Ophthalmology Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC)

Meeting held on 20 September 2017

(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 8 & 9 February 2018, the record of which will be available in due course.

Record of the Ophthalmology Subcommittee meeting held at PHARMAC on 20 September 2017

1 Correspondence/ Matters arising

Prednisolone eye drops update

1.1 The Subcommittee noted the temporary stock issue affecting the supply of prednisolone acetate 1.0% eye drop in New Zealand. The Subcommittee noted that prednisolone acetate eye drop has high potency and good penetrative properties, which made it particularly suitable for the treatment of a number of vision threatening, inflammatory eye diseases. The Subcommittee noted that prednisolone acetate eye drop was currently the only steroid eye drop funded in New Zealand that has this combination of potency and penetration, and considered that it was important to ensure the continuity of supply of steroid eye drops with these properties.

1.2 The Subcommittee noted that prednisolone acetate 1.0% eye drop is indicated for the treatment of a broad range of ocular indications such as acute iritis, iridocyclitis, uveitis, cystoid macular oedema, and post-surgical inflammation. The Subcommittee considered that prednisolone acetate 1.0% eye drops were most frequently prescribed for the short-term management of acute ocular inflammation or in a post-surgical setting. The Subcommittee considered that the perceived universality and the ease of use of prednisolone acetate eye drops meant that it was frequently prescribed for indications where alternative funded eye drops were available. The Subcommittee considered that for many indications, other funded steroid eye drops such as fluorometholone or dexamethasone may be appropriate alternatives. The Subcommittee however considered that for conditions such as uveitis or corneal graft rejection, prednisolone acetate 1.0% eye drop was currently the only appropriate treatment option and that many of these patients would likely remain on treatment over the long term. The Subcommittee considered that few patients with other ophthalmic conditions would be clinically indicated to use prednisolone acetate 1.0% eye drops over the long term.

1.3 The Subcommittee noted the steroid eye drops with similar properties that are currently being used in Australia, such as Prednefrin Forte (containing prednisolone acetate 1% in combination with phenylephrine 0.12%) which is funded by the Pharmaceutical Benefits Scheme, and Lotemax (containing loteprednol etabonate 0.5%) eye drops which is available to patients via the private market. The Subcommittee noted that at the time of this discussion, neither product was registered nor pending registration with Medsafe in New Zealand.

1.4 The Subcommittee noted that Australia does not have funded access to prednisolone acetate 1.0% eye drops, and that Australian ophthalmologists used Prednefrin Forte (containing prednisolone acetate 1.0% and phenylephrine 0.12%) to treat similar conditions that prednisolone acetate 1.0% eye drops were being used to treat in New Zealand. The Subcommittee therefore considered that the two products were likely to have equivalent efficacy and were interchangeable. The Subcommittee noted that whilst Prednefrin Forte contained phenylephrine 0.12% as a vasoconstricting agent, correspondence from Australian ophthalmologists had suggested that the phenylephrine component is unlikely to cause clinically significant intolerance issues or lead to poorer

clinical outcomes. The Subcommittee considered that the clinical effect of using Prednefrin Forte would largely be the same as using prednisolone acetate 1.0% eye drops alone.

1.5 The Subcommittee noted the high health need of patients with vision threatening inflammatory ocular diseases, and considered that at there should be two such potent steroid eye drops with high penetrability listed in the Pharmaceutical Schedule and available for use in New Zealand at any time. The Subcommittee considered that prednisolone acetate 1.0% would continue to be the preferred first-line agent of this type, however based on the risks of prednisolone acetate 1.0% eye drop becoming unavailable in New Zealand, the Subcommittee **recommended** that PHARMAC staff seek suppliers of Prednefrin Forte or loteprednol eye drop to enter the New Zealand market, and **recommended** that Prednefrin Forte and loteprednol be listed with a high priority.

Provisc – Healon

1.6 The Subcommittee noted correspondence received from an ophthalmologist regarding the change in brands of sodium hyaluronate prefilled syringes and perceived differences in the viscoelastic properties of the new brands of the sodium hyaluronate syringes versus the incumbent.

