NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Clinical evidence review of mercaptamine hydrochloride for treating corneal cystine deposits in people with cystinosis aged older than 2 years

NHS England unique reference number URN1832 / NICE ID019

First published: April 2019

Updated: not applicable

Prepared by: NICE on behalf of NHS England Specialised Commissioning

About this clinical evidence review

Clinical evidence reviews are a summary of the best available evidence for a single technology within a licensed indication, for commissioning by NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

This evidence review considers mercaptamine (also known as cysteamine) hydrochloride 0.55% viscous eye drops (Cystadrops; Orphan Europe) for treating corneal cystine deposits in people aged 2 years and older with cystinosis. Cystinosis is a condition characterised by accumulation of the amino acid cystine (a building block of proteins) within cells. Excess cystine damages cells and often forms crystals that can build up and cause problems in many organs and tissues. The increase of these crystals in the eye causes pain and an increased sensitivity to light (photophobia). Untreated cystinosis can lead to blindness.

Evidence of the effect of mercaptamine hydrochloride 0.55% viscous eye drops comes from a phase III, 90 -day, double-blind, randomised superiority trial which compared mercaptamine hydrochloride 0.55% viscous eye drops with mercaptamine hydrochloride 0.10% aqueous eye drops and included 31 patients (mean age 17.1 years; Liang et al. 2017 [CHOC]). This was supported by a phase I/IIa long-term (up to 60 months) uncontrolled, dose-response open-label observational study including 8 patients (mean age 12.1 years; Labbé et al. 2014 [OCT-1]). Patients in these studies had a confirmed diagnosis of corneal cystine crystals caused by cystinosis. Additional supportive evidence came from data considered by the European Medicines Agency (EMA) during its regulatory process and published in the European Public Assessment Report (EPAR), in 106 patients receiving mercaptamine hydrochloride 0.55% viscous eye drops on a named-patient use (NPU) programme.

Effectiveness

The primary outcome of interest was the reduction in corneal cystine crystal deposits. Evidence from the 90-day phase III superiority trial (Liang et al. 2017) found that treatment with mercaptamine hydrochloride 0.55% viscous eye drops is associated with a statistically significant greater reduction of corneal cystine crystal deposits measured by in vivo confocal microscopy (a laser imaging technique which examines the 7 corneal layers) than mercaptamine hydrochloride 0.10% aqueous eye drops (40.4% and 0.7% respectively; $p<0.0001$). The evidence from Liang et al. (2017) also reported a statistically significant mean reduction in corneal cystine

crystal density at 90 days follow-up of -0.59 (SD 0.52) for people receiving viscous eye drops compared with a mean increase of 0.11 (SD 0.24) in corneal cystine crystal score (assessed using a slit lamp and graded on a scale from 0 to 3.0) for people receiving aqueous eye drops (p=0.0015). Results from anterior segment optical coherence tomography (AS-OCT) also showed a statistically significant reduction in corneal cystine crystal depth at 90 days follow-up of -46.3 (SD 55.3) micrometres (µm) 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 at 4-year follow-up from the phase I/IIa observational study (Labbé et al. 2014) found the mean in vivo confocal microscopy score had reduced by 29.9% (SD 26.29) representing a statistically significant decrease (p=0.001). At 5-year follow-up, results also reported a mean reduction from baseline in corneal cystine crystal deposits by -3.4 (SD 2.8) in vivo confocal microscopy points, representing a 32.7% (SD 25.4) reduction, although statistical significance was not reported (details reported in the EPAR only). This outcome suggests that people who use mercaptamine hydrochloride 0.55% viscous eye drops as a treatment for corneal cystine crystals in cystinosis can expect a statistically significant greater reduction in the number of crystals compared to treatment with mercaptamine hydrochloride 0.10% aqueous eye drops.

Maintenance of vision was assessed by visual acuity and visual contrast sensitivity testing. Evidence from Liang et al. (2017) found visual acuity improved in both treatment groups at 90 days follow-up, although statistical significance was not reported. Using the logMAR scale, improvements in visual acuity of -0.10 (SD 0.15) units were observed in people receiving viscous eye drops compared with an improvement of -0.07 (SD 0.15) units (statistical significance not reported) for people receiving aqueous eye drops (where a negative score indicates an improvement). Visual contrast sensitivity also improved at 90 days follow-up. Using a logarithmic scale, improvements in visual contrast sensitivity of -0.20 (SD 0.27) units were observed in people receiving viscous eye drops compared with an improvement of -0.14 (SD 0.20) units for people receiving aqueous eye drops. In Labbé et al. (2014), best corrected visual acuity remained stable throughout the study period with a mean change in logMAR of 0.1 (SD 0.1) units from baseline to 48 months (4 years) follow-

up. These results suggest that over a 90-day follow-up period of treatment with viscous mercaptamine hydrochloride 0.55% eye drops is just as effective as treatment with aqueous mercaptamine hydrochloride 0.10% eye drops in maintaining visual acuity in people with corneal cystine crystal deposits, however statistical significance can only usually be shown over a period of years. Normal vision was maintained over a 5-year period in a cohort of 8 people.

Changes in photophobia (light sensitivity) were assessed in each eye by a clinician on a 0 (absence of light sensitivity) to 5 (extreme sensitivity) point scale using a slit-lamp. Results from Liang et al. (2017) found a statistically significant reduction 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 increase (0.07 [SD 0.44]) in people receiving aqueous eye drops ($p=0.0048$) and an estimated mean difference between groups of 0.69 (95% CI 0.23 to 1.14) points ($p<0.0048$). Labbé et al. (2014) also reported a decline in the mean clinician assessed photophobia scores from 2.8 (SD 1.1) points during the run-in period (while patients were receiving standard aqueous eye-drops regimen) to a mean score of 1.6 (SD 1.0) points at 60 months (5 years) follow-up, although they did not report statistical significance. These results suggest that photophobia can continuously decrease over a 5 year follow–up as a result of treatment with viscous mercaptamine hydrochloride 0.55% eye drops and can result in a statistically significant greater reduction in photophobia over a 90 day follow-up in people with corneal cystine crystal deposits compared with aqueous mercaptamine hydrochloride 0.10% eye drops.

Corneal irregularities (caused by epithelial erosions indicating damage to the cornea or ocular surface) were identified using a fluorescein corneal staining test (which helps detect corneal damage). Liang et al. (2017) reported the total number of epithelial erosions 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, although statistical significance was not reported. These results suggest there was no worsening of corneal staining in either treatment group during the 90-day follow-up period.

Changes in intraocular pressure (IOP), the pressure within the eye, was measured in the studies. In Liang et al. (2017) the mean measure of IOP recorded at 90 days follow-up was 15.0 (SD 3.2) mmHg for people receiving viscous eye drops compared with a mean value of 13.0 (SD 3.0) mmHg in people receiving aqueous eye drops but did not report statistical significance. study In Labbé et al. (2014), the mean IOP increased during the study period from 11.8 (SD 2.5) millimetres of mercury (mm Hg) at baseline to 14.8 (SD 2.3) mm Hg at 48 months (4 years follow-up) but did not report statistical significance but remained in the normal range for healthy eyes which is between 5 mm Hg and 22 mm Hg. Results suggest intraocular pressure changes varied and over a long-term follow-up showed increases but this could be explained by normal, age-related annual increase in children's IOP.

Health related quality of life was assessed using the Comparison of Ophthalmic Medications for Tolerability (COMTol) questionnaire (a 37-item tool which 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. Results from Liang et al. (2017) reported at 90 days follow-up found, of the 5 people completing the questionnaire, 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. Health related-quality of life was not reported in Labbé et al. (2014). These results suggest that at 90 days follow-up of the 5 patients who completed the questionnaire, reported overall satisfaction with receiving viscous mercaptamine hydrochloride 0.55% eye drops.

Safety and tolerability

Safety was the main purpose of Labbé et al. (2014) but was also considered in Liang et al. (2017). In Labbé et al. (2014), 7 out of 8 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 at 5 years follow-up. There were no AEs reported as leading to discontinuation and no deaths. Local adverse drug reactions were also reported. Out of 8 patients, 7 people (87.5%) reported stinging after eye drops were administered; 6 people (75%) reported blurred vision after eye drops were

administered and 4 people (50%) reported burning or eye irritation after administration. The medium length of time for experiencing a local adverse drug reaction was 5 seconds. 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 local adverse drug reactions were described as mild or moderate in intensity (83.4%). More than 98% of the local adverse drug reactions at instillation lasted less than 1 hour. These results suggest treatment with viscous mercaptamine hydrochloride 0.55% eye drops were generally well-tolerated.

Pain when eye drops were administered was reported on a 0-100 mm visual analogue scale (VAS) and was reported in Labbé et al. (2014) only. Results found at 30 days follow-up the mean pain-intensity VAS score was 27 (SD 19.7) mm higher for people treated with viscous eye drops compared with people receiving aqueous eye drops, which reported a mean score of 7.3 (SD 8.7) mm, although statistical significance was not reported. At 5 years (60 months) follow-up, the reported pain when eye drops were administered decreased to a mean value of 7mm on the VAS. The results suggest the reported experience of pain at instillation of people receiving viscous mercaptamine hydrochloride 0.55% eye drops decreases over time.

Evidence gaps and limitations

There were several limitations with the main study, although Liang et al. (2017) was a phase III superiority design. The strength of concentration (0.10%) of the aqueous formulation comparator in Liang et al. 2017 does not represent the current standard of care in England (which is a 0.55% concentration), and the EPAR noted that the comparator is generally recommended to be applied every hour while awake rather than the 4 times per day dose used during the study, however, in practice, hourly administration is not usually maintained and therefore efficacy can be compromised.

There are some questions surrounding the methods used in the studies. In OCT-1, (Labbé et al. 2014), it is unclear if clinician assessed photophobia scores were made by masked assessors and this therefore has some concern for potential bias. In addition, the baseline data from Liang et al. (2017) showed people receiving viscous

eye drops had a higher mean baseline corneal straining reading than those receiving aqueous eye drops. Although statistical significance of baseline reading was not reported, it is not clear how this may have influenced follow-up results.

The unit of analyses in both studies was per eye, rather than by the unit of randomization (per patient). The authors of both studies corrected for this by adjusting their statistical analysis using the generalised estimator equation (GEE) which accounted for the correlation between each eye and the repeated observations for each patient.

Both Liang et al. (2017) and Labbé et al. (2014) were conducted in a French population with nephropathic cystinosis, additionally, although 38.7% of people taking part in Liang et al. (2017) were adults, the mean ages of both populations (17.1 years in Liang et al. 2017 and 12.1 years in Labbé et al. 2014) means there is limited evidence representing older age groups and for the sub-types with juvenile nephropathic cystinosis or non-nephropathic cystinosis.

There is limited evidence of health-related quality of life. The COMTol questionnaire was only completed by 5 adults only in Liang et al. 2017 and therefore it is difficult to generalise findings.

Liang et al. 2017 had a short-term follow-up of 90 days, providing limited efficacy and safety analysis. Data from un-controlled settings provides support for longer term efficacy and safety. The French NPU programme (reported in the EPAR) provides observational analysis over a mean period of 7 months however published evidence is limited. Longer term data is available from Labbé et al. 2014; up to 5-year follow-up), but this involved a small sample of 8 patients and again, it is therefore difficult to generalise findings.

