroid-resistant AKC.

- 2.9 With keratoconjunctivitis sicca, Chen et al. (J Ocul Pharmacol Ther. 2010;26:361-6) was a multi-centre, randomised, double-blind (n=233) study evaluating the efficacy and safety of ciclosporin 0.05% ophthalmic emulsion against vehicle in Chinese patients with moderate to severe dry eye disease. Results reported both ciclosporin and vehicle showed significant reduction in mean symptoms score of 7.83 and 7.19, respectively, from baseline. No statistically significant differences were observed in visual acuity, ocular itching, and ocular tolerance at any time point ($P>0.05$).
- 2.10 Baiza-Dura'n et al. (Br J Ophthalmol 2010;94:1312-15) was a multicentre, randomised, double-blind, (n=183) study evaluating the efficacy and safety of two different concentrations of ciclosporin, 0.1% and 0.05% in aqueous solution (Sophisen) compared with vehicle in patients with dry eye syndrome. Results reported ciclosporin 0.1% had the greatest effect, and there was no statistical difference between ciclosporin 0.05% and vehicle. No serious adverse effects were reported in any of the groups during follow-up.
- 2.11 Rao (Ocul Pharmacol Ther. 2010;26:157-64) was a small single-centre, investigator-masked, prospective, randomised trial (n=58) evaluating the prognosis of dry eye in patients treated (i.e. halt or slow disease progression relative to control) with ciclosporin 0.05% or artificial tears (control Glycerin 1% + polysorbate 80 1%). Results at 12 months reported 32% of the control group progressed to higher disease severity compared with 6% of ciclosporin group ($p<0.007$); and 18% in the control group improved to lower disease severity compared with 39% of the ciclosporin group ($p=0.007$). No adverse events were reported other than discomfort upon installation.
- 2.12 The Subcommittee noted the TGA's November 2011 Public Assessment Report, that declined Restasis' (Allergan, ciclosporin 0.05% eye drops) registration in Australia due to lack of evidence for its use in dry eye disease (keratoconjunctivitis sicca). PHARMAC staff note that it was unlikely the supplier of ciclosporin 0.05% drops (Restasis) would seek registration in New Zealand as products often get registered in Australia first, then submit subsequent registration in New Zealand through Medsafe. Members also noted NICE has recommended the funding of a UK registered and higher strength of ciclosporin 1mg/mL emulsion (Ikervis eye drops).
- 2.13 The Subcommittee noted there was some uncertainty on what the ideal dose to achieve significant therapeutic benefit was, and considered that 0.05% (Restasis) could be sub-therapeutic; however, this was the only commercially available product in New Zealand.

Atopic Keratoconjunctivitis

- 2.14 The Subcommittee noted that VKC and AKC were subcategories of allergic conjunctivitis, and that severe AKC and VKC had a high clinical need, as the diseases were sight threatening. Members noted that VKC and AKC with severe symptoms often presented with corneal epithelium damage, corneal lesions, and/or progressive limbus hypertrophy/thickening. Members further noted that VKC was more common than AKC and that VKC had higher prevalence in people with darker pigmentation such as Māori and Pacific populations and some refugee groups. Members considered Māori and

Pacific patients often presented with more severe and sometimes sight threatening vernal disease compared with non-Maori/Pacific.