1.7 The Subcommittee noted that the sodium hyaluronate prefilled syringes were used during ophthalmic surgery and that this was a very niche area. The Subcommittee noted that these products were also known as ophthalmic viscoelastic devices (OVDs). The Subcommittee noted that OVDs can be separated into either cohesive OVDs or dispersive OVDs, with the main differences being the molecular weight and chain length of the sodium hyaluronate. The Subcommittee noted that cohesive OVDs contained long chained molecules which tended to intertwine, and were effective at maintaining surgical space under conditions of zero shear. The Subcommittee noted that dispersive OVDs contained short chained molecules which tend to slide over one another and are effective at coating intraocular structures.

1.8 The Subcommittee noted that as a result of the 2015/16 Invitation to Tender, the Healon range of sodium hyaluronate prefilled syringes were listed in the Hospital Medicines List (10 mg/mL 0.85 mL syringe, 14 mg/mL 0.55mL syringe, 14 mg/mL 0.85 mL syringe, and 23 mg/mL 0.6mL syringe), and the incumbent Provisc product (10 mg/mL, 0.85mL syringe) was delisted.

1.9 The Subcommittee noted that both Healon (the new sodium hyaluronate brand) and Provisc (the incumbent) were both cohesive OVDs, and it was unlikely that there would be clinically significant difference in the physicochemical properties of these products.

1.10 The Subcommittee noted the currently listed range of sodium hyaluronate prefilled syringes in the Hospital Medicines List, and considered that the current listing of Healon (a cohesive OVD), Healon GV (a cohesive OVD), and Duovisc (a combination cohesive and dispersive OVD) is sufficient to cover almost all situations where OVDs may be used.

1.11 The Subcommittee considered that future tenders for sodium hyaluronate prefilled syringes should explicitly state whether the tendered product is a cohesive OVD or dispersive OVD, to ensure that at least one cohesive and one dispersive OVD is listed in the HML at any time.

Chloramphenicol eye drops/ointment on Practitioner Supply Order (PSO) correspondence

1.12 The Subcommittee noted correspondence received from a rural locum GP requesting for chloramphenicol 0.5% eye drops/ointment be funded on a Practitioners Supply Order (PSO). The Subcommittee noted that centres considered rural can already access medicines on the Pharmaceutical Schedule via a PSO. The Subcommittee noted that the intent of the correspondence was to add chloramphenicol eye drops to the list of PSO medicines so it can be use in centres considered to be 'semi-rural' or in localities where there is no after-hours pharmacy.

1.13 The Subcommittee noted that chloramphenicol was a very effective first line antibiotic, and considered that the indications likely to require urgent access to it would be severe conjunctivitis, as prophylactic treatment after the removal of foreign body from the eye, and for corneal abrasions. The Subcommittee considered that the highest need would be for those patients who cannot access a pharmacy within 2-4 hours after presentation clinically, and considered that this would timewise most likely occur outside of usual pharmacy weekday opening hours.

1.14 The Subcommittee noted that topical chloramphenicol is an old antibiotic with an extensive history of use, and did not consider that if topical chloramphenicol were to be made available via PSO that it would raise additional concerns around safety.

1.15 The Subcommittee considered that from a usage and fiscal perspective, that unless topical chloramphenicol had some form of restriction if made available on a PSO, that it was likely that its use would increase substantially.

1.16 The Subcommittee considered that there was an unmet health need in a select group of individuals, and considered that if topical chloramphenicol were to be made available via a PSO, that it should be chloramphenicol ointment (not eye drops) and be limited to a maximum quantity of one 4g tube per PSO. The Subcommittee **recommended** that chloramphenicol eye ointment be made available on a PSO with a medium priority.

Compounded antibiotic eye drops correspondence

1.17 The Subcommittee noted correspondence received from a hospital pharmacist asking whether PHARMAC could consider sourcing the following antibiotic eye drops:

- cefuroxime 5% eye drops
- tobramycin 2% eye drops
- vancomycin 2.5% to 5% eye drops

1.18 The Subcommittee noted that the correspondence provided no information about the indications for these requested antibiotic eye drops. The Subcommittee noted that the above antibiotic eye drops are currently being compounded by some hospital pharmacies in New Zealand, either by dilution of the intravenous (IV) preparation of the relevant antibiotic in water for injection or by using a higher concentration of the IV antibiotic to fortify commercially available antibiotic eye drops. The Subcommittee considered that based on the high concentration of the requested antibiotic eye drops, the likely indication would be for the treatment of microbial keratitis. Members noted that from time of diagnosis, treatment would typically be required within two hours.