Table of contents

Summary 2
Effectiveness 2
Safety and tolerability 5
Evidence gaps and limitations 6
Table of contents 8
Abbreviations 9
Medical definitions 9
1 Introduction 10
Disease background 10
Focus of review 12
Epidemiology and needs assessment 12
Product overview 16
Treatment pathway and current practice 17
2 Evidence 18
Literature search 18
Overview of included studies 19
Key outcomes 20
Evidence gaps and limitations 29
Overall conclusions 31
3 Related NICE guidance and NHS England clinical policies 40
4 References 40
Appendix 1 Search strategy 43
Appendix 2 Study selection 48
Appendix 3 Evidence tables 53
Appendix 4 Results tables 59
Appendix 5 Grading of the evidence base 64

Abbreviations

Term	Definition
vCH	Cysteamine hydrochloride (viscous formulation)
CH	Cysteamine hydrochloride (aqueous formulation)
IVCM	In vivo confocal microscopy
AS-OCT	Anterior segment optical coherence tomography
IOP	Intra ocular pressure
EMA	European medicine's agency
EPAR	European public assessment report
VAS	Visual analogue scale
AE	Adverse event
LADR	Local adverse drug reaction
COMTol	Comparison of ophthalmic medications for tolerability questionnaire

Medical definitions

Term	Definition
Cystinosis	A rare inherited disease caused by a mutation to the CTNS gene (which encodes the protein cystine) and produces the build-up of cystine crystals in the human body
Cystine	A natural chemical (amino acid) which is found in proteins in the body
Corneal cystine crystals	The build-up of cystine crystals in the cornea of the eye
Cysteamine (also known as mercaptamine)	A medicine which reduces the build-up of cystine in areas of the body and reduces symptoms caused by cystinosis
Instillation	Administration of a liquid drop by drop

1 Introduction

Disease background

1.1 Cystinosis is a rare inherited disease caused by a genetic metabolic disorder which causes the build-up of a natural chemical called cystine. This creates damaging crystals to form in areas of the body such as the kidneys and tissues of the eye. These crystals can also develop in other areas of the body, including the muscles, pancreas, liver, thyroid gland and white blood cells.

1.2 There are 3 different subtypes of cystinosis: nephropathic infantile cystinosis (which starts in the kidneys and is seen in babies and children under the age of 2); nephropathic juvenile cystinosis (starting in the kidneys and found in children aged older than 2); and adult non-nephropathic or ocular cystinosis (involving only crystals in the cornea of the eyes and mainly seen in people later in life). Corneal crystals start in the first year of life and are visible in all areas of the cornea by around 16 months of age (Gahl et al. 2000). All people with cystinosis (regardless of specific subtypes) have corneal cystine crystals (Shams et al. 2014).

People with cystinosis may develop crystal deposits initially in the conjunctiva and cornea and may develop symptoms such as photophobia (light sensitivity), blepharospasm (involuntary closure of the eye) or eye pain. More severe complications can develop as patients grow older. These symptoms can include increased glare disability, reduced visual contrast sensitivity (ability to distinguish between finer increments of light versus dark; affected especially in situations of low light, fog or glare), increased corneal thickness, secondary glaucoma and visual impairment which can increasingly progress with age. Visual acuity is usually not affected in very young people, but corneal complications in older people may lead to visual impairment or blindness. As patients with the condition are now living longer, the long term consequences of the ocular effects of cystinosis are significant and can include symptoms such as corneal

calcific band keratopathy, corneal punctate epithelial erosions or filamentary keratopathy (diseases of the eye surface); corneal neovascularisation (the growth of blood vessels into the cornea which can interfere with vision) and iris abnormalities, such as posterior synechiae, (where the iris adheres to the lens surface and can lead to secondary glaucoma) and iris thickening are increasingly seen in older patients (Tsilou et al. 2002).

A survey designed by Metabolic Support UK and Cystinosis Foundation UK to capture patients' experience and thoughts on the treatment options available for people living with corneal cystine crystal deposits caused by cystinosis. Including both patients and carers, 22 people based in the UK responded, (18 people were based in England and 4 were based in Scotland). Of those responding, 21 reported using aqueous eye drops.

Most patients described their eyes as feeling itchy, gritty and "like they have sand in their eyes". Other symptoms included watery eyes, blurred vision, eye soreness, eye pain, eye irritation and dry eyes, as well as migraines and headaches. Of the 10 patients, each reported some degree of light sensitivity which ranges from being uncomfortable looking at bright lights to not being able to tolerate daylight at all. Conducting daily activities like driving or playing outside are made difficult due to needing sunglasses all the time (indoors and outdoors).

The 12 carers responding emphasised how disruptive the disease is to patients and their families lives. Examples of the disruption includes, having to administer the aqueous eye drops frequently and at regular intervals which can be time consuming and can be difficult. Having to carry cool bags and ice packs when out of the house to store the eye drops is also extremely disruptive.

Patients find it difficult to comply with treatment due to the long order and delivery wait times (3 weeks), the short shelf life (3-4 weeks). Most patients responding stated they were not satisfied with their current

treatment and described the difficulty of refrigerating, using and storage as a major issue.

The main treatment for people with cystinosis is oral cysteamine (given as capsules) which reduce the build-up of cystine and reduce or delay organ and tissue damage. Although cysteamine tablets are effective at reducing cystine crystals in other areas of the body, they do not help to reduce the crystals in the eye (Shams et al. 2014) because the drug cannot permeate the cornea due to its lack of blood vessels.

Focus of review

1.3 In line with the marketing authorisation the focus of this review is on viscous mercaptamine (also known as cysteamine) hydrochloride 0.55% eye drops "for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis".

Epidemiology and needs assessment

1.4 The global incidence of cystinosis is estimated between 1 in 100,000 and 1 in 200,000 live births worldwide (Emma et al. 2014). Prevalence is estimated at 2000 individuals worldwide (Doyle & Werner-Lin. 2015). There are between 2 and 3 new cases diagnosed in England each year. A UK study on the incidence of certain genetic disorders in the West Midlands (1981-1991) recorded 21 new cases of cystinosis born in this time period (Hutchesson et al. 1998), and there is no particular geographical distribution in the UK. There are 159 patients (84 children and 75 adults) in England who are currently receiving treatment with systemic cysteamine (Cystagon, Orphan Europe, internal data). Table 1 below shows a breakdown of patient numbers. Only 6 patients registered with the Cystinosis Foundation UK (CF UK) have the rare form of ocular (non-nephropathic) cystinosis.

Table 1 Patient numbers

Estimates	Data Source	Number of people
Population in England in mid-2016	Office for National Statistics	55,268,000
Prevalence: 1/100,000 to 1/200,000 of live births	Orphanet	553 (low end of the range)
Diagnosed	Orphan Europe UK	220 (UK and Ireland)
Treated with systemic cystinosis treatment	Orphan Europe UK	208 (UK and Ireland) 159 England
Number of people registered with ocular cystinosis	Cystinosis Foundation UK	6 England
Number of people covered by licence in England (eligibility)	Combination of above sources	165 England

1.5 Cystinosis is a rare condition which means diagnosis and treatment can be frequently delayed (Emma et al. 2014). Current treatment for corneal cystine crystals requires administration of aqueous mercaptamine hydrochloride eye drops which dissolve the cystine crystal deposits in the cornea of the eye (Iwata et al. 1998). In England, there have previously been no licensed treatments for corneal cystine crystals, although unlicensed solutions of aqueous mercaptamine hydrochloride (0.55%) are produced under the terms of a `Specials` licence and stored locally by Guy's and St Thomas' NHS trust. The active substance oxidises within the first week after storage at a temperature of +4°C (stored in a refrigerator) and this makes the preparation less effective. The preparation therefore

needs to be stored in the freezer at a temperature of −20°C to maintain effectiveness (Reda et al. 2017).

1.6 Aqueous mercaptamine 0.5% eye drops have been shown to be effective at reducing crystals from the cornea administered hourly during waking hours. In a case report of 2-year-old patient with nephropathic cystinosis and severe corneal crystal deposits, Jones et al. (1991) found that after 3 months treatment with aqueous mercaptamine 0.5% eye drops in 1 eye only, crystals were completely cleared from the central corneal region, and substantially cleared from the peripheral cornea. Photophobia had also reduced. However, a recent retrospective case series based in England of 22 paediatric patients with infantile nephropathic cystinosis (median age at first ophthalmological examination 2.6 years) noted a high presence of photophobia even in young people who were receiving aqueous mercaptamine hydrochloride (0.55%) eye drops up to 10 or 12 times a day. Other eye-related complications included, red and swollen eyes (blepharitis), eye-lid styes (chalazia)eyelid and irregularities of the eyelid margins, corneal erosions, and optic nerve swelling (Biswas and Sornalingam. 2018).

1.7 Recent international consensus statements on the treatment and care of people with cystinosis have recommended aqueous mercaptamine hydrochloride (0.55%) at a dose of 1 drop per eye and a frequency of 6 to 10 or 10 to 12 times per day (Emma et al. 2014; Ariceta et al. 2015).

1.8 The frequent application and storage requirements of the current aqueous eye drop solutions make it difficult for people with corneal cystine crystals to comply with administration of the existing treatment options (Shams et al, 2014). The acidic formulations can cause burning sensations which can be annoying for children and hinder compliance (Elmonem et al, 2016). Previous evidence from a randomised controlled trial (RCT) comparing 2 solutions of the aqueous mercaptamine hydrochloride 0.5% eye drops found that of the 5 patients who did not show a significant reduction in crystal score at 6 months follow-up, 3 of these 5 patients reported poor compliance, whereas the 2 patients whose crystal score

had significantly reduced at 6 months follow-up reported administering the eye drops eight times a day (Iwata et al, 1998).

1.9 Additional evidence from an RCT comparing hourly administration of aqueous mercaptamine hydrochloride 0.1% and 0.5% eye drops with placebo in 29 people found that more than half of the patients whose eyes showed no difference to treatment, were not compliant with their therapy. Although the authors did not report reasons for non-compliance, they suggested this may have been due to a lack of adherence to medical recommendations, creating a lapse in administering eye drops (Kaiser-Kupfer et al. 1990).

1.10 When aqueous mercaptamine formulations are applied less frequently, results have shown mixed findings. In a double-blind, non-randomised study of 4 patients with corneal cystine crystal deposits, MacDonald et al (1990) compared 1 drop of topical cysteamine 0.3% eye drops in one eye, with 1 drop of saline eye drops in the other eye, 4 times a day. Over a 7-month follow-up results found there was no reduction in crystal formation and no difference in visual acuity of the treated and untreated eyes.

1.11 The efficacy of aqueous mercaptamine hydrochloride 0.55% eye drops was recently studied in 32 people with nephropathic cystinosis and corneal crystals by Al-Hemidan et al. (2017). Over an average (mean) period of 4.1 years observational follow-up, patients received aqueous mercaptamine hydrochloride 0.55% eye drops every 2 hours during waking hours. The authors stated the response to topical aqueous cysteamine therapy was variable. 21 patients maintained the same grade of corneal deposits before and after treatment. There was a statistically significant increase of corneal cystine deposits in the remaining 11 patients and there was no clinically significant improvement of photophobia in symptomatic patients despite reported good compliance with the treatment regime. The authors suggested this may be due to a low concentration of cysteamine, poor absorption and severity of nephropathic cystinosis, and high concentrations of cystine in the cornea and interpreted these results to suggest that topical aqueous

mercaptamine hydrochloride (0.55%) eye drops may have limited effects in decreasing the corneal cystine deposits in patients with severe forms of nephropathic cystinosis.