Keratoconjunctivitis Sicca

- 2.15 The Subcommittee noted that dry eye disease was a multifactorial disease that could be classified into two main categories: an aqueous tear deficiency state (decreased production) and evaporative state (increased evaporated loss). Members noted that severe keratoconjunctivitis sicca was significantly symptomatic and potentially blinding. Members also noted Sjogrens syndrome was part of the wider keratoconjunctivitis sicca patient group.
- 2.16 The Subcommittee noted that aqueous tear deficiency (ATD) was a common cause of dry eye and was caused by insufficient tear production. Members considered patients with severe keratoconjunctivitis sicca who responded to corticosteroids would also respond to ciclosporin and, conversely, patients who were unresponsive to corticosteroids would likely also be unresponsive to ciclosporin.
- 2.17 The Subcommittee considered that there was a significant population group with AKC and VKC, approximately 500 patients nationally and, if any listing of ciclosporin on the Schedule was not carefully restricted, this would be a significant fiscal risk to the Combined Pharmaceutical Budget.
- 2.18 The Subcommittee also considered that listing ciclosporin 0.05% for the severe keratoconjunctivitis sicca, could be a significant fiscal risk to the combined pharmaceutical budget due to its high prevalence, and increasing incidence due to an ageing population. Members considered a Special Authority criteria would need to be applied to manage fiscal risk. Members also considered the initial applications should be for 3 months and renewals for 6 months. Members also considered that patients with evaporative tear dysfunction had alternative options available which were more clinically appropriate, and more cost-effective.
- 2.19 The Subcommittee considered that the initiation of ciclosporin eye preparation in patients with severe AKC, VKC and keratoconjunctivitis sicca should be done by an ophthalmologist. Members considered this would be clinically appropriate and subsequent renewal prescriptions could include optometrists if the condition was within the scope of their practice.
- 2.20 The Subcommittee considered that the listing of ciclosporin would not result in a substantial reduction in ophthalmic corticosteroid use as, in most cases, patients would continue topical corticosteroid treatment, and ciclosporin would only be steroid sparing rather than a substitute. Members noted that the objective of therapy was to reduce the use of topical corticosteroid so as to decrease the risks of glaucoma, cataracts and microbial keratitis. Members considered there was some evidence suggesting that commencing ciclosporin therapy in conjunction with topical steroids may result in a better clinical effect. Members noted that ciclosporin 0.05% (Restasis) was not always adequate for severe patients and a higher dose was required; however, no proprietary product was available in New Zealand and the Optimus compounded product came in a form that was often intolerable for some patients. Members further considered ciclosporin 0.05% for dry eye and other abnormalities of the ocular surface such as

limbal stem cell deficiency, allergy, and vernal and atopic disease. However in most cases concomitant treatment only reduced the amount of steroid rather than replacing it.

- 2.21 The Subcommittee considered that the cost of ciclosporin eye preparations was high, and specifically ciclosporin 0.05% (Restasis), approximately \$95 per pack or \$700 for a 3-6 month supply when sought directly from the supplier. Members noted Restasis came in a pack of 30 single use vials, and considered that due to the cost, most patients kept vials in the fridge and use a single-dose vial over 2-3 days. Members considered this to be an adequate practice provided the patient did not touch their lid margins with the dispenser.
- 2.22 The Subcommittee noted serum eye drops were currently not within the scope of PHARMAC as they were made from either the patient's or donated blood, and were used for some patients with severe dry eye disease. Members noted ciclosporin was sometimes trialled before progressing on serum eye drops, due to the significant cost. Members noted the cost of serum was currently met by the Blood Bank for private patients, and that the Blood Bank attempted to recoup those costs from DHB eye departments. Members considered that funding ciclosporin for severe dry eyes could lead to significant cost savings to the wider health budget if this reduced the number of patients using serum eye drops.

3 Correspondence

Atropine 0.01%

- 3.1 The Subcommittee noted a presentation from a Member requesting that the Subcommittee examine low-dose atropine therapy for the prevention of myopia progression in children.
- 3.2 The Subcommittee noted that myopia was a condition with significant prevalence in children under 15 years of age, especially in Asian populations where the prevalence could be as high as 90%. Members noted that it was a difficult condition to treat, given that changes in the axial length and refraction did not always progress together. Members considered that axial length could be measured using a biometry machine not usually found in optometrists offices but present in most ophthalmologists rooms.
- 3.3 The Subcommittee considered there was now good evidence to suggest that low-dose atropine eye drops are able to prevent or slow the progression of myopia in some patients. Members considered that treatment of low-dose atropine may result in a 50% reduction in progression to myopia (Chia A, et al. Ophthalmology. 2016;123:391-9). Members noted the main challenge was that there was no known registered commercial preparation of atropine 0.01% drops, and due to it being off-patent, it was unlikely a commercially registered product would be available in the near future. Members noted that Optimus, a third party compounding pharmacy in Auckland, was compounding low-dose atropine eye drops for some patients.
- 3.4 The Subcommittee noted that there were access issues with currently available treatments including corrective contact lenses, which currently cost \$500-1800 per pair and were often prohibitive in cost for low income families. Members noted some patients were privately paying for compounded low-dose atropine drops from Optimus.

