



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### *Application No. 1392 – Corneal Collagen Cross Linking as early intervention in progressive keratoconus*

**Applicant:** Royal Australian and New Zealand College of Ophthalmologists (RANZCO)

**Date of MSAC consideration:** MSAC 67<sup>th</sup> Meeting, 28-29 July 2016

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at [MSAC Website](#)

#### **1. Purpose of application and links to other applications**

An application requesting a new Medicare Benefit Schedule (MBS) listing of Corneal Collagen Cross Linking (CCXL) as early intervention in progressive keratoconus was received by the Department of Health from RANZCO.

#### **2. MSAC's advice to the Minister**

After considering the available evidence presented in relation to safety, clinical effectiveness and cost effectiveness, MSAC deferred its advice to the Minister on public funding for CCXL in patients with corneal ectatic disorders due to concerns that the revised economic model had not been adequately verified and that the riboflavin drops used in rendering this service were not registered on the Australian Register of Therapeutic Goods (ARTG).

MSAC requested the following information to enable it to finalise its advice:

- a more detailed rationale for the proposed fee, including the range of applicable protocols to render the service, and how these range in both complexity and duration
- an assessment by its Evaluation Sub-Committee (ESC) comparing the revised modelled economic evaluation with the version initially developed, and examining the sensitivity of these models to variations in the proposed fee
- clarification from the Therapeutic Goods Administration (TGA) regarding the consequences of the varying regulatory status of the codependent ultraviolet lamp device and the various riboflavin eye drop options used in rendering the service
- MSAC noted reports that several large well-designed clinical trials due to report in 2016–17 have discontinued their control arms. Any further assessment of this application may want to address the progress of those trials.
- Data cited in the pre-MSAC response said to be available in patients with ectasias other than keratoconus.

### **3. Summary of consideration and rationale for MSAC's advice**

CCXL is a novel treatment claimed to halt progression of corneal ectasia (bulging of the cornea that can cause significant visual impairment). Treatment involves soaking of the cornea with a solution of riboflavin 0.1% and dextran. An ultraviolet A light source is then shone onto the cornea. This increases inter molecular bonds between collagen fibres and stiffens the cornea reducing the risk of ectasia progression.

The intended use of CCXL is in patients with corneal ectatic disorders with evidence of disease progression. Keratoconus accounts for approximately 90% of these disorders, with an estimated prevalence of one in 2000, or 0.05% of the population. The onset of keratoconus can occur anywhere between the ages of 8 and 45years, with the majority of cases occurring in patients aged 16-30years of age. MSAC acknowledged the consumer feedback from the consultation process highlighting the value patients with these disorders place on reducing progression of visual impairment.

Once progression of a corneal ectatic disorder has been identified, current treatment involves attempting to improve vision firstly with glasses or soft contact lenses before progressing to hard contact lenses. If hard contact lenses cannot be fitted or are unsuitable, the patient may require corneal transplantation.

MSAC accepted that CCXL is intended as a first-line treatment once there is evidence of disease progression. The proposed treatment pathway utilises CCXL as preventive treatment (intending to halt the progression of the disease). MSAC therefore considered the early interventions in the current treatment pathway to be the appropriate comparators.

In considering the evidence for efficacy and safety of CCXL, MSAC noted that the few published randomised controlled trials (RCTs) available were small and of low quality. The evidence base presented primarily consisted of non-randomised studies which analysed CCXL results at various time points after the procedure compared to baseline. Comparisons with the current treatment pathway are therefore either not possible or difficult due to limitations in the quality of the evidence available. MSAC also noted that all evidence available was for patients with keratoconus. In the pre-MSAC response, the applicant noted that some data were available for other conditions, though these were not included with the response.