1.19 The Subcommittee noted that the currently funded antibiotic eye drops that could be used for the treatment of bacterial keratitis include chloramphenicol 0.5%, chloramphenicol 1% and ciprofloxacin 0.3% eye drops. The Subcommittee noted that whilst these antibiotics could be used for the treatment of microbial keratitis, that there is no agreed international consensus on which antibiotic should be used. The Subcommittee noted that other countries also use fortified antibiotic eye drops made by specialist compounding pharmacies for the treatment of bacterial keratitis. The Subcommittee considered that the pathogens causing bacterial keratitis were highly variable, with different causative pathogens across the different regions within New Zealand as well as around the world. The Subcommittee noted that several DHB hospitals around New Zealand currently compound their own antibiotic eye drops. The Subcommittee recommended that PHARMAC staff write to hospital pharmacies to ascertain the formulation of antibiotic eye drops that are being compounded, and **recommended** that these formulations be made available to other hospital pharmacies that may wish to compound these drops.

Mixed salt solution for eye irrigation

1.20 The Subcommittee discussed the equivalence and interchangeability of two brands of balanced salt solutions currently available on the market (Alcon and Bausch & Lomb). The Subcommittee noted that the Alcon brand of balanced salt solution was currently listed in the Hospital Medicines List (HML). The Subcommittee considered that the two brands were interchangeable.

1.21 The Subcommittee considered that balanced salt solutions were generally used during ocular procedures to keep the eye moist, as well as for irrigation and washing of the eye post-surgery.

1.22 The Subcommittee considered that 15 ml and 500 ml balanced salt solutions were commonly used in private and public practice. Members considered that if both the 15 mL and 500 mL bottles of the balanced salt solution were listed, that there is no clinical need for the 250 mL bottles of balanced salt solution.

2 Second line anti-VEGF in wAMD and DMO restrictions

Recommendation

Wet Age Related Macular Degeneration (wAMD)

2.1 The Subcommittee **recommended** that the bevacizumab retrial criteria is removed from the 2nd line anti-VEGF renewal criteria for wet age related macular degeneration (wAMD).

2.2 The Subcommittee **recommended** that access to a 2nd line anti-VEGF for wAMD should only be in those patients who have had 3 doses of bevacizumab at 4 weekly intervals, and whose disease have not responded to bevacizumab.

2.3 The Subcommittee **recommended** the following restrictions for 2nd line anti-VEGF agent for the treatment of wAMD:

Restricted
Initiation
Reassessment required after 3 doses
All of the following:

1. Any of the following:
    1.1 Wet age-related macular degeneration (wet AMD); or
    1.2 Polypoidal choroidal vasculopathy; or
    1.3 Choroidal neovascular membrane from causes other than wet AMD; and
2.Either:
    2.1 The patient has developed severe endophthalmitis or severe posterior uveitis following treatment with bevacizumab; or
    2.2 There is worsening of vision or failure of retina to dry despite three intraocular injections of bevacizumab four weeks apart; and
3. There is no structural damage to the central fovea of the treated eye.

Continuation
Re-assessment required after 12 months
All of the following:
1. Documented benefit must be demonstrated to continue; and
2. Patient's vision is 6/36 or better on the Snellen visual acuity score; and
3. There is no structural damage to the central fovea of the treated eye.

Diabetic Macular Oedema (DMO)

2.4 The Subcommittee **recommended** the following restrictions for a 2nd line anti-VEGF agent, for the treatment of DMO:

Initiation
Re-assessment required after 4 doses
All of the following:
1. Patient has centre involving diabetic macular oedema (DMO); and
2. Patient's disease is non responsive to 4 doses of intravitreal bevacizumab when administered 4-6 weekly; and
3. Patient has reduced visual acuity between 6/9 – 6/36 with functional awareness of reduction in vision; and
4. Patient has DMO within central OCT (ocular coherence tomography) subfield > 350 micrometers; and
5. There is no centre-involving sub-retinal fibrosis or foveal atrophy.

Continuation
Re-assessment required after 12 months
All of the following:
1. There is stability or two lines of Snellen visual acuity gain; and
2. There is structural improvement on OCT scan (with reduction in intra-retinal cysts, central retinal thickness, and sub-retinal fluid); and
3. Patient's vision is 6/36 or better on the Snellen visual acuity score; and
4. There is no centre-involving sub-retinal fibrosis or foveal atrophy; and
5. After each consecutive 12 months treatment with [2nd line anti-VEGF agent], patient has retrialled with at least one injection of bevacizumab and had no response.