- 3.5 The Subcommittee noted that there would be a large group of patients requiring low-dose atropine treatment, which could have a significant impact on the CPB and a funding application would be required for a full review. The Subcommittee **recommended** that the Members work with RANZCO and PHARMAC staff to submit a funding application.

4 Dexamethasone implant for DMO

Application

- 4.1 The Subcommittee reviewed an application from Allergan for the funding of Ozurdex (dexamethasone intravitreal implant 0.7 mg) in Section H of the Pharmaceutical Schedule for the treatment of diabetic macular oedema (DMO).

Recommendation

- 4.2 The Subcommittee **recommended** that the application for dexamethasone intravitreal implant 0.7 mg as a first-line treatment for DMO be declined.
- 4.3 The Subcommittee **recommended** that dexamethasone intravitreal implant 0.7 mg be funded as second-line treatment for DMO with strict entry criteria with a medium priority.
- 4.4 The Subcommittee **recommended** that dexamethasone intravitreal implant 0.7 mg be funded as a second-line treatment of DMO for pregnant women with a high priority due to the unmet health need of this group.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 4.5 The Subcommittee noted that diabetic macular oedema (DMO) is a serious complication of type 1 and 2 diabetes with significant morbidity. Members noted diabetic retinopathy shows a gradual and slow progression, unlike wAMD where the disease onset and progression is often rapid. Members also noted Maori and Pacific people had higher rates of diabetic macular oedema compared with non-Maori/Pacific. The prognosis of these patients was associated with their diabetic control, and a regression of disease was often seen in patients with a reduced HbA1c.
- 4.6 The Subcommittee noted the standard treatment pathway for DMO currently was macular laser treatment as a first-line treatment, or bevacizumab for patients with centre-involving DMO where laser therapy was not possible, and intravitreal triamcinolone for patients not responding on bevacizumab. The Subcommittee considered approximately

10% of patients with diabetic macular oedema would require a second line agent after bevacizumab.

- 4.7 The Subcommittee considered that the quality of evidence in the application was high and strength to be moderate. Members noted a number of clinical trials including two studies included by the supplier by Gillies MC, et al. (BEVORDEX) (Ophthalmology 2014;1: 2472-81), and Boyer DS, et al (MEAD) (Ophthalmology. 2014;121:1904-14).
- 4.8 The Subcommittee noted a phase 2 RCT by Gillies MC, et al. (Ophthalmology 2014;1:2472-81) comparing dexamethasone 0.7 mg implant (DEX 0.7) every 16 weeks against intravitreal bevacizumab every 4 weeks in patients with DMO affecting the central fovea in 88 eyes out of 61 patients. Members noted the dosing of DEX 0.7 every 16 weeks was realistic of true clinical effect, which was shorter than the 6 months of effect claimed by the supplier. Members noted the primary outcome of an improvement in BCVA (Best Corrected Visual Acuity) of ≥ 10 letters was similar in each group at 12 months with 41 % and 40 % of eyes ($p=0.83$) in DEX 0.7 and bevacizumab groups, respectively achieving primary outcome. Members noted analysis of pseudophakic eyes showed no significant difference in effect between the two treatments. Members noted 11% of eyes in the DEX 0.7 group lost 10 letters or more compared with none in bevacizumab group, and this was attributed to increased cataract density in these patients. Members also noted approximately 50% of DEX 0.7 group reported increased intraocular pressure (IOP) by at least 5 mmHg from baseline at 1 year compared with 20% in the bevacizumab group.
- 4.9 The Subcommittee noted a study by Boyer DS, et al (Ophthalmology. 2014;121:1904-14) which was composed of two phase 3 RCT's comparing dexamethasone implant 0.7 mg (DEX 0.7), 0.35 mg (DEX 0.35) against sham injections in patients with DMO affecting the central fovea in 1048 patients. Patients were randomised to receive treatment on day 0, and could be retreated no more often than every 6 months, and maximum of 7 treatments over 3 years. Members noted the primary outcome of BCVA improvement of ≥ 15 letters from baseline in the study eye at 24 months was achieved in 22% ($P<0.001$), 18.4% ($P=0.018$) and 12 % of eyes treated with DEX 0.7, DEX 0.35 and sham injections, respectively. Members considered this increase to be clinically significant, but considered the 10% increase from placebo (sham injections) was less than expected. Members noted some patients would lose effect after the first year of treatment due to increased development of cataracts as reported in the study. Members noted subgroup analysis showed BCVA improvement provided by DEX 0.7 implant relative to sham in pseudophakic eyes was consistent across time over the 3 years, and there was no reduction in treatment benefit observed in year 2 for this sub-group of patients. Members noted the most common ocular adverse events reported in study eyes were cataract and increased IOP related to DEX implant.
- 4.10 The Subcommittee noted the clinical presentation of patients with DMO in the Boyer et al (2014) and prevalence of pseudophakic eyes were similar to the clinical circumstances seen in DHB hospitals. Members noted the expected clinical outcomes would be similar to a real-life setting, however study criteria of HbA1cB1AC of 7.7, exclusion of untreated and unstable diabetes was unrealistic. Members noted 11% of patients in this study got worse due to cataracts.
- 4.11 The Subcommittee noted three smaller studies provided by PHARMAC staff: Kuppermann BD, et al. (Arch Ophthalmol. 2007;125:309-31); Boyer DS, et al. (Retina.