Three systematic reviews and meta-analyses (Craig JA et al 2014, Li J et al 2015 and Meiri Z et al 2016) formed the basis of the safety and efficacy effect estimates in the contracted assessment report. These were supplemented with the findings of RCTs and non-randomised studies which had been excluded from or published after these reviews. MSAC noted that the Craig JA et al 2014 review on the safety and efficacy of epithelium-off CCXL was used as the basis of approval of this intervention in the United Kingdom. MSAC was advised that approval had also been granted in the United States, Europe and New Zealand.

MSAC noted that adverse events and complications after CCXL were not well reported in the RCTs and hence there are few comparative safety data available. The contracted assessment indicated that a range of adverse events have been reported with CCXL, but these were generally minor and transient in nature. Minor corneal haze was found to be common but was noted to resolve over time. A small number of cases of serious corneal oedema, infection, repeat surgery and stromal scarring were also reported. Despite the lack of direct comparative safety data, MSAC considered that on aggregate it was reasonable to assume from the available evidence that the absolute complication rate arising from the procedure is low.

MSAC was however concerned that, while the ultraviolet lamp devices are included in the ARTG, the 0.1% riboflavin eye drops used in rendering this service are not. The riboflavin drops are accessed via the TGA's Special Access Scheme. This means that the quality, safety and efficacy of these drops has not been formally evaluated by the TGA and places responsibility for use of an unapproved product on the prescribing physician in terms of safety and efficacy. Special access requests are processed by the TGA on a per patient basis, placing an additional administrative burden on the prescriber to obtain the necessary approvals. MSAC noted that there have been no adverse events for the riboflavin solution recorded in the TGA database of adverse event notifications. MSAC requested clarification from the TGA regarding the consequences of the varying regulatory status of these two components of this service.

In considering the efficacy of CCXL, MSAC was concerned that the presented clinical data did not definitively demonstrate that CCXL delays the need for a corneal transplant. MSAC recognised that due to the extended period of time between diagnosis and transplant

(10–20years) it was unlikely that RCT data answering this question would become available. MSAC noted that two studies which reviewed registry data (Sandvik GF et al 2015, Godefrooij DA et al 2016) indicated that there was a reduction in the number of corneal transplants for patients with keratoconus in the years since the introduction of CCXL. However, MSAC was concerned that these were observational studies and hence other factors could be driving the reductions seen, for example the time between increases in CCXL and decreases in corneal transplant did not match the plausible time course of disease progression. MSAC noted that a CCXL register has recently been set up at the University of Sydney.

As comparisons with the current treatment pathway were not possible, the efficacy of CCXL per se was reviewed. MSAC accepted that the evidence available, while limited, does show that CCXL leads to improvements over baseline in corrected visual acuity, uncorrected visual acuity, Kmax and spherical equivalent refractive error. These improvements were maintained over at least 2years with one study (Raiskup F et al 2015) indicating that improvements remain evident at 10years.

MSAC noted that some additional, but very low quality, data on quality of life (QOL) was also identified, suggesting possible QOL improvements over baseline in those who have undergone CCXL compared to those with contact lenses.

Scant data pertaining to the use of CCXL in children and adolescents were evident. MSAC noted that, where the procedure has been attempted in this population, the outcomes have been similar to those for adults or all ages. However, MSAC noted that there was emerging evidence which indicated that the effect of halting disease progression in this population might not be as sustained as in adults (Godefrooij DA et al 2016, Chatzis N and Hafezi F 2012) in particular incidence of disease progression in 22% of treated eyes cited by Godefrooij DA et al 2016.

MSAC noted that research on CCXL continues with over 70 trials, primarily focusing on procedure variations, currently registered in clinicaltrials.gov. MSAC considered that it was unlikely that these trials would provide long-term efficacy data as most were to be conducted over a one-year period and involved surrogate outcomes. MSAC was concerned with reports that several large well-designed clinical trials due to report in 2016–17 have discontinued their control arms. MSAC considered that details about the reasons for the premature cessation of these trials may assist in its assessment of the current application.