Product overview

Mode of action

1.12 The viscous mercaptamine hydrochloride 0.55% eye drops provide a similar mode of action to the standard aqueous cysteamine eye drop formulations and work by reducing the build-up of cystine in the cornea, helping to reduce the volume and size of corneal crystal deposits and improve symptoms. The increased viscosity and gel-formulation allows greater permeation of the active ingredient into the cornea and extends the amount of contact the active substance has with the cornea. This allows the dosing frequency to be reduced. The viscous eye drops can also be stored at room temperature for the total period of in-use shelf life.

Regulatory status

1.13 Mercaptamine hydrochloride (0.55%) eye drops was granted a marketing authorisation by the European Medicines Agency (EMA) on the 19th January 2017. It is indicated for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.

Dosing information

1.14 The recommended dose is 1 drop in each eye, 4 times a day during waking hours, with a recommended interval between each instillation of 4 hours.

Depending upon ophthalmic examination results (such as, corneal cystine crystal deposits, photophobia) the dose can be gradually decreased (to a minimum dose of 1 drop in each eye per day).

For further details of dosing please see the summary of product characteristics.

Treatment pathway and current practice

1.15 Following a clinical suspicion of cystinosis, in young people aged 24 -36 months (based on symptoms of Fanconi syndrome) patients are usually referred to a regional specialist cystinosis centre for confirmatory diagnosis which are organised through 13 regional centres in the UK; 10 of these centres are based in England. Cystinosis is usually diagnosed by a nephrologist who refers the patient to an ophthalmologist to carry out an ophthalmic assessment and record symptoms of photophobia or watery eyes. Visual assessments involve an assessment of visual acuity (using Snellen or logMAR charts), and detection of crystals using the slit lamp biomicroscope or using a hand held slit-lamp in very young children (Biswas et al. 2018).

For people who have ocular symptoms only, diagnosis happens later in life, when corneal crystals develop in adults. An optician may see visible signs of corneal cystine crystals during an eye examination and will refer the patient to an ophthalmologist for an ophthalmic assessment (including assessments of visual acuity (using Snellen or logMAR charts), and detection of crystals (based on slit lamp assessments using a Gahl score, in vivo confocal microscopy and assessing the front section of the eye with anterior segment optical coherence tomography).

Once crystals are identified, treatment should start immediately. Patients usually receive the oral cysteamine capsules for non-ocular symptoms and will be offered treatment with the unlicensed aqueous eye drops for ocular symptoms. Treatment is usually overseen by a consultant nephrologist, but patients may also receive follow-up appointments by other medical specialists, including ophthalmologists, neurologists, endocrinologists, clinical geneticists, as well as specialist nurses (Cystinosis Foundation, UK). The timing and frequency of the follow-up appointments depends on the clinical status of the patient and is therefore variable but is usually on a 6-month or annual basis.

In the current pathway of care, patients receive unlicensed formulations of the aqueous cysteamine eye drops (Biswas et al, 2018). The only

currently available formulation in England is produced and distributed by Guys and St Thomas NHS Foundation Trust. In a report of a 5-year old's experience of using the aqueous eye drop formulation, Biswas et al. (2018) noted that "the patient complained about the dosage of the topical cysteamine solution and preservation method". In addition, after 4 years there was no obvious reduction in corneal cystine deposits identified using a slit-lamp and other microscopic corneal imaging assessment.

It is proposed that the new viscous cysteamine (mercaptamine) hydrochloride 0.55% eye drops will completely replace use of the unlicensed aqueous mercaptamine 0.55% eye drops in the treatment pathway. However, all other existing arrangements in the current treatment pathway would continue.

2 Evidence

Literature search

2.1 A literature search was done, which identified 499 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 19 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and 2 studies were included in the clinical evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

The company submission also identified the 2 studies previously identified for inclusion from the search strategy.

Additional data came from evidence published in the European Public Assessment Report (EPAR), which formed the base of the European Medicine's Agency (EMA) regulatory process. This related to an observational analysis of 106 patients over a mean duration of 7 months follow-up, receiving the viscous eye drops treatment on a named patient use (NPU) programme.

Overview of included studies

2.2 The evidence on clinical effectiveness is based upon 2 studies conducted in a French population. The best evidence came from a phase III randomised controlled superiority trial with 31 people and a 90-day follow-up comparing viscous mercaptamine hydrochloride eye drops CH 0.55% (n=15) with aqueous mercaptamine hydrochloride eye drops CH 0.10% (n=16; Liang et al. 2017). This evidence is supported by a phase I/IIa single arm dose-response trial of viscous mercaptamine hydrochloride eye drops CH 0.55% involving 8 people over a 5 year-follow up (Labbé et al. 2014; OCT-1). Both were open label studies that recruited adults and children with nephropathic cystinosis and corneal cystine crystal deposits. In Liang et al. 2017, the dose was fixed at 4 instillations per day for the duration of the trial whereas the daily dose was adjusted by the patient periodically throughout the follow-up period in Labbé et al. (2014). Additional efficacy data for these studies was considered by the European Medicines Agency and provided in the European Public Assessment Report (EPAR).

The main purpose of Labbé et al. (2014) was safety. Safety and tolerability data was also collected in Liang et al. 2017. Additional safety data was reported in the EPAR which analysed patient exposure to treatment in 106 patients from France who were provided viscous eye drops on a named patient use (NPU) basis. Data analysis for the NPU was based upon the period between September 2013 and March 2015.

A summary of the characteristics of the included studies is shown in Table 2 (please see Appendix 3- evidence tables for full details).

Table 2 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Liang et al. 2017 open label randomised phase III superiority trial	People aged 2 years or older with nephropathic cystinosis mean age 17.1 years n=31	vCH 0.55% eye drops compared with aCH 0.1% eye drops administered 4 times per day	Change from baseline in corneal cystine crystal density (measured by IVCM)

Labbé et al. 2014 open label dose response phase I/IIa safety trial	People aged 3 years or older with infantile nephropathic cystinosis and corneal crystal deposits mean age 12.1 years n=8	vCH 0.55% eye drops administered at median of 4 times per day (dose adaptation up to 48 months)	Absolute change in corneal cystine crystal density (measured by IVCM)
Abbreviations: vCH: viscous cysteamine hydrochloride; aCH: aqueous cysteamine hydrochloride; IVCM: In vivo confocal microscopy			

Key outcomes

2.3 The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 2 below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study are in appendices 3 and 4.

Effectiveness

Reduction of corneal cystine crystal deposits

2.4 The primary outcome in both studies was the change in total number of corneal cystine crystal deposits (corneal cystine crystal density). This was measured by in vivo confocal microscopy (IVCM). IVCM is a laser imaging technique which examines the 7 different layers of the cornea. The images were graded from 0 to 4 depending upon the density of crystals found in each corneal layer. The sum of scores for each corneal layer was totalled to give a 0-28 point composite overall score. In the studies the results showed the average (mean) score of 5 photographs for each corneal layer.

Liang et al (2017), reported the results for CHOC. At baseline, the mean IVCM total score was 10.6 (standard deviation [SD] 4.2; range 3.2 to 19.0) points for people receiving viscous eye drops compared to a mean score of 10.8 (SD 3.5; range 4.2 to 16.2) points for people receiving aqueous eye drops. At 90 days follow-up the IVCM total score reduced to a mean value of 6.0 (SD 2.1; range 2.0 to 9.6) points for people receiving viscous

eye drops compared with a mean value of 9.8 (SD 3.8; range 5.0 to 17.7) points for people receiving aqueous eye drops. This showed a statistically significant difference between treatment groups at 90 days follow-up (p=0.001). The EPAR reported this showed a statistically significant estimated mean difference between treatment groups of 3.84 points [95% confidence intervals (CI) 2.11 to 5.56 points; p<0.0001)]. The differences indicated a benefit of reduced deposits for people receiving viscous eye drops. The absolute change from baseline in IVCM score at 90 days follow-up showed a statistically significant reduction of corneal cystine deposits -4.6 points (SD 3.1), representing a 40.4% (range -64.7 to -8.3) reduction in people receiving viscous eye drops compared with a reduction of -0.5 points (SD 3.4) representing a 0.7% (range -46.9 to 63.1) reduction in people receiving aqueous eye drops, (p<0.0001).

Labbé et al (2014) reported the results for OCT-1. At 48 months (4 years) follow-up the mean IVCM showed a statistically significant reduction from baseline by -3.2 (SD 3.0) points, representing a 29.9 % (SD 26.29) (p<0.001). The results at 60 months (5 years) follow-up were only reported in the EPAR. Although statistical significance was not reported, the results showed a mean reduction from baseline by -3.4 (SD 2.8) points, representing a 32.7% (SD 25.4) reduction from baseline.

The second way the change in corneal cystine crystal deposits was measured was by examining the patient's eyes using a slit lamp. The slit-lamp is a high-intensity light which is used alongside a low-powered microscope to look closely at the eye. The slit-lamp was used to take photographs of the cornea and identify the density of corneal cystine crystals which were graded using Corneal Cystine Crystal Scores (CCCS) ranging from 0.00 (showing clarity in the centre of the cornea) to 3.00 (showing greatest crystal density).

In Liang et al. (2017), the mean baseline CCCS for people receiving viscous eye drops was 2.26 (SD 0.56) points compared with a mean baseline score of 1.98 (SD 0.50) points for people receiving aqueous eye drops. The change in corneal cystine crystal density at 90 days follow-up

showed a statistically significant mean reduction 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).

In Labbé et al. (2014) the mean CCCS decreased from 2.91 (SD 0.13) points at baseline to 2.78 (SD 0.22) points at 90 days follow-up. It decreased to 2.75 (SD 0.32) points at 48 months (4 years) follow-up. The results at 60 months (5 years) follow-up were not reported.

Another imaging technique (anterior segment optical coherence tomography; AS-OCT) was used to analyse the depth of corneal cystine crystal deposits and central corneal thickness in the front of the eye AS-OCT provides a cross-sectional view of anterior segment (front of the eye) anatomy and depth is measured in micrometres (µm). In Liang et al. (2017), the mean baseline value of the depth of corneal deposits was 306.4 (SD 98.9) µm for people receiving viscous eye drops compared with a mean value of 260 (SD 167) µm for people receiving aqueous drops. There was a statistically significant reduction -46.3 (SD 55.3) µm in corneal cystine crystal depth 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). In Labbé et al. (2014) the depth of crystal deposits decreased from a mean of 306.4 (SD 98.9) µm at baseline to a mean of 265.1 (SD 119.3) µm at 48 months (4 years) follow-up. The results at 60 months (5 years) follow-up were not reported.

Optical coherence tomography was also used to assess the central corneal thickness. In Labbé et al. (2014) the mean central corneal thickness increased from 543.1 (SD 28.6) µm at baseline to 552.8 (SD 27.3) µm at 48 months (4 years) follow-up. The results at 60 months (5 years) follow-up were not reported. Labbé et al. (2014) stated that the assessment of central corneal thickness and anterior segment structures “were not adversely modified during the 48-month follow-up”.

Maintenance or improvement of vision

2.5 Maintenance of vision was assessed by looking at ocular 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 (an eye chart comprised of several rows of letters which decrease in size on each row. LogMAR values quantify vision from 0.0 (normal vision) to 1.68 (unable to read any letter on a chart). Every letter has a value of 0.02 log units. A logMAR score reduces for every additional letter the patient is able to read correctly on the following lines of the chart, showing an improvement in visual acuity. Visual contrast sensitivity was assessed using a logarithmic scale, however the parameters of this scale were not reported.