2011;31:915–923); and Medeiros, MD et al. (Journal of Ocular Pharmacology and Therapeutics. 2014;30:709-16). Members noted all three studies examined the efficacy and safety of one dose DEX 0.7 mg implant over 6 months.

- Kuppermann BD, et al. (2007) reported primary outcome of ≥ 10 -letter improvement in BCVA at day 90 was achieved in 24%, ($P=0.04$), 35% ($P.001$), and 13% in the dexamethasone 0.35 mg, 0.7 mg and observation group, respectively. Members considered this similar to results seen in the BEVORDEX and MEAD studies.
- Boyer DS, et al. (2011) examined treatment resistant DMO patients with vitrectomised eyes. Members noted 55% of patients had previously been treated with anti-VEGF therapy and 66% had received laser therapy. Primary endpoint at 26 weeks, was change in central retinal thickness (CRT) from baseline (403 μm) measured by Optical coherence tomography (OCT) report mean CRT was 364.5 μm at 26 weeks i.e. a reduction of -38.9 μm (range: -65, -13 μm $P = 0.004$). Key secondary efficacy measure of mean change in BCVA, reported the mean (95% CI) increase in best-corrected visual acuity from baseline (54.5 letters) was 6.0 letters (range: 3.9, 8.1 letters) at Week 8 ($P < 0.001$) and 3.0 letters (range: 0.1, 6.0 letters) at Week 26 ($P = 0.046$).
- Medeiros, MD et al. (2014) also examined the 6 month anatomic and BCVA response of DEX 0.7 mg treatment between vitrectomised and non- vitrectomised eyes in resistant DMO. Members noted that the majority of both non-vitrectomised and vitrectomised group had received anti-VEGF treatments, 73.5% and 79.2%, respectively. Members noted improvements in BCVA and foveal thickness by 6 months was more pronounced in the vitrectomised group.

4.12 The Subcommittee noted that the supplier had stated DEX 0.7 could provide up to 6 months of effect, however considered the actual effect would be around 2-4 months.

4.13 The Subcommittee considered clinically significant best-corrected visual acuity (BCVA) score improvements was sometimes dependent on the patient's baseline BCVA, as a 5 letter improvement for a patient with baseline 6/15 vision could be clinically significant as this improvement would mean the patient could legally drive, however a one line improvement for a patient with very poor visual acuity from 6/48 to 6/36 would not be clinically significant. Members noted the FDA requires an improvement of BVA ≥ 15 letters to be significant, however most studies included in the application included BCVA greater than 10 as a primary outcome. Members noted anti-VEGF treatments would continue to be their preferred and first line option for DMO.

4.14 The Subcommittee considered DEX 0.7 would be of considerable risk to the fiscal budget and DHB hospital capacity if listed as first-line agent for DMO. Members considered DEX 0.7 implant would have an advantage for certain sub-groups such as vitrectomised eyes, pseudophakic patients and those who were geographically isolated due to its prolonged duration of action compared to anti-VEGF injections. Members noted intravitreal triamcinolone would be effective for most patients within this group, with the exception of vitrectomised patients.