MSAC noted that both ESC and the applicant had reviewed the original economic model for this application and raised a number of concerns. A revised economic model was subsequently submitted however the timing did not allow review by ESC or the applicant. MSAC noted that the revised model included inputs to address a number of the issues initially raised. However, MSAC was concerned that variations between the two models indicated the incremental cost per QALY was unstable. MSAC was also unable to determine the extent to which cost effectiveness was driven by avoidance of corneal transplant and requested that the revised economic evaluation enable a comparison with and without inclusion of corneal transplants avoided. MSAC noted that the study by Salmon H et al 2015, which was used to inform the structure and assumptions of the revised model, indicated that the effect of CCXL after 5 years was a key driver of cost effectiveness, although there were no clinical data to support any assumptions made after three years. MSAC considered that the utility weights, their origin and their application in the economic model also needed adjustment. MSAC requested that ESC review the revised model and compare it with the version initially developed as MSAC was concerned that the revised economic model had not been adequately verified. MSAC also requested that ESC examine the sensitivity of these models to variations in the proposed fee.

MSAC noted that the proposed fee for this service had not yet been agreed. The Protocol Advisory Sub-Committee had suggested a value between \$900 and \$1300 based upon the current fees for cataract surgery and corneal transplant MBS items, respectively. However, MSAC was concerned about using these MBS items as fee-setting benchmarks, noting that the fees may be higher than appropriate for CCXL. MSAC noted that Godefrooij DA et al 2016 detailed the costs associated with CCXL in clinical practice for 43 patients (86 eyes) in the Netherlands. Costs varied depending on who was undertaking the procedure (optometrist versus ophthalmologist) and the protocol used to render the service. MSAC requested that a revised fee for CCXL be developed with the rationale for the costs and charges detailed.

MSAC noted further that as variations of the CCXL procedure exist, ranging in both complexity and duration, the revised fee should also take into account the range of applicable protocols currently available to render the service.

MSAC considered whether the proposed MBS item descriptor should be restricted to patients with keratoconus as data for the use of CCXL in other corneal ectatic disorders was not presented. MSAC foreshadowed that any MBS item descriptor would remain inclusive of other corneal ectatic disorders and requested that the applicant provide data on other ectasias referred to in their pre-MSAC response to assist in informing this decision. MSAC also foreshadowed that the item would not be restricted to one service per lifetime per eye, as not enough data was currently available on long-term disease progression to inform this restriction. MSAC noted that the department had received advice of use of CCXL in patients with post-LASIK<sup>1</sup> ectasia and foreshadowed that wording may be required in any descriptor to exclude use in this population for a CCXL item. MSAC also foreshadowed that it would be reasonable to require mandatory recording of services provided and their outcomes on a CCXL register.

MSAC was satisfied that, on the basis of the evidence presented, CCXL has acceptable safety and clinical effectiveness in the proposed population. However, MSAC was unable to support public funding at this time due to concerns that the revised economic model had not been adequately verified and that the riboflavin drops used were not registered in the ARTG.

---

<sup>1</sup> LASIK: Laser-Assisted *In Situ* Keratomileusis (commonly referred to as laser eye surgery)

MSAC requested the following information before it could finalise its advice:

- a more detailed rationale for the proposed fee, including across the range of applicable protocols to render the service, which range in both complexity and duration
- an assessment by ESC comparing the revised modelled economic evaluation with the version initially developed, and examining the sensitivity of these models to variations in the proposed fee
- clarification from the TGA regarding the consequences of the varying regulatory status of the ultraviolet lamp device and the various riboflavin eye drop options used in rendering the service
- MSAC noted reports that several large well-designed clinical trials due to report in 2016–17 have discontinued their control arms. Any further assessment of this application may want to address the progress of those trials.

#### **4. Background**

MSAC has not previously considered Corneal Collagen Cross Linking.

#### **5. Prerequisites to implementation of any funding advice**

The CCXL procedure requires 0.1% riboflavin eye drops, which are not currently registered on the Australian Register of Therapeutic Goods. The riboflavin drops may be accessed via the TGA’s Special Access Scheme.