Discussion

2.5 The Subcommittee noted the previous PTAC and Subcommittee recommendations for anti-VEGF agents for wet age related macular degeneration (wAMD) and diabetic macular oedema (DMO). The Subcommittee noted PTAC's view that aflibercept is the preferred 2nd line anti-VEGF agent for the treatment of both wAMD and DMO. The Subcommittee noted that PTAC had recommended declining 3rd line anti-VEGF agents for wAMD and DMO, as PTAC had considered that there was very limited evidence supporting 3rd line use.

2.6 The Subcommittee noted PTAC's concerns that there may be tendency for some patients to continue treatment even where the disease has progressed to an extent that further treatment is considered ineffective. The Subcommittee noted that PTAC had considered that restrictions with objectives measures of both visual acuity and structural improvement may prevent this, and would target treatment to patients that are most likely to benefit.

2.7 The Subcommittee noted that PTAC had referred this application to the Ophthalmology Subcommittee to formulate objective entry and exit criteria for the use of 2nd line anti-VEGFs for wAMD and DMO.

wAMD

2.8 The Subcommittee noted there is a potential risk with listing treatments for wAMD in that there are particular ocular diseases that present much like wAMD that do not respond to anti-VEGF treatment.

2.9 The Subcommittee noted the restrictions for 2nd line anti-VEGF for wAMD and other similar indications as recommended by PTAC in February 2015. The Subcommittee considered that the wording of the criteria could be made more specific and less ambiguous.

2.10 The Subcommittee considered that the current indications in the criteria are appropriate, and that those with wAMD, polypoidal choroidal vasculopathy, and chroidal neovascular membrane are patients who would likely benefit from treatment.

2.11 The Subcommittee noted that currently in DHB hospitals around New Zealand, due to capacity constraints around 1/3 of anti-VEGF injections are given outside of the normal hospital hours, often being administered on Saturdays. The Subcommittee considered that for wAMD it was especially important to promptly treat patients newly diagnosed with the disease, as wAMD is progressive and vision may be difficult to restore after it has deteriorated.

2.12 The Subcommittee noted that some DHBs are training nurses to administer intraocular anti-VEGF injections. The Subcommittee noted at ADHB more than 95% of anti-VEGF injections are administered by trained nurses.

2.13 The Subcommittee considered that there should be a central database set up to collect data around the rates and frequency of patients using 2nd line anti-VEGF agents.

2.14 The Subcommittee considered that if aflibercept were to be listed as the sole 2nd line anti-VEGF agent for wAMD, that those patients who are currently eligible and being treated with ranibizumab could switch to being treated with aflibercept. The Subcommittee considered that the majority of patients who were responding to ranibizumab should also respond to aflibercept, however considered that those patients who do not respond to aflibercept could continue receive treatment with ranibizumab as a grand-parented treatment, applying for this via the Named Patient Pharmaceutical Assessment pathway.

2.15 The Subcommittee noted that PTAC had requested the entry criteria specify both structural and function measurements of disease. The Subcommittee also considered that the entry criteria should specify the frequency of administration with bevacizumab injections prior to assessing response to treatment, and that the criteria should incorporate

the exclusion criteria of 'structural damage to central fovea' as patients with damage to the central fovea are unlikely to benefit from treatment.

2.16 The Subcommittee noted that the 2nd line anti-VEGF for wAMD restrictions proposed by both the October 2014 Ophthalmology Subcommittee and the February 2015 PTAC had a bevacizumab retrial restriction in the renewal criteria, and that the current ranibizumab restrictions in the HML also had this criterion. The Subcommittee noted that the retrial restriction was added as a means to reduce the fiscal impacts of 2nd line anti-VEGF agent, and that there was limited evidence to support this practice. The Subcommittee considered that a retrial with bevacizumab was unlikely to yield any benefit if a previous non-response or injection reaction was observed. The Subcommittee **recommended** that the bevacizumab retrial criteria be removed from the 2nd line anti-VEGF renewal criteria, in line with PTAC's recommendations from its May 2017 meeting.