4.15 The Subcommittee noted that both the PBAC in Australia and The Canadian Drug Expert Committee (CDEC) had declined the application for dexamethasone. The PBAC

cited that the application had failed to show non-inferiority of OZURDEX to bevacizumab and CDEC referred to the poor data and uncertainty around the duration of treatment and cost-effectiveness. The Subcommittee noted dexamethasone 0.7 mg implant was funded in the UK (including Scotland) for pseudophakic patients only.

- 4.16 The Subcommittee noted cost minimisation analysis by the supplier to be an underestimate of the true cost of treatment, and the assumption of an eventual 40% market switch from bevacizumab to DEX 0.7 mg was unlikely. Members noted anti-VEGF injections were now administered by ophthalmic nurses in a small procedure room at many DHB's. Dexamethasone implant could lead to more treatment related costs as it is implanted by an ophthalmologist in a theatre room and the gauge of the needle used is larger, resulting in increased risk of infection or wound leak. Members noted patients would require extra ophthalmologist visits than outlined in the proposal with an additional post-operative visit and a visit every 3 months to assess treatment progress.
- 4.17 The Subcommittee considered restriction criteria would be needed if DEX 0.7 was listed in Section H. Members considered the initiation criteria should include patients with centre involving diabetic macular oedema with pseudophakic eyes, unresponsive to bevacizumab and laser therapy. It could be considered in patients who showed benefit from intravitreal triamcinolone but either a short duration of benefit or a significant steroid response. Members considered a minimum time period of 4 months between each implant, and maximum of 3 implants per year be included in the restriction.
- 4.18 The Subcommittee considered patients would require monthly specialist review after the initial implant for the first three months. Members considered it was unlikely that DEX 0.7 would be used together with intravitreal bevacizumab as there was no evidence for this setting.
- 4.19 The Subcommittee noted the cost-minimisation analysis provided by the supplier. The Subcommittee considered if treatment with DEX 0.7 was successful, then treatment would be continued for longer than 2 years. Members considered the savings estimated in the analysis due to fewer DEX 0.7 doses compared to bevacizumab injections were overestimated in the model and would not equate to real savings. Members noted DEX treatment would incur greater costs than those included in the model from side effects, glaucoma treatment and extra visits for monitoring. Members considered 30-50% of patients would experience increased intraocular pressure and potential glaucoma from the DEX 0.7 implant, however this could be managed in most by anti-glaucoma eye drops. Members considered there could also be an increased risk of infection. Members also noted the average number of doses of bevacizumab would be slightly higher, and estimate patients would receive on average 6 doses of anti-VEGF in year 2.
- 4.20 The Subcommittee considered an anti-VEGF agent would be the preferable second line treatment for DMO, and if both DEX 0.7 and a second-line anti-VEGF were available, DEX implant would have a niche use with approximately 20% uptake. The Subcommittee considered DEX 0.7 would have a niche use in some 2nd or 3rd line patients with pseudophakic eyes, and vitrectomised eyes as triamcinolone injections would wash out too quickly leading to a reduced therapeutic benefit. Members considered there could also be some use in pregnancy as some anti-VEGF agents are contraindicated, and patients who were geographically isolated in DMO; and in uveitis for vitrectomised eyes.

5 Aflibercept for DMO

Application

- 5.1 The Subcommittee noted an application from Bayer NZ Ltd for the funding of aflibercept for the treatment of diabetic macular oedema (DMO). Members noted that the application had been reviewed by PTAC at its November 2015 meeting and recommended that aflibercept as a first-line anti-vascular endothelial growth factor (anti-VEGF) treatment for DMO be declined and be referred to the Ophthalmology Subcommittee for consideration as a second-line treatment.

Recommendation

- 5.2 The Subcommittee **recommended** that the application for listing aflibercept as a first-line anti-VEGF treatment of DMO be declined.
- 5.3 The Subcommittee **recommended** that aflibercept be funded on the Pharmaceutical Schedule as a second-line anti-VEGF treatment of DMO with a high priority.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vii) The direct cost to health service users.*