In Liang et al. (2017), the mean baseline visual acuity (logMAR value) was 0.24 (SD 0.36) log units for people receiving viscous eye drops compared with a mean visual acuity (logMAR) of 0.16 (SD 0.30) log units for people receiving aqueous eye drops. Visual acuity improved in both treatment groups at 90 days follow-up, however statistical significance was not reported. The absolute change in visual acuity showed an improvement in logMAR of -0.10 (SD 0.15) log units for people receiving viscous eye drops compared with an improvement of -0.07 (SD 0.15) log units for people receiving aqueous eye drops, although statistical significance was not reported. In Labbé et al.(2014), best corrected visual acuity remained stable throughout the study period with a mean change in logMAR of 0.1 (SD 0.1) log units from baseline to 48 months (4 years) follow-up. The results at 60 months (5 years) follow-up were not reported.

In Liang et al. (2017), the mean baseline value for visual contrast sensitivity was 0.57 (SD 0.37) log units for people receiving viscous eye drops, compared with a mean value of 0.44 (SD 0.31) log units for people receiving aqueous eye drops. 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. Changes in contrast sensitivity were not considered in Labbé et al. (2014).

Improvement in symptoms

2.6 Changes in photophobia (light sensitivity) were assessed by the clinician using a slit-lamp and graded using a 0 to 5 point scale (where 0 showed an absence of symptoms and 5 showed extreme symptoms).

The mean baseline clinician assessed photophobia score in Liang et al. (2017) was 1.87 (SD 1.17) points for people receiving viscous eye drops compared with a mean score of 1.68 (SD 1.05) points for people receiving aqueous eye drops. The absolute change in clinician assessed photophobia showed a statistically significant reduction 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 increase of 0.07 (SD 0.44) points for people receiving aqueous eye drops (p=0.0048). The EPAR reported the estimated mean treatment difference between groups was statistically significant showing a small increase between treatment groups by an increase of 0.69 points (95% CI 0.23 to 1.14; p<0.0048).

To better understand what this outcome meant for patients, the EPAR reported the results of a responder analyses describing the number of eyes with photophobia at baseline whose photophobia score reduced by at least 1 or 2 units in each treatment arm. In people receiving viscous eye drops 22 eyes presented with photophobia at baseline, 35 % of these had reduced their photophobia score by 1 point and 19 % had reduced their photophobia score by 2 points at 90 days follow-up. In people receiving aqueous eye drops 24 eyes presented with photophobia at baseline, of which 7% reduced their photophobia score by 1 point and 0% reduced their photophobia score by 2 points. Although the results did not report statistical significance, the EPAR states “the difference between treatment arms is clear and thus seems to support a meaningful benefit of

treatment". The EPAR also reported the results of a patient rated photophobia assessment. Baseline values were not reported, however, 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.

In Labbé et al. (2014) the mean clinician assessed photophobia score changed from 2.8 (SD 1.1) points during the run-in period (while patients were receiving their standard aqueous eye-drops regimen) to 2.5 (SD 0.9) points at baseline and a mean score of 1.6 (SD 1.0) points at 48 months (4 years) follow-up. The EPAR reported the mean score remained at 1.6 (SD 1.0) points at 60 months (5 years) follow-up. Statistical significance was not reported.

Further support of improvements in photophobia came from the NPU programme reported in the EPAR. The EPAR reported "after 7 months on treatment, the proportion of subjects with a ≥ 2 step reduction increased while the corresponding proportions with a ≥ 1 step reduction increased compared to the analysis made after 3 months".

Eye staining tests using a dye can identify any corneal irregularities or damage to the corneal surface. The fluorescein corneal staining test was used in Liang et al. (2017) to identify any corneal epithelial erosions, or irregularities on the corneal surface, or alterations in corneal shape, which would show on the surface of the eye. At baseline the mean corneal staining score was 2.1 (SD 4.4) points for people receiving viscous eye drops and 0.9 (SD 2.6) points for people receiving aqueous eye drops. The absolute change in total number of irregularities 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, although statistical significance was not reported. These results suggest there was no worsening of corneal staining in either

treatment group during the 90-day follow-up period. Results of corneal staining were not reported in Labbé et al. 2014.

Safety of the viscous eye drops was assessed by looking for changes in intraocular pressure. The normal range for healthy eyes is between 5 mm Hg and 22 mm Hg and ocular hypertension is an eye pressure of greater than 22 mm Hg. In Liang et al. (2017) the mean value of intraocular pressure at 90 days follow-up was 15.0 (SD 3.2) mm Hg for people receiving viscous eye drops compared with a mean value of 13.0 (SD 3.0) mm Hg in people receiving aqueous eye drops, although the results did not report statistical significance. Liang et al (2017) reported “no clinically significant changes to intraocular pressure, eye fundus or corneal irregularities were assessed in CHOC”. In Labbé et al. (2014) the intraocular pressure increased from 11.8 (SD 2.5) mm Hg at baseline to 14.8 (SD 2.3) mm Hg at 48 months (4 years follow-up). Labbé et al (2014) noted this increase was explained by the mean age of patients (12.1 years) included in OCT-1. They stated that “previous studies have showed that in children intraocular pressure normally raises about 0.85 mm Hg per year until they reach adult levels”.

Patient reported outcomes

2.7 In Labbé et al. (2014) pain at instillation was assessed on a 0-100 mm visual analogue scale (VAS). Baseline values were not reported, however Labbé et al (2014) reported that at 30 days follow-up the mean pain-intensity VAS score was 27 (SD 19.7) mm higher for people treated with viscous eye drops compared with people receiving aqueous eye drops, which reported a mean score of 7.3 (SD 8.7) mm. During the 48-month follow-up period the reported pain at instillation decreased to less than 10 mm on the VAS at study end-point. The EPAR reported at 60 months (5 year) follow-up the mean VAS score was 7.

Health related quality of life

2.8 The Comparison of Ophthalmic Medications for Tolerability (COMTol) questionnaire was used to measure the extent to which side effects interfered with health-related quality of life, medication compliance, and

patient's satisfaction with the medication. 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. In Liang et al. (2017), only the adult patients receiving the viscous eye drops were asked to complete the COMTol questionnaire at baseline, 30 days follow-up and 90 days follow-up and 5 out of 7 patients completed it. Results found the scores for all questionnaire items were generally low at baseline, which Liang et al (2017) suggested that this implied most patients were satisfied with their existing treatment. 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.

Safety and tolerability

2.9 As a phase I/II trial, safety assessments were the main purpose of Labbé et al. (2014) and were also carried out in Liang et al. (2017). Labbé et al. (2014) stated 7 out of 8 people reported a total of 44 adverse events (AEs) during the 48-month (4 years) follow-up of OCT-1. During the run-in period (where patients were using aqueous eye drops) 5 of the 8 people reported experiencing stinging after instillation, however, in the last 30 days of the 48-month period (where patients were using viscous eye drops) 2 of the 8 people reported experiencing this symptom. All patients reported some symptoms after instillation in the first 24 months of the study period. The most frequent were stinging (reported by 55%), blurred vision (reported by 25%) and burning (reported by 19%).

The EPAR reported additional safety data covering the 60 months (5 year) follow-up. At 5 years (60 months) follow-up 7 of the 8 patients had reported 73 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 reported as leading to discontinuation and no deaths during the 60 months follow-up period. The EPAR noted several systemic AEs were reported which mainly related to surgical and medical procedures, musculoskeletal and connective tissue disorders and nervous system disorders. None of these were thought to be related to treatment. The most frequently reported local adverse drug reactions (LADRs) after instillation were stinging (reported by 7 people; 87.5%), blurred vision (reported by 6 people; 75%), burning or eye irritation (reported by 4 people; 50%) eye discomfort, itching and sticky eyes (reported by 2 people; 25%) and watering, eye irritation and redness (reported by 1 person; 12.5%). The medium length of time for experiencing a LADR was 5 seconds, with a maximum time reported as 17.5 seconds.

In Liang et al. (2017), 10 out of 15 people (66.7%) receiving viscous eye drops, compared with 13 out of 16 people (81.3%) receiving aqueous eye drops reported experiencing an AE during the 90-day follow-up period. Two people in each treatment group reported these were serious AEs. The EPAR stated most AEs from this study were mild. People receiving viscous eye drops, reported one event each of conjunctival hyperaemia (redness and irritation caused by conjunctivitis), allergic conjunctivitis and increased lacrimation (watery eyes) increased (all Cystadrops treatment arm) were reported as moderate. There were no treatment emergent serious AEs in either treatment group and no severe AEs or deaths. All the people receiving viscous eye drops (15 out of 15; 100%) compared with 11 of 16 people (68.8%) receiving aqueous eye drops reported experiencing a LADR. The most frequently reported LADRs in people receiving viscous eye drops were stinging (reported by 12 people; 80%); burning (reported by 10 people; 66.7%); redness and blurred vision (reported by 9 people; 60%) and itching (reported by 6 people; 40%), compared with the people receiving aqueous eye drops where the most frequent LADRs were stinging (reported by 5 people; 50%); redness (reported by 7 people; 43.8%); burning, blurred vision and itching (reported by 4 people; 25%). 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. The LADRs which lasted more than 1 hour, were reported as redness (42.5%) and blurred vision (22.5%). There were no discontinuations due to experiencing an LADR.

The number of AEs recorded in the French NPU programme was reported in the EPAR. The most frequently recorded LADRs were eye irritation (reported by 9 people; 8.5%), eye pain and blurred vision (reported by 4 people; 3.8%), ocular hyperaemia (red eyes) and lacrimation increase (watery eyes, reported by 1 person (0.9%).

In Liang et al. (2017), patients received a standard number of 4 instillations of viscous eye drops per day throughout the 90-day follow-up period. In OCT-1 the mean number of instillations per day of viscous eye drops began at 4 (range 3 to 5) instillations at baseline and matched the number of installations the patients had been receiving during the run-in period (where patients received aqueous eye drops). This reduced to a mean of 3 (range 1 to 4) instillations per day at 6 months and remained at this number of instillations at 48 months (4 years) follow-up. The results for 60 months (5 years) follow-up were not reported.

Evidence gaps and limitations

2.10 There were several limitations identified in the evidence base. Although the main study (Liang et al. 2017) was a randomised open label trial comparing viscous mercaptamine eye drops against an active aqueous eye drops comparator. The strength of concentration (0.10%) of the aqueous formulation, however, does not represent the current standard of care in England (0.55%). The EPAR noted that the comparator is generally recommended to be applied every hour while awake rather than the 4 times per day dose used during the study. In practise, however this is rarely maintained. Both studies were conducted in a population with nephropathic cystinosis. People with non-nephropathic cystinosis (also known as ocular cystinosis which only affects the eye) were not included in the study. Additionally, although 38.7% of people taking part in Liang et al. (2017) were adults, the mean ages of both trial populations (17.1 years

in Liang et al. 2017 and 12.1 years in Labbé et al. 2014) means there is limited evidence representing older age groups. However, due to the rarity of people diagnosed with non-nephropathic (ocular) cystinosis, it is difficult to recruit this group of people into a study. People with non-nephropathic cystinosis were also excluded from the trial but are included in the marketing authorisation for viscous mercaptamine hydrochloride eye drops.

The EPAR suggested there may have been a potential for selection bias in Liang et al. (2017), whereby the slit-lamp and IVCM images used in evaluation were based on images pre-selected by an unmasked investigator which leaves the study “without any truly masked evaluations”. The EPAR concluded that although the overall effect size seemed convincing, this adds uncertainty to the magnitude of effect.