2.17 The Subcommittee considered that after initial diagnosis of wAMD, many patients notice a rapid improvement in their symptoms following anti-VEGF injection, however considered that for some patients improvements may take longer. The Subcommittee considered that an initial trial with 3 bevacizumab injections every 4 weeks is important for establishing whether or not there is a response to bevacizumab, and that following non-response to bevacizumab, patients would then be eligible for the 2nd line anti-VEGF agent. The Subcommittee considered that the target of 3 initial bevacizumab injections every 4 weeks is reasonable and achievable. The Subcommittee **recommended** that access to a 2nd line anti-VEGF should only be in those patients who have had 3 doses of bevacizumab at 4 weekly intervals, and whose disease have not responded to bevacizumab.

2.18 The Subcommittee considered that approximately 5-10% of patients may require a 2nd line anti-VEGF for the treatment of wAMD, and that the average treatment duration while on aflibercept is likely to be approximately 5 years.

2.19 The Subcommittee noted that wAMD is a progressive disease and many patients are likely to eventually lose vision due to atrophic and dry macular degenerative changes not responsive to anti-VEGF agents. The Subcommittee considered that patients' whose vision deteriorates to worse than 6/36 (Snellen's visual acuity score) should discontinue treatment with 2nd line anti-VEGF as ongoing treatment beyond this point would likely yield little benefit. The Subcommittee considered that the renewal criteria should include a new criterion whereby if the patient's vision deteriorates to worse than 6/36, that treatment with the 2nd line anti-VEGF agent should cease. The Subcommittee noted that patients whose vision is worse than 6/36 would be able to continue accessing bevacizumab.

2.20 The Subcommittee **recommended** the following restrictions for 2nd line anti-VEGF agent (deletions in ~~strikethrough~~, additions in **bold**):

Restricted
Initiation
Reassessment required after 3 doses
All of the following:
1. Any of the following:
    1.1 Wet age-related macular degeneration (wet AMD); or
    1.2 Polypoidal choroidal vasculopathy; or
    1.3 Choroidal neovascular membrane from causes other than wet AMD; and
2. ~~Either:~~ **Either**:

2.1 ~~The patient has had a severe ophthalmic inflammatory response following bevacizumab; or~~ **The patient has developed severe endophthalmitis or severe posterior uveitis following treatment with bevacizumab; or**

2.2 ~~Treatment with bevacizumab has proven ineffective following at least three intraocular injections.~~ **There is worsening of vision or failure of retina to dry despite three intraocular injections of bevacizumab four weeks apart; and**

3. There is no structural damage to the central fovea of the treated eye.

Continuation

~~*Re-assessment required at 6 months, 12 months and 24 months from initiation of treatment, then 2 yearly thereafter.*~~

Re-assessment required after 12 months

All of the following:

1. Documented benefit must be demonstrated to continue; and
2. ~~In the case of previous non-response to bevacizumab, a retrial of at least one dose of bevacizumab is required at 6 months, 12 months and 24 months to confirm non-response before continuing with aflibercept.~~ **Patient's vision is 6/36 or better on the Snellen visual acuity score; and**
3. **There is no structural damage to the central fovea of the treated eye.**

DMO

2.21 The Subcommittee noted the access criteria proposed by PTAC in February 2016 to a 2nd line anti-VEGF agent for the treatment of diabetic macular oedema (DMO). The Subcommittee noted that the proposed initiation criteria already contain both functional and structural measurements associated with disease. The Subcommittee noted the criterion of non-response to a minimum of 4 doses of the first line anti-VEGF agent currently does not state a timeframe within which these injections should be given, and considered that the criterion should be amended to state that each injection should be administered four to six weeks apart.

2.22 The Subcommittee considered that patients with DMO whose vision deteriorates whilst receiving treatment should be reassessed rather than discontinue treatment. The Subcommittee considered that a decline in vision in some patients may be due to a reversible symptom such as a cataract, and that the patient would still likely benefit from treatment with an anti-VEGF agent.

2.23 The Subcommittee considered that patients whose vision deteriorates to worse than 6/36 (Snellen's visual acuity score) in the absence of a reversible symptom should discontinue treatment with 2nd line anti-VEGF, as ongoing treatment beyond this point would likely yield little benefit. The Subcommittee considered that the renewal criteria should include a criterion whereby if the patient's vision deteriorates to worse than 6/36, that treatment with the 2nd line anti-VEGF agent should cease. The Subcommittee considered that patients whose vision is worse than 6/36 would be able to continue accessing bevacizumab.