Discussion

- 5.4 The Subcommittee noted that diabetic macular oedema (DMO) is a serious complication of type 1 and 2 diabetes with significant morbidity. Members noted diabetic retinopathy shows a gradual and slow progression, unlike wAMD where the disease onset and progression is often rapid. Members also noted Maori and Pacific people had higher rates of diabetic macular oedema compared with non-Maori/Pacific. The prognosis of these patients was associated with their diabetic control, and a regression of disease was often seen in patients with a reduced HbA1c.
- 5.5 The Subcommittee noted that intravitreal bevacizumab was currently the only anti-VEGF treatment listed on the HML for DMO. Members noted it is an off-label medication compounded by DHB pharmacies or third-party manufacturers. Members noted they were unaware of any safety issues with the compounded intravitreal bevacizumab injections in New Zealand. Members also noted there were issues with access to anti-VEGF treatments for DMO in parts of New Zealand, and injections were typically dosed at 4-6 weekly intervals.
- 5.6 The Subcommittee noted other alternatives therapies include focal laser treatment and intravitreal triamcinolone. Members considered that anti-VEGF agents were generally used as a monotherapy, however retinal laser could be used as an adjunctive therapy, and that intravitreal corticosteroids have a niche role in DMO.

- 5.7 The Subcommittee noted the prevalence of diabetes in Maori, Pacific Island and Indo-Asian populations was 2 to 3 times higher than Europeans. Members also noted Maori had higher rates of diabetic retinopathy and maculopathy compared with non-Maori (Papali'i-Curtin et al, NZ Med J 2013; 126:1383-8). Members considered approximately, 10% of diabetic patients would develop DMO in their lifetime, and approximately 10% of patients requiring anti-VEGF treatment for centre-involving diabetic macular oedema would not respond to the currently listed first-line agent. Members noted Bayer's modelling and were uncertain where Bayer's patients numbers came from. Members also considered there would not be many patients paying privately for aflibercept.
- 5.8 The Subcommittee noted a number of reviews and clinical trials including two key studies by supplier: Korobelnik JF et al. Ophtha 2014;121:2247-54 (VIVID and VISTA) and Wells JA et al. N Engl J Med 2015;372:1193-203 (DCRCR). Members considered studies provided in the application were of high strength and quality.
- Korobelnik et al (2014) was composed of 2 studies, VIVID (n=404) and VISTA (n=461), which compared aflibercept against macular laser photocoagulation. Patients were randomised to receive either 2mg intravitreal aflibercept injection (IAI) every 4 weeks (2q4), 2mg IAI ever 8 weeks (2q8) or laser control group (laser). Results of the primary outcome of best-corrected visual acuity (BCVA) at 52 weeks reported a change in BCVA from baseline in +12.5 +/- 9.5 letters and +10.7 +/- 8.2 letters versus +0.2 +/- 12.5 letters (P < 0.0001) in VISTA, respectively; and +10.5 +/- 9.5 letters and +10.7 +/- 9.3 letters versus +1.2 +/- 10.6 letters (P < 0.0001) in VIVID, respectively. Secondary outcomes showed significantly more eyes treated with IAI gained ≥ 15 letters, and greater mean reductions in central retinal thickness compared with laser from baseline at week 52.
 - Wells JA et al. (2015) was a randomised head to head study (n=660), which compared intravitreal bevacizumab 2mg; aflibercept 1.25mg; or ranibizumab 0.3mg for the treatment of DMO. Patients were randomised into three treatment groups, and the median number of intravitreal injections administered was 9.2 in the aflibercept group, 9.7 in bevacizumab and 9.4 in the ranibizumab group. Fewer patients receiving aflibercept required rescue laser treatment for persisting macular oedema (37%) compared with ranibizumab (46%) or bevacizumab (56%), p < 0.01. Results reported a greater mean improvement in the visual-acuity (VA) letter score at one year with aflibercept than with bevacizumab and ranibizumab (13.3 vs. 9.7 and 11.2, respectively; P<0.001 for aflibercept vs. bevacizumab and P = 0.03 for aflibercept vs. ranibizumab). Members considered difference between the three treatment groups were statistically but not clinically significant. Members considered all three anti-VEGF agents were equivalent in maintaining visual acuity for patients with baseline visual acuity (VA) from 20/32 to 20/40. Serious adverse events were similar across all treatment groups.
 - Members noted the sub-analysis of Wells JA et al. 2015 (Protocol T study) indicated there was evidence that aflibercept resulted in greater VA improvement in patients with baseline VA of 20/50 or worse. Results reported a mean change in BCVA of 19, compared with 14 and 12 for ranibizumab and bevacizumab, respectively, in this patient group. BCVA >15 letters was achieved 63% more in eyes treated with aflibercept compared with ranibizumab (P<0.01). Aflibercept and ranibizumab demonstrated a statistically significant greater reduction of

central subfield thickness (CSFT) compared with bevacizumab, with values of -169 µm, -147 µm, and -101 µm, respectively.