There are some questions surrounding the methods used in the studies. In Labbé et al. (2014) it is unclear if clinician assessed photophobia scores were made by masked assessors and this therefore has some concern for potential bias. In addition, the demographic data from Liang et al. (2017) showed people receiving viscous eye drops had a higher mean baseline reading than those receiving aqueous eye drops.

The unit of analyses in both studies was per eye, rather than by the unit of randomization (per patient). This could have led to an over inflation in precision by increasing the number of observations for each patient. The authors of both studies corrected for this by adjusting their statistical analysis using the generalised estimator equation (GEE) which accounted for the correlation between each eye and the repeated observations for each patient. There is limited evidence of health-related quality of life. The COMTol questionnaire was only completed by 5 adults only in Liang et al. (2017) and therefore it may be difficult to generalise these findings.

Liang et al. (2017) had a short-term follow-up of 90 days, providing limited efficacy and safety analysis. Data from un-controlled settings provides support for longer term efficacy and safety. The French NPU programme

(reported in the EPAR) provides observational analysis over a mean period of 7 months however published evidence is limited. Longer term data is available from Labbé et al.2014; (OCT-1; up to 5-year follow-up), but this was an open label design involving a small sample of 8 patients and again, it is therefore difficult to generalise findings.

Overall conclusions

2.11 Results suggest that people using mercaptamine hydrochloride 0.55% viscous eye drops (4 times a day) to treat corneal cystine crystals can have a statistically significant greater reduction in the number of crystals compared to treatment with mercaptamine hydrochloride 0.10% aqueous eye drops (an average of 4 times a day) over a 90 day follow-up (based on slit lamp assessments graded using CCCS; IVCM assessments graded using a 0-28 point composite score; and AS-OCT measurements). At 4-year follow-up people can expect to have a statistically significant reduction in corneal cystine crystals when using mercaptamine hydrochloride 0.55% viscous eye drops (an average of 3 times a day) compared to treatment with aqueous eye drops (an average of 4 times a day; based on IVCM assessments). Over a 5-year follow-up period, people using mercaptamine hydrochloride 0.55% viscous eye drops (an average of 4 times a day) can expect a reduction in corneal cystine crystals (from their baseline reading when using mercaptamine hydrochloride 0.55% viscous eye drops an average of eye drops an average of 4 times a day) based on slit lamp assessments graded using CCCS and AS-OCT measurements.

Although statistical significance was not reported, over a 90-day period treatment with viscous mercaptamine hydrochloride 0.55% eye drops was 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. It is however, difficult to show a statistical significance over a short period of time, as visual ability usually deteriorates over a period of years. Over a 5 year period normal vision was maintained in a small cohort of 8 people.

At 90 days follow-up, clinician assessed photophobia can result in a statistically significant greater reduction in people using viscous eye drops, compared with treatment with aqueous eye drops and can decrease over a 5-year period. Patient reported photophobia can decrease over a 90 day follow up period as a result of receiving treatment with viscous mercaptamine hydrochloride 0.55% eye drops (based on slit lamp assessments graded using a 0-5 point scale, showing absence of symptoms to extreme symptoms).

There was no worsening of corneal irregularities identified through corneal staining in either treatment group at 90 days follow-up for people receiving treatment with viscous mercaptamine hydrochloride 0.55% eye drops or people receiving aqueous cysteamine eye drops, as both treatment groups reported a reduction.

Results of intraocular pressure changes varied and over a long-term follow-up showed increases in intraocular pressure, but this could be explained by normal annual increase in children's intraocular pressure.

The reported experience of pain at instillation of people receiving viscous mercaptamine hydrochloride 0.55% eye drops decreases over time. (Based on 0-100 mm VAS ratings).

At 90 days follow-up of the 5 patients who completed the COMtol questionnaire, satisfaction was overall reported with receiving viscous mercaptamine hydrochloride 0.55% eye drops. (Based on completion of the COMtol 37-item tool).

Treatment with viscous mercaptamine hydrochloride 0.55% eye drops were generally well-tolerated, with few serious adverse events which were not thought to be related to treatment. Although most patients reported local adverse drug reactions, these were generally short-lasting and did not result in withdrawal of treatment.

Table 3 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Reduction of corneal cystine crystal deposits	Liang et al (2017)	7/10	Directly applicable	A	The corneal cystine crystal density (change in total number of corneal cystine crystal deposits) was measured in both studies using various imaging techniques. The change in corneal cystine crystal deposits in patient's eyes was assessed using a slit lamp. The slit-lamp is a high-intensity light which was used to take photographs of the cornea and the density of corneal cystine crystals was graded using Corneal Cystine Crystal Scores (CCCS) ranging from 0.00 (showing clarity in the centre of the cornea) to 3.00 (showing greatest crystal density). In vivo confocal microscopy (IVCM) was also used to examine the cornea. IVCM is a laser imaging technique which examines the different layers of the cornea and allows clinicians to look at cells in the eye which may not be visible using a slit-lamp. The images were graded from 0 to 4 depending upon the density of crystals found in each corneal layer and a 0-28 point overall composite score was calculated. In the studies the results showed the average (mean) score of 5 photographs for each corneal layer. Another imaging technique (anterior segment optical coherence tomography; AS-OCT) provided a cross-sectional view of anterior segment anatomy and size of crystal deposits. It was measured in micrometres (µm). **<u>Change in in vivo confocal microscopy (IVCM) scores</u>** 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. The study found a statistically significant reduction of corneal cystine deposits measured by mean IVCM score of -4.6 points (SD 3.1), representing a 40.4 % (range -64.7 to -8.3) reduction in people receiving viscous eye drops compared with a reduction of -0.5 points (SD 3.4) representing a 0.7 % (range -46.9 to 63.1) reduction in people receiving aqueous eye drops, ($p<0.0001$) at 90 days follow-up. The 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 caused by nephropathic cystinosis which showed the mean in vivo confocal microscopy score had reduced by 29.9% (SD 26.29) representing a statistically significant decrease ($p=0.001$ at 4 years-follow-up. Although statistical significance was not reported at 5 years follow-up, the mean reduction from baseline in corneal cystine
	Labbé et al (2014)	8/10	Directly applicable		

					crystal deposits was -3.4 (SD 2.8) IVCM points, representing a 32.7 % (SD 25.4) reduction. **Change in corneal cystine crystal scores (CCCS)** The findings from Liang et al. (2017) also 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 from 2.91 (SD 0.13) points at baseline to 2.75 (SD 0.32) points at 48 months (4 years) follow-up. The results at 60 months (5 years) follow-up were not reported. **Change in anterior segment optical coherence tomography (AS-OCT) measurement** In Liang et al. (2017), the AS-OCT results also showed a statistically significant reduction in corneal cystine crystal depth of -46.3 (SD 55.3) µm 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 decreased from a mean of 306.4 (SD 98.9) at baseline to a mean of 265.1 (SD 119.3) at 48 months (4 years) follow-up. The results at 60 months (5 years) follow-up were not reported. 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. 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 very small population of 8 people.
Maintenance or improvement of vision	Liang et al (2017)	7/10	Directly applicable	A	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). LogMAR values quantify vision from 0.0 (normal vision) to 1.68 (unable to read any letter on a chart). Every letter has a value of 0.02 log units. A logMAR score reduces for every additional letter the patient can read correctly on the following lines of the chart, so a negative (-) value
	Labbé et al (2014)	8/10	Directly applicable		

					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 in logMAR of -0.10 (SD 0.15) log units for people receiving viscous eye drops compared with an improvement of -0.07 (SD 0.15) log units 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. Changes in contrast sensitivity were not considered in Labbé et al. (2014).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-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 OCT-1 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 and decline in visual acuity and contrast sensitivity usually develops over a much longer period (years) as crystal deposition worsens and complications may occur.
Improvement in symptoms- Clinician and patient assessed photophobia	Liang et al (2017)	7/10	Directly applicable	A	Changes in photophobia (light sensitivity) were objectively assessed by the clinician using a slit-lamp and graded using a 0 to 5 point scale (where 0 showed an absence of symptoms and 5 showed extreme symptoms).). Patients were also asked to rate their photophobia on a similar scale). **Clinician 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 no change of 0.07 (SD 0.44) points for
	Labbé et al (2014)	8/10	Directly applicable		

					people receiving aqueous eye drops (p=0.0048) and showing a small estimated mean increase between treatment groups by of 0.69 points (95% CI 0.23 to 1.14; p<0.0048).In the population of people with photophobia at baseline whose photophobia score reduced by at least 1 or 2 units in the each treatment arm found 22 eyes of the group receiving viscous eye drops presented with photophobia at baseline. At 90 days follow-up, 35 % of this sub-group had reduced their photophobia score by 1 point and 19 % had reduced their photophobia score by 2 points. This was compared with people receiving aqueous eye drops 24 eyes presented with photophobia at baseline, of which 7 % reduced their photophobia score by 1 point and 0 % reduced their photophobia score by 2 points. **Patient reported photophobia** 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. In Labbé et al. (2014) the mean clinician assessed photophobia score changed from 2.8 (SD 1.1) points during the run-in period (while patients were receiving their standard aqueous eye-drops regimen) to a mean score of 1.6 (SD 1.0) points at 60 months (5 years) follow-up. 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. 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 very small population of 8 people.
Improvement in symptoms-Corneal irregularities	Liang et al (2017)	7/10	Directly applicable	A	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. Results of corneal staining were not reported in Labbé et al. (2014).
	Labbé et al (2014)	8/10	Directly applicable		

					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. 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.
Change in intraocular pressure	Liang et al (2017)	7/10	Directly applicable	A	Changes in intraocular pressure (IOP), measured in millimetres of mercury (mm Hg), was also used to identify changes of fluid pressure in the eye above 22 mm HG which could represent ocular hypertension and could identify a risk of eye diseases such as glaucoma. The best evidence came from Liang et al. (2017) which found the mean measure of IOP recorded at 90 days follow-up was 15.0 (SD 3.2) mm Hg for people receiving viscous eye drops compared with a mean value 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 48 months (4 years follow-up). Results at 5 years (60 months) follow-up were not reported. These results suggest IOP changes varied and over a long-term follow-up showed increases in IOP, but these remained within the normal range of IOP in healthy eyes (which is between 5 mmHg and 22 mm Hg), and the increases could be explained by normal annual increase in children's IOP. 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 OCT-1 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.
	Labbé et al (2014)	8/10	Directly applicable		

Patient reported outcomes	Labbé et al (2014)	8/10	Directly applicable	A	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). It was reported at 30 days follow-up the mean pain-intensity VAS score was 27 (SD 19.7) mm higher for people treated with viscous eye drops compared with people receiving aqueous eye drops, which reported a mean score of 7.3 (SD 8.7) mm. At 5 years (60 months) follow-up, the reported 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. 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
Health related quality of life	Liang et al (2017)	7/10	Directly applicable	B	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. The best evidence came from Liang et al. (2017), 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. Health related-quality of life was not reported in Labbé et al. (2014). 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).

