MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
4th November 2019

Agenda Item No	
National Programme	Internal Medicine
Clinical Reference Group	Specialised Renal and Specialised Ophthalmology
URN	1832

Title
Mercaptamine hydrochloride for corneal cystine deposits in people aged older than 2 years.

Actions Requested	1. Support the policy proposition.
	2. Recommend its relative priority

Proposition
This policy proposition is to provide a treatment for patients with a rare metabolic disease called cystinosis. All people with cystinosis have cystine crystals in their corneas which if left untreated can cause damage to the eye and visual impairment later in life. The current treatment is unlicensed and requires dosing up to 12 times a day. The new licensed product is considered more effective, is more stable as a compound and requires much less frequent application.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; and Clinical Panel Report.
2.	The Head of Acute Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the

	budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition – Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.		
No	*Metric*	*Summary from evidence review*
1.	Survival	Not assessed
2.	Progression free survival	Not assessed
3.	Mobility	Not assessed
4.	Self-care	Not assessed
5.	Usual activities	Not assessed
6.	Pain	Patients reported pain at instillation on a 0-100mm visual analogue scale (VAS) where higher values indicated more pain. The best evidence of changes in the pain at instillation VAS) came from Labbé et al. (2014). At 30 days follow-up the mean pain-intensity VAS score was 27mm (standard deviation; SD 19.7) higher for people treated with viscous eye drops than people receiving aqueous eye drops (mean score of 7.3 [SD 8.7] mm). At 5 years (60 months) follow-up, pain at instillation decreased to a mean value of 7mm on the VAS. These results suggest the reported experience of pain at instillation of people receiving viscous mercaptamine hydrochloride 0.55 % eye drops decreases over time and that patients may become more tolerant of the pain as time goes on which may be decrease over time.

		The results should be interpreted with caution because although Labbé et al. (2014) provides longer term evidence, this was a small phase I/ phase II study, which mainly focused upon safety and was considered in a very small population of 8 people.
7.	Anxiety / Depression	Not Assessed
8.	Replacement of more toxic treatment	Not Assessed
9.	Dependency on care giver / supporting independence	Not Assessed
10.	Safety	Safety assessments were carried out in both studies. The best evidence comes from Labbé et al. (2014), because safety was the main purpose of that study. At 5 years (60 months) follow-up 7 patients reported 73 adverse events (AEs) of which 4 people (50%) reported severe AEs; 6 people (75%) reported serious AEs and 2 people (25%) reported drug-related AE and 1 person (12.5%) reported a treatment emergent AE. There were no AEs which lead to discontinuation and no deaths. Local adverse drug reactions (LADRs) were reported by 7 people (87.5%) experiencing stinging after instillation; 6 people (75%) with blurred vision after instillation and 4 people (50%) reported burning or eye irritation after instillation. The medium length of time for experiencing a LADR was 5 seconds, with a maximum length of 17.5 seconds. Similar results were reported in Liang et al. (2017), 2 people in each treatment group reported serious AEs. There were no treatment emergent serious AEs in either treatment group and no severe AEs or deaths. Most of the LADRs were described as mild or moderate in intensity (83.4%). More than 98% of the LADRs at instillation lasted less than 1 hour. These results suggest treatment with viscous mercaptamine hydrochloride 0.55% eye drops were generally well-tolerated. Pain and stinging subside soon after eye drops are administered. Results should however be considered with caution because Liang et al. (2017) had an open-label design and short-term (90 day) follow-up. Although Labbé et al. (2014) 1 provides longer term evidence, this was a small phase I/ phase II study, which mainly focused upon safety and was considered in a small population of 8 people.