2.24 The Subcommittee considered that approximately 10-20% of patients with DMO may need a 2nd line anti-VEGF agent.

2.25 The Subcommittee noted that DMO is a very different disease to wAMD, and that following treatment with anti-VEGF agents there may be a period of stability whereby frequent administration of anti-VEGF agents may no longer be required. Some patients may have significant periods without any requirement for ongoing anti-VEGF agent treatment, who would then re-start treatment once disease relapses. The Subcommittee considered that

for DMO, the continuation criteria requiring a retrial with bevacizumab after the first 12 months approval is appropriate.

2.26 The Subcommittee **recommended** the following change to the proposed restriction for 2nd line anti-VEGF agent for DMO (deletions in ~~strikethrough~~, additions in **bold**):

Initiation
Re-assessment required after 4 doses
All of the following:

1. Patient has centre involving diabetic macular oedema **(DMO)**; and
2. **Patient's disease is n**on responsive to ~~minimum of~~ 4 doses of intravitreal ~~[first line anti-VEGF agent]~~ **bevacizumab when administered 4-6 weekly**; and
3. ~~Patient has all of the following:~~
   Patient has reduced visual acuity **between** 6/9 – 6/36 with functional awareness of reduction in vision; and
4. **Patient has DMO** ~~Diabetic macular oedema~~ within central OCT (ocular coherence tomography) subfield > 350 micrometers; and
5. **There is no centre-involving sub-retinal fibrosis or foveal atrophy.**
   ~~Exclusion: centre-involving sub-retinal fibrosis or photoreceptor loss~~

Continuation
Re-assessment required after 12 months
~~**Both**~~ **All of the following:**

1. ~~Reassess after four doses of intravitreal aflibercept and then annual retrial of [first line anti-VEGF agent] if ongoing treatment is required All of the following:~~ There is stability or two lines of Snellen visual acuity gain; and
2. There is structural improvement on OCT scan (with reduction in intra-retinal cysts, central retinal thickness, and sub-retinal fluid); and
3. **Patient's vision is 6/36 or better on the Snellen visual acuity score; and**
4. **There is no centre-involving sub-retinal fibrosis or foveal atrophy; and**
5. **After each consecutive 12 months treatment with [2nd line anti-VEGF agent], patient has retrialled with at least one injection of bevacizumab and had no response.**

3 Ciclosporin

Recommendation

3.1 The Subcommittee **recommended** the following special authority criteria for ciclosporin eye drops for the treatment of keratoconjunctivitis sicca:

Severe keratoconjunctivitis sicca (severe aqueous deficient dry eye disease)
Initial application – only from an ophthalmologist. Approvals valid for 3 months for applications meeting the following criteria
All of the following:

1. Patient has dry eye predominantly due to aqueous deficiency, and dry eye of evaporative aetiology (i.e. Meibomian gland dysfunction) has either been excluded or managed; and
2. Patient's disease is responsive to short-term ophthalmic; and
3. Patient has severe secretive tear deficiency diagnosed by Schirmer test without anaesthesia of <10mm in 5 minutes.

Renewal – approvals valid for 12 months for applications meeting the following criteria
All of the following:

1. Patient has responded to treatment and continues to benefit; and
2. Patient's disease has not progressed or worsened.

3.2 The Subcommittee **recommended** the following special authority criteria for ciclosporin eye drops for the treatment of vernal and atopic keratoconjunctivitis:

Severe AKC/VKC
Initial application - only from an Ophthalmologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has severe atopic keratoconjunctivitis/vernal keratoconjunctivitis; and
2. Any of the following:
    2.1 Corneal epithelium breakdown; or
    2.2 Progressive limbus thickening/hypertrophy; or
    2.3 Steroid induced intraocular pressure rise; or
    2.4 Requiring longer than 6 weeks of continuous steroid therapy.

Renewal criteria - Only from an ophthalmologist. Approvals valid for 12 months for applications meeting the following criteria:
Any of the following:
1. Treatment remains appropriate and patient is benefitting from treatment as measured by a 75% improvement in subjective symptom measure from baseline; or
2. Treatment has resulted in a reduction in the usage of ocular steroids from baseline; or
3. There has been an improvement in corneal epithelium measure from baseline.