Safety and tolerability	Liang et al (2017)	7/10	Directly applicable	A	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 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 reported as leading to discontinuation and no deaths. Local adverse drug reactions 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. 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 very small population of 8 people.
	Labbé et al (2014)	8/10	Directly applicable		

3 Related NICE guidance and NHS England clinical policies

There are no related NHS England clinical policies or NICE guidelines on managing corneal cystine deposits with mercaptamine hydrochloride (0.55%) eye drops

4 References

Al-Hemidan A, Shoughy S, Kozak I and Tabbara K (2017) Efficacy of topical cysteamine in nephropathic cystinosis. British Journal of Ophthalmology 101:1234-1237

Ariceta G, Camacho J, Fernández-Obispo M, Fernández-Polo A, Gamez J, García-Villoria J, Monteczuma EL, Leyes P, Martín-Begué, N. Oppenheimer F, Perelló M, Pintos Morell G, Torra R, Vila Santandreu A, Güell A and Grupo T –CiS.bcn (2015) Cystinosis in adult and adolescent patients: Recommendations for the comprehensive care of cystinosis. Nefrologia 35(3):304-321

Biswas S, Gaviria M, Malheiro L, Marques JP, Giordano V, Liang H (2018) Latest Clinical Approaches in the Ocular Management of Cystinosis: A Review of Current Practice and Opinion from the Ophthalmology Cystinosis Forum. Ophthalmology and Therapy, 7:307-322

Biswas S and Sornalingam K (2018) The ocular status of cystinosis patients receiving a hospital pharmacy-made preparation of cysteamine eye drops: a case series. Ophthalmology and Therapy, https://doi.org/10.1007/s40123-018-0156-4 (Accessed Feb 2019)

Doyle M,and Werner-Lin A (2015) That eagle covering me: transitioning and connected autonomy for emerging adults with cystinosis. Pediatric Nephrology 30:281-291

Elmonem MA, Veys KR, Soliman NA, van Dyck M, van den Heuvel LP, Levtchenko E (2016) Cystinosis: A review. Orphanet Journal of Rare Diseases 11:47

Emma F, Nesterova G, Langman C, Labbé A, Cherqui S, Goodyer P, Janssen MC, Greco M, Topaloglu R, Elenberg E, Dohil R, Trauner D, Antignac C, Cochat P, Kaskel F, Servais A, Wühl E, Niaudet P, Van't Hoff W, Gahl W, and Levtchenko E (2014) Nephropathic cystinosis: An international consensus document. Nephrology Dialysis Transplantation 29 (Suppl. 4):iv87-iv94

Hutchesson A, Bundey S, Preece M, Hall S, and Green, A. (1998) A comparison of disease and gene frequencies of inborn errors of metabolism among different ethnic groups in the West Midlands, UK. Journal of Medical Genetics 35:366-370

Iwata F, Kuehl E, Reed G, McCain L, Gahl W, and Kaiser-Kupfer, M. (1998) A randomized clinical trial of topical cysteamine disulfide (cystamine) versus free thiol (cysteamine) in the treatment of corneal cystine crystals in cystinosis. Molecular Genetics and Metabolism, 64(4):237-242

Jones NP, Postlethwaite RJ, and Noble JL (1991) Clearance of corneal crystals in nephropathic cystinosis by topical cysteamine 0.5%. British Journal of Ophthalmology 75(5):311-2

Labbé A, Baudouin C, Deschênes G, Loirat C, Charbit M, Guest G and Niaudet P (2014) A new gel formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis: the Cystadrops OCT-1 study. Molecular Genetics and Metabolism, 111(3):314-320

Liang H, Labbé A, Le Mouhaër J, Plisson C and Baudouin C (2017) A New viscous cysteamine eye drops treatment for ophthalmic cystinosis: an open-label randomized comparative phase III pivotal study. Investigative Ophthalmology and Visual Science *58*(4):2275-2283

MacDonald IM, Noel LP, Mintsioulis G, and Clarke WN. (1990) The effect of topical cysteamine drops on reducing crystal formation within the cornea of patients affected by nephropathic cystinosis. Journal of Pediatric Ophthalmology & Strabismus 27(5):272-4

Radojkovic, B. (2015). Cysteamine eye drops in the treatment of cystinosis - an Australian perspective. Jornal of Pharmaceutical Practice and Research, 45(4), 440-445

Reda A, Van Schepdael A, Adams A, Paul P, Devolder D, Elmonem M A, Veys K, Casteels I, van den Heuvel L,(2017) Effect of storage conditions on stability of ophthalmological compounded cysteamine eye drops. Journal of Inherited Medical Disease, Reports 42:47-51

Shams F, Livingstone I, Oladiwura D and Ramaesh K (2014) Treatment of corneal cystine crystal accumulation in patients with cystinosis. Clinical Ophthalmology 8:2077-2084

Tsilou E T, Rubin, B I, Reed G F, Iwato F, Gahl WKaiser-Kupfer M I (2002) Age-related prevalenceof anterior segmentcomplications in patients with infantile nephropathic cystinosis. Cornea 2:173-176

This clinical evidence review has been written by NICE, following the process set out in the standard operating procedure for the commissioning support programme.

Appendix 1 Search strategy

Search strategies

Databases

Database: Ovid MEDLINE(R) Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
Platform: Ovid
Version: 1946 - date
Search date: 07/11/2018
Number of results retrieved:
Ovid MEDLINE(R) 1946 to November 06 2018 284
Ovid Medline In Process November 06 2018 24
Ovid Medline e pub ahead of print November 06 2018 7
Ovid Medline daily update November 06 2018 1

Search strategy:

Database: Ovid MEDLINE(R) <1946 to November 06, 2018>
Search Strategy:
---
1 Cysteamine/ (3030)
2 (mercaptamine or cysteamine or cystadrops* or cystaran* or dropcys*).tw. (2903)
3 1 or 2 (3993)
4 CYSTINOSIS/ (1175)
5 (cystin* or ((aberhalden or fanconi) adj2 (disease* or syndrome* or disorder*))).tw. (11591)
6 4 or 5 (11738)
7 3 and 6 (386)
8 limit 7 to english language (352)
9 animals/ not humans/ (4479417)
10 8 not 9 (284)

Database: Embase
Platform: Ovid
Version: 1974 to 2018 November 06
Search date: 07/11/2018
Number of results retrieved: 412
Search strategy:

Database: Embase <1974 to 2018 November 06>
Search Strategy:
---
1 mercaptamine/ (3976)
2 (mercaptamine or cysteamine or cystadrops* or cystaran* or dropcys*).tw. (3244)
3 1 or 2 (4793)
4 cystinosis/ (1641)
5 (cystin* or ((aberhalden or fanconi) adj2 (disease* or syndrome* or disorder*))).tw. (13188)
6 4 or 5 (13493)
7 3 and 6 (689)

8 limit 7 to (conference abstract or conference paper or "conference review" or editorial or letter) (165)
9 7 not 8 (524)
10 limit 9 to english language (471)
11 nonhuman/ not human/ (4251748)
12 10 not 11 (412)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR – [11…] of 12, November 2018
CENTRAL – 10 of 12, October 2018

Search date: 07/11/2018
Number of results retrieved: CDSR 0–; CENTRAL 29–;.
Search strategy:

Cochrane

Search Name: mercaptamine
Date Run: 07/11/2018 06:27:59
Comment:

ID	Search	Hits
#1	MeSH descriptor: [Cysteamine] explode all trees	29
#2	(mercaptamine or cysteamine or cystadrops* or cystaran* or dropcys*):ti,ab,kw	61
#3	#1 or #2	61
#4	MeSH descriptor: [Cystinosis] explode all trees	20
#5	(cystin* or ((aberhaden or fanconi) near/2 (disease* or syndrome* or disorder*))):ti,ab,kw	228
#6	#4 or #5	228
#7	#3 and #6	29

CRD databases

Searched 07/11/2018
1 ref (EED)
Combine selections with AND OR NOT

ID	Line	Search	Hits
1	MeSH DESCRIPTOR Cysteamine explode all trees		1
2	(mercaptamine) OR (cysteamine) OR (cystadrops* or cytsaran* or dropcys*)		2
3	#1 OR #2		2
4	MeSH DESCRIPTOR Cystinosis EXPLODE ALL TREES		1
5	MeSH DESCRIPTOR Fanconi Syndrome EXPLODE ALL TREES		1
6	(cystin*) OR (aberhalden) OR (fanconi)		9
7	#4 OR #5 OR #6		9
8	#3 AND #7		1

Trials registries

Clinicaltrials.gov

Search date: 06/11/2018
Number of results retrieved: 6
Search strategy and link to results page:
Cystinosis | mercaptamine OR cysteamine OR cystadrops | Phase 2, 3, 4
Also searched for **Cysteamine** and **RP103**.

Clinicaltrialsregister.eu

Search date: 06/11/2018
Number of results retrieved: 8
Search strategy and link to results page:

cystinosis AND (mercaptamine OR cysteamine OR cystadrops)

Excluded results from trials registry searches

Study title	Reason discarded
An Open-Label, Safety and Effectiveness Study of Cysteamine Bitartrate Delayed-release Capsules (RP103) in Cysteamine Treatment Naïve Patients With Cystinosis	Capsule form
Open-Label, Safety and Superior Effectiveness Study of Cysteamine Bitartrate Delayed-Release Capsules (RP103) in Cystinosis	Capsule form
A Randomized, Crossover Pharmacokinetic and Pharmacodynamic Study to Determine the Safety and Efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103), Compared to Cystagon® in Patients With Nephropathic Cystinosis	Capsule form
A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-release Capsules (RP103) in Patients With Cystinosis	Capsule form
A Pilot Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Cysteamine Bitartrate Delayed-release Capsules (RP103), Compared to Cysteamine Bitartrate (Cystagon®) in Patients With Nephropathic Cystinosis	Capsule form

CrYSTobs A cohort of patients with cystinosis: compliance to cysteamine and neurological complications	Capsule form
An open label investigation of the tolerability and pharmacokinetics of oral cysteamine in adults with Cystic Fibrosis	Wrong form and indication
A Long-Term Open-Label, Safety and Superior Effectiveness Study of Cysteamine Bitartrate Delayed-release Capsules (RP103) in Patients with Cystinosis	Capsule form
A Randomized, Crossover, Pharmacokinetic and Pharmacodynamic Study to Determine the Safety and Efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103), Compared to Cystagon® in Patients with Nephropathic Cystinosis	Capsule form
A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-release Capsules (RP103) in Patients with Nephropathic Cystinosis	Capsule form

Appendix 2 Study selection

The search strategy presented in appendix 1 yielded 499 studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

Inclusion criteria	
Population	People aged 2 years and over with corneal crystal deposits caused by cystinosis
Intervention	Mercaptamine hydrochloride (cysteamine hydrochloride) 0.55% eye drops (Cystadrops)
Comparator	• Cysteamine hydrochloride between 0.10% and 1.13% eye drops
Outcomes	Reduction of corneal crystals including: • Reduction in number of corneal crystal deposits • Decrease in size of corneal crystal deposits • Decrease in depth/thickness of corneal crystal deposits Maintenance or improvement of vision including: • Visual acuity • Visual contrast sensitivity Improvement in symptoms including: • Photophobia (light sensitivity) • Corneal ulcers/erosions, scarring (scratches of the cornea) • Punctuate, filamentary and/or band keratopathy (diseases of the cornea) • Corneal neovascularisation (the growth of blood-vessels into the cornea of the eye) • Closed-angle glaucoma (rapid increase in eye pressure which can cause damage to the optic nerve) • Need for keratoplasty (surgery of cornea) Patient reported outcomes including: • Presence of photophobia, blepharospasm (abnormal eyelid twitches), foreign body sensation, glare disability, pain and/or eye irritation, blindness
Study design	Any
Date limit	None. Due to rarity of disease and newly licensed status of medicine no date limits will be applied
Language limit	English