#### **6. Proposal for public funding**

The application proposed fee and MBS item descriptor is shown in Table 1.

**Table 1 - Proposed MBS item descriptor for corneal collagen cross-linking**

Category 3 – Therapeutic Procedures – Ophthalmology Services
MBS [item number]  Corneal Collagen Cross Linking, for patients with corneal ectatic disorders with evidence of progression  Fee: \$1500  Anaes.
Explanatory Note:  Evidence of progression in patients over the age of twenty five is determined by the patient history including an objective change in tomography or refraction over time. Evidence of progression in patients aged twenty five years or younger is determined by patient history including an objective change in tomography or refraction over time and/or posterior elevation data and objective documented progression at a subclinical level.

The application proposed fee is \$1500. PASC suggested a fee of \$900-\$1300 would be appropriate (between the cost of cataract surgery and corneal transplant). During the public

consultation, consumers advised that currently, they are being charged between \$2000–3000 per eye (\$4000–\$6000 for both eyes).

The CCXL procedure can be performed in day surgery facilities or other facilities that have adequate air handling systems and sterile conditions.

## **7. Summary of Public Consultation Feedback/Consumer Issues**

PASC received three responses from peak bodies, two responses from organisations, 14 responses from specialists, 20 responses from consumers and 12 responses from carers.

Consultation feedback for the proposal was positive. Issues raised in the responses were:

- The proposed population should be expanded to patients with corneal ectatic disorders.
- Corrective lenses including hard lenses only address the symptoms of the medical condition. The two treatments for the medical condition are the proposed procedure and penetrating corneal grafts, therefore the procedure should be used as a first line treatment.
- Additional measures should be used to determine evidence of progression of the medical condition in patients under 25 as there is a high risk of rapid progression in this population group. These measures may include posterior elevation data and objective documented progression at a subclinical level.
- The MBS Item fee should be revised from \$1500 to greater than \$2000 to reflect current procedure costs.

## **8. Proposed intervention's place in clinical management**

CCXL will be used in patients with corneal ectatic disorders (primarily keratoconus) with evidence of progression of the disease.

Keratoconus accounts for 90 per cent of patients with corneal ectatic disorders, with an estimated prevalence of one in 2000, or 0.05 per cent of the population.

The current approach to treating patients with corneal ectatic disorders involves, in the first instance, attempting to improve the patient's vision with glasses (or soft contact lenses), if possible. If the condition progresses, and the glasses/soft contact lenses no longer improve the patient's vision, hard contact lenses are fitted. If the lenses cannot be fitted, or are unsuccessful, patients undergo penetrating corneal graft. Some patients currently access corneal collagen cross-linking as an alternative to corneal grafting by self-funding the procedure.

Under the proposed clinical management algorithm, CCXL would be used as a first line treatment once there is evidence of progression, regardless of whether glasses or contact lenses have been tried. The proposed treatment pathway utilises CCXL as a preventative treatment (intending to halt the progress of the disease early). It involves glasses/soft contact lenses, then CCXL, then hard contact lenses and then penetrating corneal graft.

## **9. Comparator**

The current treatment pathway involves attempting to improve the patient's vision with glasses or soft contact lenses, and if no improvement or deterioration then hard contact

lenses. If hard contact lenses cannot be fitted or are unsuccessful, then patients undertake penetrating corneal graft.

## **10. Comparative safety**

Adverse events and complications after CCXL are not well reported in the randomised trials, so there are few comparative safety data. A range of adverse events were described but these are generally minor and transient. Corneal haze was common but resolves over time.

The assessment report stated that it was not possible to assess the safety of CCXL relative to the conventional management pathway without CCXL. Therefore, at best, CCXL can be assessed to be non-inferior with respect to safety.

## **11. Comparative effectiveness**

The included studies comprised 7 randomised controlled trials, 8 systematic reviews and 50 nonrandomised studies (cohort studies and case series). Primary effectiveness outcome measures analysed were best corrected visual acuity, uncorrected visual acuity, corneal topography, and spherical equivalent refractive error.