11.	Delivery of intervention	Not assessed

Other health metrics determined by the evidence review		
No	Metric	Summary from evidence review
1	Reduction of corneal cystine crystal deposits	The best evidence came from Liang et al. (2017), a 90-day, phase III randomised open-label superiority trial in 31 people aged 2 years and older with corneal cystine crystals caused by nephropathic cystinosis. This study reported a 40.4 % (range -64.7 to -8.3) reduction in people receiving viscous eye drops compared with a 0.7 % (range -46.9 to 63.1) reduction in people receiving aqueous eye drops, representing a statistically significant decrease ($p<0.0001$) at 90 days follow-up. The statistically significant findings from Liang et al. (2017) were supported by longer term evidence from Labbé et al. (2014), an open label single arm 5-year follow-up study in 8 people with corneal cystine crystals. **Change in corneal cystine crystal scores (CCCS)** The findings from Liang et al. (2017) reported a statistically significant mean reduction in corneal cystine crystal density at 90 days follow-up of -0.59 (SD 0.52) CCCS points for people receiving viscous eye drops compared with a mean increase of 0.11 (SD 0.24) CCCS points for people receiving aqueous eye drops ($p=0.0015$). Although statistical significance was not reported, the results from Labbé et al. (2014) found the mean CCCS decreased over a 4 year follow up. **Change in anterior segment optical coherence tomography (AS-OCT) measurement** In Liang et al. (2017), the AS-OCT results showed a statistically significant reduction in corneal cystine crystal depth of -46.3 µm (SD 55.3) at 90 days follow-up for people receiving viscous eye-drops compared with a mean increase of 10.6 (SD 43.6) µm for people receiving aqueous eye drops ($p=0.0031$). Results from Labbé et al. (2014) found the depth of crystal deposits also decreased over a 4-year follow-up. These results suggest that people receiving treatment with viscous mercaptamine hydrochloride 0.55% eye drops can result in a statistically significant greater reduction in corneal cystine deposits compared with treatment with aqueous cysteamine eye drops. For patients, this means that over time, they can expect their corneal crystals to reduce which can lead to lead to an improvement in vision and photophobia (if they had it prior to starting treatment).

		Results should however be considered with caution because Liang et al. (2017) had an open-label design and short-term (90 day) follow-up. Although, Labbé et al. (2014) provides longer term evidence, this was a small phase I/ phase II study, which mainly focused upon safety and was considered in a small population of 8 people.
2	Maintenance or improvement of vision	Maintenance of vision was assessed by looking at ocular safety outcomes. These included an assessment of visual acuity (clarity of vision) and visual contrast sensitivity (the ability to differentiate between certain shades of light versus dark colours). Visual acuity was assessed using a logMAR scale (several rows of letters which decrease in size on each row). A negative (-) value shows an improvement in visual acuity. Visual contrast sensitivity was measured using a logarithmic scale (where the contrast compared to the letter background varied on each row). **Visual acuity** The best evidence came from Liang et al. (2017). Visual acuity improved in both treatment groups at 90 days follow-up, although statistical significance was not reported. The absolute change in visual acuity showed an improvement of -0.10 (SD 0.15) logMAR for people receiving viscous eye drops compared with an improvement of -0.07 (SD 0.15) logMAR for people receiving aqueous eye drops. **Visual contrast sensitivity** In Liang et al. (2017) there was also an improvement in visual contrast sensitivity. The absolute change in visual contrast sensitivity showed an improvement of -0.20 (SD 0.27) log units at 90 days follow-up for people receiving viscous eye drops compared with an improvement of -0.14 (SD 0.20) log units for people receiving aqueous eye drops but did not report statistical significance. These results suggest that over a 90-day period treatment with viscous mercaptamine hydrochloride 0.55% eye drops is just as effective (no better or worse) as treatment with aqueous mercaptamine hydrochloride 0.10% eye drops in maintaining visual ability in people with corneal cystine crystal deposits and normal vision was maintained in a small cohort of 8 people over a 5-year follow-up. For patients, this suggests they could expect their vision to be maintained over time and not deteriorate due to corneal cystine crystals. The results should be considered with caution, as it is very difficult to show statistical significance at a short follow-up,

		because visual ability usually declines over a period of years in patients with cystinosis. Additionally, Liang et al. (2017) had an open-label design and short-term (90 day) follow-up and decline in visual acuity and contrast sensitivity usually develops over a much longer period (years) as crystal deposition worsens and complications may occur. Although Labbé et al. (2014) provides longer term evidence, this was a small phase I/ phase II study, which mainly focused upon safety and was considered in a small population of 8 people.
3	Improvement in symptoms- Clinician and patient assessed photophobia	The best evidence came from Liang et al. (2017) where the absolute change in clinician assessed photophobia showed a statistically significant decline in photophobia scores at 90 days follow-up of -0.63 (SD 0.77) points for people receiving viscous eye drops compared with a small change of 0.07 (SD 0.44) points for people receiving aqueous eye drops (p=0.0048). This was supported by findings from Labbé et al. (2014) which also found the mean clinician assessed photophobia score decreased over a 5 year follow up (statistical significance was not reported). **<u>Patient reported photophobia</u>** In Liang et al. (2017) the patients reported mean photophobia score decreased from baseline by -0.27 (SD 0.58) points at 90 days follow-up for people receiving viscous eye drops compared with a small increase of 0.23 (SD 0.72) points for people receiving aqueous eye drops. These results suggest that photophobia can decrease over a 5-year period and result in a statistically significant greater reduction in photophobia over a 90 day follow up in people with corneal cystine crystal deposits. For patients, this means that over time, they can expect a reduction in photophobia (if they had it prior to starting treatment) which can lead to improved vision. The results should however be considered with caution because Liang et al. (2017) had an open-label design and short-term (90 day) follow-up. Although Labbé et al. (2014) provides longer term evidence, this was a small phase I/ phase II study, which mainly focused upon safety and was considered in a small population of 8 people.
4	Improvement in symptoms- Corneal irregularities	The fluorescein corneal staining test was used to identify any corneal abrasions and scratches, or irregularities on the cornea, or degenerative changes in corneal shape, which would show on the surface of the eye. The best evidence came from Liang et al. (2017) which