Exclusion criteria	
Study type	• Abstracts • Editorials/ letters • Opinion pieces • Commentaries
Outcomes	None
Other	Non-humans/ healthy volunteers
Suggested search terms	Corneal cystine crystals Nephropathic cystinosis Non-nephropathic cystinosis Cysteamine hydrochloride Mercaptamine hydrochloride Cysteamine eye drops Cystadrops

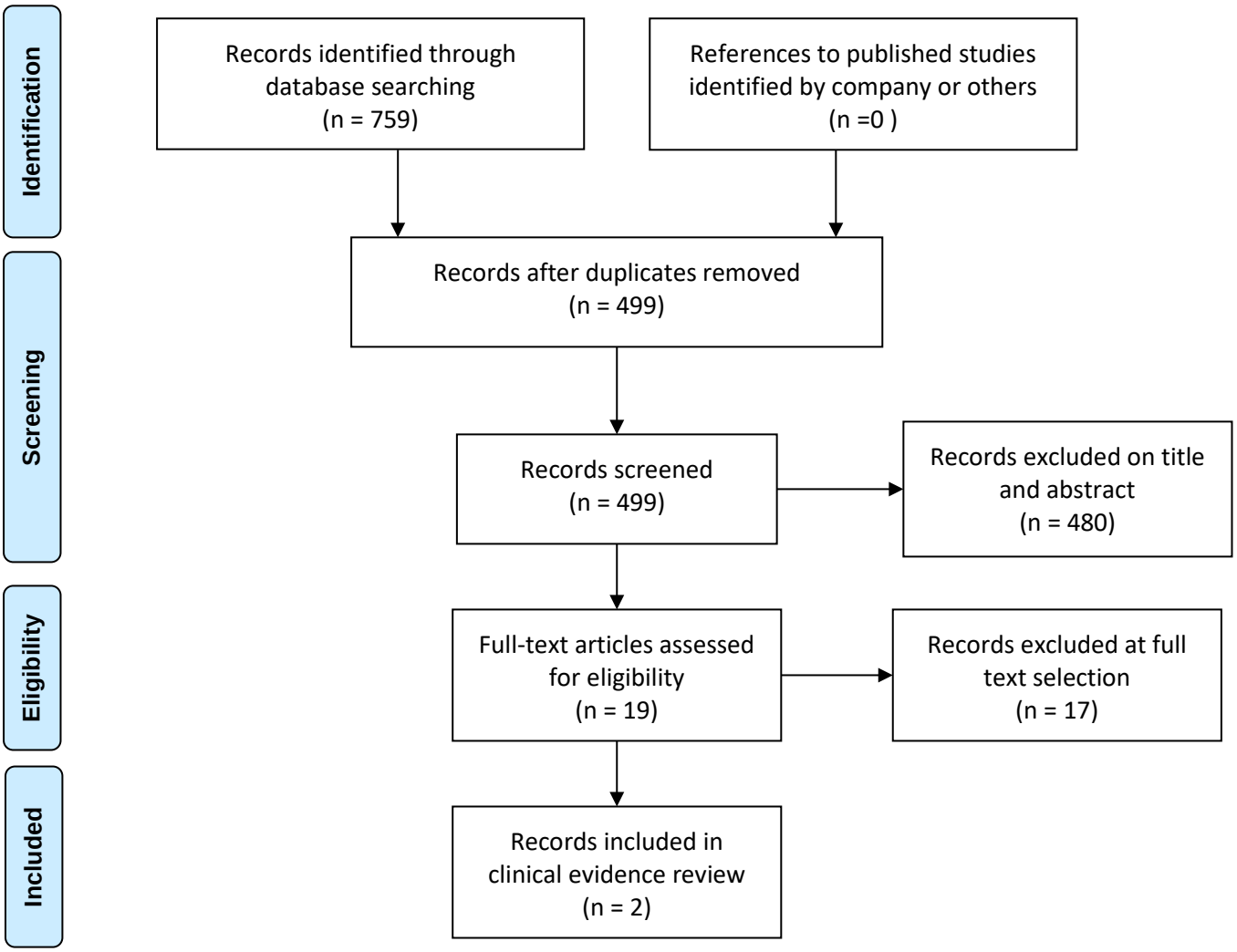
Table 4 Studies excluded at full text

Study reference	Reason for exclusion
Al-Hemidan A, Shoughy SS, Kozak I, and Tabbara K F (2017) Efficacy of topical cysteamine in nephropathic cystinosis. British Journal of Ophthalmology 101(9):1234-1237	Study considers aqueous cysteamine eye drop formulations but does not consider viscous cysteamine eye drops
Blanksma L J, Jansonius NM, and Reitsma-Bierens W C (1996) Cysteamin eyedrops in three patients with nephropathic cystinosis. Documenta Ophthalmologica 92(1):51-3	Study considers aqueous formulation but paper included in EPAR
Bradbury J A, Danjoux J P, Voller J, Spencer M, and Brocklebank T (1991) A randomised placebo-controlled trial of topical cysteamine therapy in patients with nephropathic cystinosis. Eye 5(6):755-60	Study considers aqueous formulation but paper included in EPAR
Dureau P, Broyer M, and Dufier JL (2003) Evolution of ocular manifestations in nephropathic cystinosis: a long-term study of a population treated with cysteamine. Journal of Pediatric Ophthalmology & Strabismus 40(3):142-6	Study considers aqueous cysteamine eye drop formulations but does not consider viscous cysteamine eye drops
Gahl W A, Kuehl E M, Iwata F, Lindblad A, and Kaiser-Kupfer MI (2000) Corneal crystals in nephropathic cystinosis: natural history and	Study considers aqueous cysteamine eye drop formulations but does not

treatment with cysteamine eyedrops. Molecular Genetics & Metabolism 71(1-2):100-20	consider viscous cysteamine eye drops
Iwata F, Wozencraft L A, Caruso R C, Li A, Gahl W A, McCain L M, and Kaiser-Kupfer M I (1995) Nephropathic cystinosis: natural history of ocular findings and results of clinical trial of cysteamine	Conference abstract only
Iwata F, Kuehl EM, Reed G F, McCain LM, Gahl W A, and Kaiser-Kupfer MI (1998) A randomized clinical trial of topical cysteamine disulfide (cystamine) versus free thiol (cysteamine) in the treatment of corneal cystine crystals in cystinosis. Molecular Genetics & Metabolism 64(4):237-42	Study considers aqueous cysteamine eye drop formulations and does not consider viscous cysteamine eye drops
Jones N P, Postlethwaite RJ, and Noble JL (1991) Clearance of corneal crystals in nephropathic cystinosis by topical cysteamine 0.5%. British Journal of Ophthalmology 75(5):311-2	Study considers aqueous formulation but paper included in EPAR
Kaiser-Kupfer M, Gazzo Ma, Datiles M, Caruso R, Kuehl E, and Gahl W (1990) A randomized placebo-controlled trial of cysteamine eye drops in nephropathic cystinosis. Archives of ophthalmology 108(5):689-693	Study considers aqueous formulation but paper included in EPAR
Labbe A, Baudouin C, Lyang H, Le Mouhaer J, and Plisson C (2015) Cysteamine hydrochloride for nephropathic cystinosis: open-label phase III study. Pediatric nephrology 30(9):1670	Conference abstract only
Lyseng-Williamson KA (2017) Cystadrops (cysteamine hydrochloride 0.55% viscous eye-drops solution) in treating corneal cystine crystal deposits in patients with cystinosis: a profile of its use. Drugs and Therapy Perspectives 33(5):195-201	Conference abstract only
MacDonald IM, Noel LP, Mintsioulis G, and Clarke WN (1990) The effect of topical cysteamine drops on reducing crystal formation within the cornea of patients affected by nephropathic cystinosis. Journal of Pediatric Ophthalmology & Strabismus 27(5):272-4	Study considers aqueous formulation but paper included in EPAR

Makuloluwa AK, and Shams F (2018) Cysteamine hydrochloride eye drop solution for the treatment of corneal cystine crystal deposits in patients with cystinosis: an evidence-based review. Clinical Ophthalmology 12:227-236	Narrative review paper only
Radojkovic B (2015) Cysteamine eye drops in the treatment of cystinosis - an Australian perspective. Journal of Pharmacy Practice and Research 45(4):440-445	Narrative review paper only
Reda A, Van Schepdael A , Adams E, Paul P, Devolder D, Elmonem MA, Veys K, Casteels I, van den Heuvel L, and Levtchenko E (2017) Effect of Storage Conditions on Stability of Ophthalmological Compounded Cysteamine Eye Drops. Journal of Inherited Metabolic Disorders Reports 42:47-5151	Study provides inappropriate comparators. It compares different storage systems of cysteamine eye drops
Tsilou ET, Rubin BI, Reed GF, Iwata F, Gahl W, and Kaiser-Kupfer MI (2002) Age-related prevalence of anterior segment complications in patients with infantile nephropathic cystinosis. Cornea 21(2):173-6	Study provides a cross-sectional analysis of prevalence of age specific complications
Tsilou E T, Thompson D, Lindblad A S, Reed G F, Rubin B, Gahl W, Thoene J, Del Monte, M , Schneider J A, Granet D B, and Kaiser-Kupfer M I (2003) A multicentre randomised double masked clinical trial of a new formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis. British Journal of Ophthalmology 87(1):28-31	Study considers aqueous formulation but paper included in EPAR

Figure 2 Flow chart of included studies



Appendix 3 Evidence tables

Table 5 Liang et al. 2017

Study reference	Liang H, Labbé A, Le Mouhaër J, Plisson C and Baudouin C (2017) A New viscous cysteamine eye drops treatment for ophthalmic cystinosis: an open-label randomized comparative phase III pivotal study. Investigative Ophthalmology and Visual Science 58(4:):2275-2283
Unique identifier	Liang et al. 2017: Cysteamine Hydrochloride for nephrOpathic Cystinosis
Study type (and NSF-LTC study code)	Open label randomised two arm superiority phase III trial (P1)
Aim of the study	To compare treatment efficacy and superiority of viscous cysteamine hydrochloride (vCH) 0.55% eye drops with cysteamine hydrochloride (CH) 0.10% eye drops in people with corneal crystals caused by cystinosis
Study dates	Dates not reported in published paper. Study was carried out over 90 days in 2013
Setting	Two sites in France
Number of participants	N=31 (mean age = 17.1 years; age <12 years, n=13; 12-<18 years, n= 6; adult, n=12) **vCH** (n=15; mean age = 19.2 years; age <12 years n=5; 12-<18 years, n=3; adult n=7) **CH** (n=16; mean age = 15.1 years; age <12 years, n=8; 12-<18 years, n=3; adult, n=5)
Population	People aged 2 years or older with cystinosis
Inclusion criteria	People with more than 1.5 nmol half-cystine/mg protein white blood cell cystine concentration and had corneal crystal deposits (identified by slit-lamp) within 3 months prior to inclusion in the study. People who were able to apply 4 instillations of eye drops per day.
Exclusion criteria[a]	People who were less than 2 years of age or had an uncontrolled hepatic disorder, cardiovascular disease, neurologic disease, or cancer. People with hypersensitivity to cysteamine or any drop excipients (disodium edetate, benzalkonium chloride solution, carmellose, sodium, citric acid, monohydrate, sodium hydroxide). People with laboratory test results outside of the normal range (unless results were considered clinically insignificant; or if the person was pregnant, breast-feeding, or of child-bearing age and not using an effective contraception method).
Intervention(s)	vCH 0.55% eye drops 4 times per day (administered at 8am; 12pm; 4pm and 8pm)
Comparator(s)	CH 0.10% eye drops 4 times per day (administered at 8am; 12pm; 4pm and 8pm)