A summary of key results for the standard CCXL procedure over 12 months or longer is shown in Table 2.

**Table 2 Evidence profile: Overall clinical effects of standard CCXL as measured in key included systematic reviews and randomised trials with 12 months followup or greater**

Outcomes (units)	Participants (studies)	Type of study	Quality of evidence (GRADE) <sup>a</sup>	Effect (summary)
Corrected visual acuity (logMAR)	Craig 2014; Meiri 2016	Meta-analysis (RCTs and NRS)	Low	-0.1 at 12&24 months: -0.09 at ≥36 months:
	Li 2015	Meta-analysis (RCTs)	Low	-0.1 (3–36 months)
	#997 Seyedian 2015 #1204,1205 Wittig-Silva 2008 and 20014	RCTs	Low	-0.1 at 12 months;
Uncorrected visual acuity (logMAR)	Craig 2014; Meiri 2016	Meta-analysis (RCTs and NRS)	Low	-0.1 to -0.2 at 12&24 months -0.1 at ≥ 36 months:
	Li 2015	Meta-analysis (RCTs)	Low	-0.18(3–36 months)
	#1204,1205 Wittig-Silva 2008 and 20014	RCTs	Low	-0.1 at 12 months
Max K (D)	Craig 2014; Meiri 2016	Meta-analysis (RCTs and NRS)	Low	Relative to baseline/preCCCXL: -1 at 12&24 months -0.4 at ≥ 36 months
	Li 2015	Meta-analysis (RCTs)	Low	Relative to controls: -2.05 D (3–36 months)
	#997 Seyedian 2015 #1204,1205 Wittig-Silva 2008 and 20014	RCTs	Low	Relative to baseline and/or controls (up to 36 months): -1 to -2 D
Spherical equivalent refractive error (D)	Craig 2014; Meiri 2016	Meta-analysis (RCTs and NRS)	Low	Relative to baseline: 0.1–0.5 at 12 months 0.7 at 24 months  0.5 at ≥36 months
	Li 2015	Meta-analysis (RCTs)	Low	Relative to controls: -0.96 (3–36 months)
	#997 Seyedian 2015 #1204,1205 Wittig-Silva 2008 and 20014	RCTs	Low	Little change to baseline and/or controls
Quality of life	NRS		Very low	Some improvements for people with CCCXL compared to those with rigid contact lenses

<sup>a</sup> Based on GRADE Working Group grades of evidence. However, the evidence collected for this review was all low quality and did not lend itself well to a formal GRADE analysis

High quality: We are very confident that the true effect lies close to that of the estimate of effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

On the basis of this evidence profile, the assessment report suggested that, relative to the current treatment pathway, CCXL has noninferior safety and noninferior (possibly superior) effectiveness.

Considerable further comparative data would be required to make a more definitive conclusion relative to the conventional management pathway. The assessment report stated that several large clinical trials are due to report in 2016–17.

## 12. Economic evaluation

The assessment report presented a cost-utility analysis over a time horizon of 50 years to reflect the long-term impact of a disease for which there is a predictable number of diagnoses per year.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, and using the base case assumptions, are shown in the Table 2. This indicates that CCXL treatment pathway has a lower cost and higher incremental benefits compared to the current treatment pathway.

**Table 2 Incremental cost effectiveness ratio, discounted**

	Cost (\$)	Incremental cost (\$)	Effectiveness (QALYs)	Incremental effectiveness	ICER
<b>Intervention</b>	21 926 707		145 145		
<b>Comparator</b>	23 057 646	-1 130 939	144 877	268	-4 215

The assessment report noted that with respect to CCXL, the ICER is an imperfect measure of value because it results in improved outcomes at a lower cost. Although CCXL treatment pathway ‘front loads’ treatment costs, there is an incremental saving as it avoids corneal transplants which are significantly more expensive due to hospital and eye bank fees. The benefit attributed to CCXL is also likely understated as the utility measures do not reflect the improved quality of life from not undergoing an invasive surgical procedure, or experiencing life as a young person without deteriorating vision. Data limitations prevent allowances being made for these factors in the analysis.