Discussion

3.3 The Subcommittee noted the recommendations and special authority criteria from the February 2016 Ophthalmology Subcommittee meeting and the August 2016 PTAC meeting proposed for ciclosporin eye drops for the treatment of severe dry eye disease (keratoconjunctivitis sicca), and vernal and atopic keratoconjunctivitis. The Subcommittee noted that in recent years there has been new evidence and updated guidance around therapies for the treatment of dry eye disease, and considered that the advice previously provided in 2016 around treatment of keratoconjunctivitis sicca no longer aligns with current best practice.

3.4 The Subcommittee considered that the previous recommendations for the treatment of atopic and vernal keratoconjunctivitis is still mostly appropriate, and considered that many of the criteria is still applicable.

Keratoconjunctivitis Sicca

3.5 The Subcommittee noted that severe dry eye disease is a serious, multifactorial vision threatening disease of the ocular surface, characterised by a loss of homeostasis of the tear film.

3.6 The Subcommittee noted the correspondence provided by Assoc Prof Jennifer Craig, an international expert in the field of ocular tear deficiency and dry eye disease, as well as the recently updated Tear Film and Ocular Surface Society Dry Eye Workshop II report (TFOS DEWS II, The Ocular Surface 2017) which provided an update on the definition, classification, and diagnosis of dry eye disease as well as critically assessing the etiology, mechanism, distribution and impact of this disorder. The Subcommittee noted that this report supersedes the previous TFOS DEWS report which was published in 2007. The Subcommittee noted that there appears to be poor correlation between ocular surface symptoms, discomfort, and the risk of vision loss to the affected person, hence the previous DEWS grading system for dry eye (DEWS grading 1 - 4) is no longer supported in the DEWS II report.

3.7 The Subcommittee noted that dry eye is caused by factors that are either predominantly evaporative or due to deficiency in tear production. The Subcommittee noted that it is not

possible to completely exclude or pinpoint the cause of the dry eye as either evaporative or aqueous deficiency as there will likely be a mixture of the two aetiologies.

3.8 The Subcommittee noted that the role of treatment in severe dry eye disease is to restore homeostasis of the tear film, which is best achieved by identifying and treating the predominant cause of the dry eye (either predominantly evaporative or aqueous tear deficiency disease), in an effort to break the disease cycle.

3.9 The Subcommittee noted that the term keratoconjunctivitis sicca refers to aqueous deficient dry eye (ADDE) rather than evaporative dry eye (EDE). The Subcommittee noted that ADDE describes a tear quantity issue, with lacrimal gland dysfunction and reduced tear production. The Subcommittee noted that EDE relates to the quality of the tear film, and is most often caused by eyelid pathology or ocular surfacing abnormalities. The Subcommittee noted that ADDE is often recognised to have an inflammatory aetiology, regardless of whether the dry eye is associated with Sjögren Syndrome or not.

3.10 The Subcommittee noted that ciclosporin is an immunomodulatory agent and that its primary indication in dry eye is for the treatment of ADDE. The Subcommittee noted that it would not be appropriate to use an immunomodulatory therapy such as ciclosporin for the treatment of EDE.

3.11 The Subcommittee noted that currently funded treatments available in New Zealand for the treatment of severe dry eye are ocular lubricants and long-term ophthalmic corticosteroids. The Subcommittee considered that ophthalmic corticosteroids should be excluded from consideration for anything other than a short term or pulsed application, as described in the Management and Therapy Report of TFOS DEWS II, for the purpose of breaking the dry eye vicious cycle. The Subcommittee considered that dry eye is a chronic disease that requires long-term management, and that while there is some evidence that corticosteroids are effective as a short-term measure for managing dry eye disease, the risks of serious side effects from long-term ongoing use far outweigh the benefits for this condition. The Subcommittee considered that the well-established risks of long-term corticosteroid use (which include cataract, glaucoma, infection and delayed healing) meant that corticosteroids are not considered as an appropriate long-term treatment option for dry eye disease.

3.12 The Subcommittee noted the special authority proposed by PTAC at its August 2016 meeting for the use of ciclosporin eye drops in the treatment of keratoconjunctivitis sicca. The Subcommittee considered that the proposed wording of the special authority was not in keeping with the updated TFOS DEWS II guidelines and was difficult to apply in a clinical setting. The Subcommittee also considered that the evidence for use of Vitamin A in the treatment of dry eye disease was limited.