		found the absolute change in total number of irregularities identified by the fluorescein staining test reduced by -1.5 (SD 3.2) points for people receiving viscous eye drops at 90 days follow-up compared with a reduction of -0.6 (SD 2.5) points for people receiving aqueous eye drops. These results suggest that corneal irregularities identified through corneal staining improved with both viscous and aqueous eye drops, but that people treated with the viscous eye drops improved by an additional point in the fluorescein staining test. For patients, this suggests they could expect corneal irregularities to reduce and their vision to not deteriorate due to complications of corneal cystine crystals. The results should be interpreted with caution because Liang et al. (2017) had an open-label design and short-term (90 day) follow-up. Although Labbé et al. (2014) provides longer term evidence, this was a small phase I/ phase II study, which mainly focused upon safety and was considered in a very small population of 8 people. In addition, the mean age (12.1 years) of the sample population included in Labbé et al. (2014) may have confounded interpreting the IOP results as the authors of that study noted that IOP normally raises by about 0.85 mm Hg per year in children until they reach adult levels.
5	Change in intraocular pressure	The best evidence came from Liang et al. (2017) which found the absolute mean change in IOP at 90 days follow-up was 15.0 (SD 3.2) mm Hg for people receiving viscous eye drops compared with a mean change of 13.0 (SD 3.0) mm Hg in people receiving aqueous eye drops but did not report statistical significance. Results from Labbé et al. (2014) found the mean IOP increased during the study period from 11.8 (SD 2.5) mm Hg at baseline to 14.8 (SD 2.3) mm Hg at 4 years follow-up. These results suggest IOP changes varied and over a long-term follow-up showed increases in IOP, but this remained in the normal range for healthy eyes which is between 5 mm Hg and 22 mm Hg and the increase could be explained by normal annual increase in children's IOP. For patients, this evidence suggests that they could expect their ocular pressure to remain in a healthy range and not deteriorate due to cystine crystals in their corneas. The results should be interpreted with caution because Liang et al. (2017) had an open-label design and short-term (90 day) follow-up. Although Labbé et al. (2014) provides longer

		term evidence, this was a small phase I/ phase II study, which mainly focused upon safety and was considered in a very small population of 8 people. In addition, the mean age (12.1 years) of the sample population included in Labbé et al. (2014) may have confounded interpreting the IOP results as the authors of that study noted that IOP normally raises by about 0.85 mm Hg per year in children until they reach adult levels.
6	Health Related Quality of Life	Health related quality of life was measured using the Comparison of Ophthalmic Medications for Tolerability (COMTol) questionnaire. COMTol is a 37-item tool with 13 domains and 4 global questions and measures the extent to which any limitations in routine living activities (caused by side effects of topical eye treatment) interfere with health-related quality of life, medication compliance, and patient satisfaction with their treatment. Liang et al. (2017), reported that prior to the study 2 patients were very satisfied, 2 patients were somewhat satisfied, and 1 patient was very dissatisfied with their aqueous eye drops treatment. At 90 days follow-up 2 patients were very satisfied and 3 patients were somewhat satisfied with the viscous eye drops treatment and all 5 patients indicated a preference for the viscous eye drops over their previous aqueous treatment). All 5 of the patients who completed the questionnaire reported overall satisfaction with receiving viscous mercaptamine hydrochloride 0.55% eye drops. The results should be interpreted with caution because Liang et al. (2017) had an open-label design and short-term (90 day) follow-up. In addition, the COMTol questionnaire was only provided to adult patients and was completed by only 5 of the adult patients participating in Liang et al. (2017).

Considerations from review by Rare Disease Advisory Group
RDAG commented that there were some uncertainties in the evidence presented. They highlighted the differences in concentrations of the drop solutions, objective measurement of outcome measures and the need for longer term data collection. RDAG also noted the potential significant positive impact on patient compliance and convenience as a result of reduced frequency of administration and were keen that rollout should not be delayed if the drug were approved by CPAG.

Pharmaceutical considerations
The clinical commissioning policy supports the use of mercaptamine hydrochloride eye drops for corneal cystine deposits in people aged older than 2 years which is its licensed indication. It is excluded from tariff.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Internal Medicine National Programme of Care Business Meeting on 14th August 2019 and reported to the full Board September 2019.