A sensitivity analysis was conducted, the key findings were:

- the incremental cost of the CCXL treatment pathway is highly sensitive to the discount rate used because, compared to the current treatment pathway, under CCXL a larger proportion of treatment costs are incurred on diagnosis.
- increasing the number of treatments for individuals previously diagnosed with corneal ectatic disorders, has a significant impact on the costs of the CCXL pathway.
- changing the costs of CCXL treatment has significant impacts on the results. Applying a range of 30 per cent either side implies costs could be between \$4.1 million lower under the CCXL pathway or \$7.1 million higher in present value terms (over 50 years).
- Overall the project generally has incremental benefits (increase QALYs) across the range of scenarios tested.

### 13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of CCXL.

The expected use of CCXL treatments depends both on the stock of potential patients in Australia, new patients that are diagnosed each year, and the suitability of CCXL to their condition.

Not all people with corneal ectatic disorders in Australia need to be counted in the model as being potentially eligible for CCXL primarily because:

- some will have already had CCXL in one or two eyes.
- some will experience stabilisation of their condition rather than deterioration.
- some will be too advanced in their condition to benefit from CCXL and are likely to continue with the current treatment pathway and receive a corneal graft.

The utilisation model begins with an estimate of prevalence (1 in 2000, or 1 in 1625 people aged 15 and over). It then increases the prevalence pool estimate on an annual basis as new patients are deemed to be diagnosed, as the severity status of existing patients changes, and as patients die.

The estimated potential patient population shows around 12,000 people might receive CCXL at some point in their lives. Forecasts change in line with expected population growth and changes in the stage of the disease for each person. Those that are estimated to receive CCXL over the next 5 years is estimated based on the evidence around progression of the disease following diagnosis, the distribution of disease severity in the literature previously mentioned, and suitability of alternative treatments such as corneal grafts.

Given CCXL activity to date, 1,642 treatments are estimated to occur in 2016-17 and then taper down substantially as much higher levels currently being treated are not believed to be sustainable.

The financial implications to the MBS resulting from the proposed listing of CCXL are summarised in Table 3. The estimated cost to the MBS of CCXL is \$2.5 million in the first financial year, which tapers off and stabilises around \$600,000 thereafter.

This is reducible by approximately \$65,000 annually as a result of avoided corneal grafts and associated complications.

**Table 3 Total costs to the MBS associated with CCXL**

	2016-17	2017-18	2018-19	2019-20	2020-21
Preliminary consultations	\$ 140 473	\$38 583	\$30 883	\$32 338	\$33 279
CCCXL procedures	\$ 2 134 600	\$ 586 300	\$469 300	\$ 491 400	\$ 505 700
Follow up consultations after 1 year	\$211 818	\$ 58 179	\$ 46 569	\$ 48 762	\$ 50 181
Total cost to the MBS	<b>\$2 486 891</b>	<b>\$683 062</b>	<b>\$546 753</b>	<b>\$572 500</b>	<b>\$589 160</b>

#### 14. Key issues from ESC for MSAC

ESC advised that the key issues below would be most relevant to MSAC decision-making.