3.13 The Subcommittee considered that the proposed special authority criteria needed to be amended so that it is both easy to administer and is able to target treatment to those with aqueous deficient dry eye who are most likely to benefit from treatment. The Subcommittee **recommended** the following changes to the PTAC special authority criteria for ciclosporin eye drops for the treatment of keratoconjunctivitis sicca (additions in bold, deletions in strikethrough):

> **Severe keratoconjunctivitis sicca (severe aqueous deficient dry eye disease)**
> **Initial application** – only from an ophthalmologist. Approvals valid for ~~6~~ **3** months for applications meeting the following criteria

All of the following:

1. Patient has ~~severe secretive tear deficiency disease with a DEWS grading of 3~~ **dry eye predominantly due to aqueous deficiency**, and dry eye of evaporative aetiology **(i.e. Meibomian gland dysfunction)** has either been excluded **or managed**; and
2. Patient**'s disease** is responsive to **short-term** ophthalmic corticosteroids ~~and requires daily treatment with ophthalmic corticosteroids for more than 6 weeks~~; and

~~Patient has developed glaucoma, or increased intra-ocular pressure requiring treatment, secondary to low dose ophthalmic corticosteroids;~~

~~Patient must have trialled a 2 month course of vitamin A eye ointment;~~

3. **Patient has severe secretive tear deficiency diagnosed by Schirmer test without anaesthesia of <10mm in 5 minutes**.

Renewal – approvals valid for 12 months for applications meeting the following criteria
All of the following:

1. Patient has responded to treatment and continues to benefit; and
2. Patient's disease has not progressed or worsened.

3.14 The Subcommittee noted that the Schirmer test comprises placing strips of test paper in each eye for 5 minutes, which measures the quantity of tears produced in the eyes. The Subcommittee noted that the Schirmer test is a true test for tear production and for aqueous deficiency dry eye, and has both good specificity and sensitivity.

3.15 The Subcommittee considered that many patients with aqueous deficiency dry eye who required ciclosporin eye drops would need treatment lifelong. The Subcommittee considered that a 12 months renewal period would be appropriate, to ensure that patients are followed up and assessed by their doctors ensuring that patients continue to respond to treatment and disease has not progressed.

3.16 The Subcommittee considered that in terms of patient numbers, approximately 15% of patients over 50 years old had dry eyes, of which approximately 5% would have ADDE, and that in turn approximately 1-2% of these patients would have severe disease requiring treatment with ciclosporin.

Vernal keratoconjunctivitis / Atopic keratoconjunctivitis

3.17 The Subcommittee noted that vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) are chronic, bilateral, and severe forms of allergic inflammation affecting the ocular surface.

3.18 The Subcommittee noted that currently funded treatments in New Zealand for VKC and AKC are ophthalmic corticosteroids, ophthalmic mast cell stabilisers, and ophthalmic antihistamines, and did not consider systemic immunosuppressants or other cytotoxics to be appropriate treatment options of VKC or AKC.

3.19 The Subcommittee noted the special authority proposed by PTAC at its August 2016 meeting. The Subcommittee considered that the initiation criteria were appropriately worded, in that treatment would be targeted to those patients who were most likely to benefit. The Subcommittee however did not consider that the proposed renewal criteria were appropriate, as patients had to meet all items in the criteria, rather than only those which were considered relevant. The Subcommittee **recommended** the following changes to the PTAC special authority criteria for ciclosporin eye drops for the treatment of vernal and atopic keratoconjunctivitis (additions in bold, deletions in strikethrough):

Severe AKC/VKC
Initial application - only from an Ophthalmologist. Approvals valid for 6 months for

applications meeting the following criteria:
All of the following:
1. Patient has severe atopic keratoconjunctivitis/vernal keratoconjunctivitis; and
2. Any of the following:
    2.1 Corneal epithelium breakdown; or
    2.2 Progressive limbus thickening/hypertrophy; or
    2.3 Steroid induced intraocular pressure rise; or
    2.4 Requiring longer than 6 weeks of continuous steroid therapy.

Renewal criteria - Only from an ophthalmologist. Approvals valid for ~~6~~ **12** months for applications meeting the following criteria:
~~All~~ **Any** of the following:
1. Treatment remains appropriate and patient is benefitting from treatment **as measured by a 75% improvement in subjective symptom measure from baseline**; or
2. Treatment has resulted in a reduction in the usage of ocular steroids from baseline; or
~~3. The patient has experienced a 75% improvement in objective and subjective symptom measure from baseline; or~~
3. There has been an improvement in corneal epithelium measure from baseline.