- 5.9 The Subcommittee noted that evidence indicated all three anti-VEGF agents were effective treatments for DMO causing vision impairment. Members noted aflibercept was non-inferior to ranibizumab, and there was no direct evidence for aflibercept's use as a second-line agent. Members however noted results from the post-hoc analysis (Protocol T) of Wells JA et al. (2015) reported that aflibercept treatment resulted in greater VA improvement in patients with poorer baseline VA of 20/50 or worse.
- 5.10 The Subcommittee considered restriction criteria would be necessary if aflibercept was listed on the HML for DMO and should include a baseline central retinal thickness (CRT) measurement. Members noted PTAC's recommended criteria of a cut-off of CRT at > 400 µm, and considered this to be too restrictive as waiting for CRT to reach 400 µm and above could lead to greater vision loss and poorer recovery; and most studies had a cut off of CRT at 300 or 350 µm. Members considered a restriction should include the presence of retinal oedema within central fovea. Members considered aflibercept would have a greater benefit in patients with a BCVA < 6/15 from centre involving DMO. Members considered a renewal criteria should include a robust reassessment of improvement to justify funding for ongoing treatment.
- 5.11 The Subcommittee **recommended** the following restriction:

Initiation:

Re-assessment required after 4 doses

1. Patient has centre involving diabetic macular oedema; and
2. Non responsive to minimum of 4 doses of intravitreal [first line anti-VEGF agent]; and
3. Patient has all of the following:
 - 3.1 Visual acuity 6/9 – 6/36 with functional awareness of reduction in vision
 - 3.2 Diabetic macular oedema within central OCT (ocular coherence tomography) subfield > 350 µm.

Exclusion: centre-involving sub-retinal fibrosis or photoreceptor loss

Continuation:

Both:

1. Reassess after four doses of intravitreal aflibercept and then annual retriial of [first line anti-VEGF agent] if ongoing treatment is required.
2. All of the following:
 - 2.1 Stability or two lines of Snellen acuity gain; and
 - 2.2 Structural improvement on OCT scan (with reduction in intra-retinal cysts, central retinal thickness, and sub-retinal fluid).

- 5.12 The Subcommittee considered this restriction criteria could also applied to ranibizumab if it was a second line agent for DMO. Members noted if ranibizumab or aflibercept was listed on the HML for second line DMO treatment, there could be increased costs to DHB's due to patients shifting from private to public setting.
- 5.13 The Subcommittee considered most patients would be on two monthly dosing of aflibercept after three monthly loading doses. Members considered aflibercept may reduce clinic visits, and associated costs, however OCT's and monitoring would still be required periodically.
- 5.14 The Subcommittee considered ranibizumab or aflibercept to be safer than dexamethasone implant 0.7 mg (Ozurdex) as it was rare for intraocular pressure to rise

with anti-VEGF treatment and ease of administration. Members noted as dexamethasone implant 0.7 mg administration currently requires an operating theatre, compared with anti-VEGF treatments can be treated in a clean Small procedure room (SPR) based in a clinic.

- 5.15 The Subcommittee noted patients with DMO were different to wAMD, and there could be the potential for visual recovery in patients with DMO. Members considered patients who still had a good potential for visual recovery i.e. no chronicity or irreversible retina structural damage, and reasonable initial visual acuity 6/9 to 6/36; would expect the most benefit from aflibercept. Members considered aflibercept would be of less benefit to patients with visual acuity worse than 6/36. Members considered 50% of current DMO patients would have visual acuity between 6/9 to 6/36, but it would still be clinically appropriate for these patients to trial bevacizumab or another first line anti-VEGF agent.
- 5.16 The Subcommittee noted that it would be possible for PHARMAC to seek data from hospitals to establish the proportion of bevacizumab prescriptions being written for DMO versus wet macular degeneration (wet-AMD) as PHARMAC was unable to differentiate between the two indications with the current data available.
- 5.17 The Subcommittee considered PHARMAC could run a competitive process for a second line anti-VEGF agent for DMO, however Members expressed it had a strong preference for aflibercept in patients with poorer baseline visual acuity.