CCXL offers, at best, non-inferior safety and non-inferior, possibly superior, effectiveness, relative to the current treatment pathway, based on low level clinical evidence. Considerable further comparative data would be required to make a more definitive conclusion relative to conventional management pathway. ESC added the following caveats:

- There were no true long-term follow-up data (longer than 3 years) that tested the durability of the procedure or the outcomes in terms of corneal grafts avoided. There was no evidence on which to base an assessment of whether patients had an inadequate or less-than-permanent response, or the risk of eventual disease progression;
- 100% of the clinical data were collected in patients with keratoconus, which, while the most prevalent of the corneal ectatic disorders, constitutes only 90% of Australian patients with corneal ectatic disorders;
- There was an overall lack of evidence for comparative safety. Adverse events were not well reported in the clinical evidence; in particular there was a lack of data to support the safety of the CCXL procedure, the types of events observed, their frequency and grade, especially with respect to complications and also in comparison with conventional management.
- Nonetheless several large, apparently well-designed clinical trials registered in [clinicaltrials.gov](http://clinicaltrials.gov) are due to report in 2016–17.

The economic model was uncertain in multiple respects, including the inputs, numbers, outcomes and the extent of current use and thus numbers eligible for future use. ESC queried the validity of including the costs of CCXL procedure in the current (comparator) management pathway, also, the modelling for number of diagnoses per year does not account for permanent net overseas migration;

- The application did not specify costs of other resources used in the CCXL procedure. These should be included in the inputs to the economic model;
- The 50 year modelled time horizon was appropriate for the target population but was otherwise unsupported by the clinical data;
- The model lacked clinical evidence for the estimates of rates of disease progression over 5 or 10 years;
- The model assumes a 0% failure rate, which was unsupported and considered unlikely. Evidence-based rates for CCXL failure and complications should be incorporated in the model;
- The ICER did not reflect patient utilities including preference to avoid corneal grafts.

The applicant's claim that CCXL had become, in effect, the standard of care for this indication (based on a reported 70% uptake rate) was not independently verified for Australian patients nor supported with dependable health outcomes data. This flowed on to uncertainty in the utilisation and financial estimates.

With respect to the age of the patients who would receive CCXL treatment:

- The applicant did not adequately specify the age group of the intended population. Nor was evidence presented for the age of disease onset of keratoconus or other types of ectatic disorders;

- ESC noted the apparently young age of diagnosis for the conditions but that relatively few clinical data were available in that patient age group;
- In general the clinical evidence represented patients with variable/heterogeneous age and disease severity;
- MSAC may wish to consider, once the above information is available, whether patient age should be specified in the MBS item descriptor.

The clinical algorithm proposed should be modified to show CCXL either at or before the trial of glasses and/or soft contact lenses, given that the procedure is proposed as first line management.

The application would benefit from including more detail to support the natural history of the conditions being treated, including rates, with evidence, of expected progression to corneal transplant; need for other interventions; and time to progression in the second eye.

With respect to an appropriate MBS item descriptor:

- Anaesthetic drops to be used during the procedure should be specified in the descriptor.
- MSAC may also wish to consider including a once per lifetime per eye treatment criterion.

A number of other interventions were likely to be co-administered with CCXL, including at least two that are not MBS items (ultrasonic pachymetry and partial coherence laser interferometry).

The proposed fee is \$1500. PASC suggested \$900-\$1300 (a range defined by current cataract surgery and corneal transplant items). However, consumers advise the procedure currently costs \$2000–3000 per eye (\$4000–\$6000 for both eyes) suggesting that patient out of pocket costs may be high.

The CCXL procedure requires 0.1% riboflavin eye drops, which are not currently registered on the Australian Register of Therapeutic Goods and would either need to be approved by TGA or continue to be supplied under the TGA's Special Access Scheme.

## **15. Other significant factors**

Nil.

## **16. Applicant's comments on MSAC's Public Summary Document**

Keratoconus is a disease primarily starting in the late teenage years or early twenties. Some cases are mild and manageable by simple measures such as glasses and contact lenses. A significant percentage however go on to need corneal transplantation. Indeed Keratoconus is the commonest single indication for corneal transplantation [Australian Corneal Graft registry]. Although transplants are relatively successful in the very long term the rate of failure increases and so a percentage of patients end up with severe disability. A treatment to prevent this sequence of events is highly desirable, and as an intervention in young people comparable to childhood immunisation and fluoridation of water.

## **17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the [MSAC Website](#).