Length of follow-up	At 30 days and 90 days
Outcomes	Primary outcome: • Reduction in corneal cystine crystal density as assessed by in vivo confocal microscopy (IVCM) total score
	Secondary outcomes: • Clinician-assessed photophobia in each eye assessed on a scale of 0 (absence) to 5 (extreme) using a slit-lamp • Corneal cystine crystal density assessed by corneal cystine crystal scores (CCCS) using a slit-lamp [range from: 0.00 (for clarity at the centre) to 3.00 (greatest recognizable crystal density)]. • Corneal cystine crystal depth in the cornea was assessed by optical coherence tomography (OCT)
	Ocular safety outcomes: • Visual acuity assessed on a Logarithm of the Minimum Angle of Resolution (logMAR) scale • Contrast sensitivity (assessed on a log units scale) • Presence of corneal irregularities or suspicion of keratoconus, and any degenerative changes in corneal shape (assessed by ocular topography; intraocular pressure; corneal epithelium integrity by corneal fluorescein staining and slit-lamp examination; ocular fundus; and refraction).
	Safety outcomes: • Tolerability of vCH 0.55% eye drops assessed using Comparison of Ophthalmic Medications for Tolerability (COMTol) questionnaire • Number of local adverse drug reactions (LADRs) • Number of adverse events • Number of serious adverse events
Source of funding	• Orphan Europe

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Yes, clearly defined as first aims to identify superiority of new viscous eye drops
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Clear justification of open label design due to different viscosities of treatment options, but randomisation method not clear and there is the potential for bias by unmasked investigator in choice of IVCM pictures for assessment.
3. Are the methods clearly described?	1/2	Clear reporting of treatment methods, but limited description on randomisation and blinding
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Partly, data is mostly well reported. Inter-eye correlations (based on a generalised estimator equation) were used to account for the unit of analyses by eyes and for the repeated results for each participant. This has corrected for imprecision in the data but the reporting from the COMTol questionnaire is limited. A full breakdown of each item on the questionnaire would have been helpful for interpreting findings.
5. Are the results generalisable?	2/2	Yes
Total	7/10	
Applicability*	Directly / indirectly applicable	Directly applicable

* Note - Direct studies focus on people with the indication and characteristics of interest.
Indirect studies are based on evidence extrapolated from populations with other conditions and characteristics.

Table 6 Labbé et al. 2014

Study reference	Labbé A, Baudouin C, Deschênes G, Loirat C, Charbit M, Guest G and Niaudet P (2014) A new gel formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis: the Cystadrops OCT-1 study. Molecular Genetics and Metabolism, 111(3):314-320
Unique identifier	Adaptive dose regimen of cystadrops for cOrneal Crysyal deposiTs and ocular manifestations in nephropathic cystinosis (OCT -1)
Study type (and NSF-LTC study code)	Open label dose response trial (Phase I/IIa design) (P1)
Aim of the study	To establish the safety and efficacy of a viscous cysteamine 0.55% eye drop formulation.
Study dates	Feb 2008 to March 2012
Setting	One site in France
Number of participants	N=8 (6 female; 2 male) Mean age = 12.1 years (range 7 to 21 years)
Population	People aged 3 years or older with cystinosis
Inclusion criteria	People diagnosed with infantile nephropathic cystinosis and receiving a fixed dose regimen of 0.1% formulation of CH eye drops prior to enrolment. Diagnosis was based on clinical presentation and leukocyte cystine concentration greater than 1.5 nmol half cystine per mg of protein.
Exclusion criteria[a]	Not reported
Intervention(s)	vCH 0.55% eye drops (administered at the same frequency as with the CH 0.1% formulation received during the run-in period)
Comparator(s)	1 month run in where both eyes were treated with control (CH 0.1% eye drops) for an average of 4 times daily (range 3 to 6 times a day)
Length of follow-up	Follow up (in published paper) every 6 months for 48 months. Dose regimen was adapted at 30 days and 90 days to adapt frequency of instillation (if ocular findings worsened then daily dose was increased by 1 instillation per day; if ocular findings improved then daily dose was decreased by 1 dose per day – this was applicable for all months except the visit during Month 3 when the daily dose was either stopped or increased by 1 instillation if worsening or decreased by 2 instillations if improvement)
Outcomes	Primary outcome: • Reduction in corneal cystine crystal density as assessed by in vivo confocal microscopy (IVCM) total score
	Secondary outcomes: • Evaluation of pain at instillation (using a visual analogue scale 0-100mm) • Best corrected visual acuity (BCVA)

	• Objective evaluation of photophobia assessed on a scale of 0 to 5 using a slit-lamp • Corneal cystine crystal thickness assessed by corneal cystine crystal scores (CCCS) using a slit-lamp [range from: 0.00 (for clarity at the centre) to 3.00 (greatest recognizable crystal density)]. • Corneal cystine crystal depth in the cornea was assessed by anterior segment optical coherence tomography (OCT)
	Safety outcomes: • Number of adverse events • Number of serious adverse events
Source of funding	• Orphan Europe

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Yes, clearly defined to establish efficacy and safety and lowest efficient dose of new viscous formulation
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Yes, as a phase I/ II study, it is appropriate design
3. Are the methods clearly described?	2/2	Yes, thorough reporting
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Partly, unit of analysis by eye is explained by use of GEE model to account for inter-eye correlation and repeated results for each participant but would have liked more tabular results rather than text only, but adequate to consider interpretations
5. Are the results generalisable?	1/2	Partly; mean age of patients was 12.1 years, which means it is difficult to generalise to older and younger populations with cystinosis
Total	8/10	
Applicability*	Directly / indirectly applicable	Directly applicable

* Note - Direct studies focus on people with the indication and characteristics of interest. Indirect studies are based on evidence extrapolated from populations with other conditions and characteristics.

Appendix 4 Results tables

Table 7 Liang et al. (2017; main study)

	vCH (0.55%) eye drops	aCH (0.10%) eye drops	P-value
N= 42 eyes	**n=22 eyes**	**n=20 eyes**	
Primary outcome: Reduction in corneal cystine crystal density as assessed by in vivo confocal microscopy (IVCM) mean (SD) **Full analysis set (FAS; all randomised patients/eyes receiving at least one treatment)**			
	n=20 eyes	n=17 eyes	
IVCM total score at baseline	10.6 (4.2) Range 3.2 to 19.0	10.8 (3.5) Range 4.2 to 16.2	
IVCM total score at 90 days follow-up	6.0 (2.1) Range (2.0 to 9.6)	9.8 (3.8) 5.0 to 17.7	P= 0.001
Absolute change in IVCM from baseline at 90 days follow-up (total score)	-4.6 (3.1) Range-11.0 to -0.6	-0.5 (3.4) Range -7.6 to 6.5	P<0.0001
Relative (%age) change in IVCM from baseline at 90 days follow-up (percentage score)	-40.4% (16.0) Range -64.7% to -8.3%	-0.7% (33.0) Range -46.9% to 63.1%	Not reported
Secondary outcome: corneal cystine crystal density (CCCS) mean (SD) **(FAS; all randomised patients/eyes receiving at least one treatment)**			
	n=30 eyes	**n=30 eyes**	
Baseline score	2.26 (0.56)	1.98 (0.50)	
Change at 90 days	-0.59 (0.52)	0.11 (0.24)	P=0.0015
Secondary outcome: corneal cystine crystal depth (OCT) mean (SD) **(FAS; all randomised patients/eyes receiving at least one treatment)**			
	n=30 eyes	**n=29 eyes**	
Baseline score	275 (159)	260 (167)	
	n=28 eyes	n=29 eyes	
Change at 90 days	-46.3 (55.3)	10.6 (43.6)	P=0.0031
Secondary outcome: clinician assessed photophobia mean (SD) **(FAS; all randomised patients/eyes receiving at least one treatment)**			
	n=30 eyes	n=32 eyes	
Baseline score	1.87 (1.17)	1.68 (1.05)	
Change at 90 days	-0.63 (0.77)	0.07 (0.44)	P=0.0048
Secondary outcome: Ocular safety evaluation **(FAS; all randomised patients/eyes receiving at least one treatment)**			
	vCH (0.55%) eye drops	**CH (0.10%) eye drops**	
N=62 eyes	**n=30 eyes**	**n=32 eyes**	
	n=22 eyes	n=29 eyes	
Baseline	0.24 (0.36)	0.16 (0.30)	
Absolute change at day 30	-0.06 (0.11)	-0.02 (0.10)	Not reported

Absolute change at day 90	-0.10 (0.15)	-0.07 (0.15)	Not reported
Visual contrast sensitivity (logMAR) mean (SD)			
	n=22 eyes	**n=27 eyes**	
Baseline	0.57 (0.37)	0.44 (0.31)	
Absolute change at day 30	-0.13 (0.17)	-0.03 (0.14)	Not reported
Absolute change at day 90	-0.20 (0.27)	-0.14 (0.20)	Not reported
Corneal staining total score mean (SD)			
	n=30 eyes	**n=31 eyes**	
Baseline	2.1 (4.4)	0.9 (2.6)	
Absolute change at day 30	-1.6 (3.5)	0.2 (0.8)	Not reported
Absolute change at day 90	-1.5 (3.2)	-0.6 (2.5)	Not reported
Intraocular pressure (mm Hg) mean (SD)			
	n=28 eyes	**n=23 eyes**	
Baseline	15.6 (4.2)	15.1 (2.9)	
	n=28 eyes	**n=24 eyes**	
Mean value at day 30	15.8 (3.2)	14.8 (2.5)	Not reported
	n=27 eyes	**n=24 eyes**	
Mean value at day 90	15.0 (3.2)	13.0 (3.0)	Not reported
Safety assessments n (%) **Safety set (SS; all randomised patients/eyes who received at least one treatment)**			
	vCH (0.55%) eye drops	**CH (0.10%) eye drops**	
	n=15	**n=16**	
All AEs	10 (66.7%)	13 (81.3%)	Not reported
Severe AEs	0	0	Not reported
Treatment related AEs	2 (13.3%)	1 (6.3%)	Not reported
SAEs	2 (13.3%)	2 (12.5%)	Not reported
Treatment related SAEs	0	0	Not reported
Deaths	0	0	Not reported
Ad**verse events by system organ class in at least three patients n (%)**			
Eye disorders	5 (33.3%)	11 (68.8%)	Not reported
Infections and infestations	5 (33.3%)	6 (37.5%)	Not reported
Local adverse drug reactions n (%)			
Any	15 (100%)	11 (68.8%)	Not reported
Stinging	12 (80%)	5 (50%)	Not reported
Redness	9 (60%)	7 (43.8%)	Not reported
Burning	10 (66.7%)	4 (25%)	Not reported
Blurred vision	9 (60%	4 (25%)	Not reported
Itching	6 (40%)	4 (25%)	Not reported
Other	3 (20%)	3 (18.8%)	Not reported
Abbreviations: vCH viscous cysteamine hydrochloride; CH aqueous cysteamine hydrochloride;			

Table 8 CHOC (Cysteamine Hydrochloride for nephrOpathic Cystinosis - main study) data reported in EPAR only

	vCH (0.55%) eye drops	CH (0.10%) eye drops	P-value
N= 42 eyes	**n=22 eyes**	**n=20 eyes**	
Primary outcome: Reduction in corneal cystine crystal density as assessed by in vivo confocal microscopy (IVCM) mean (SD) **Full analysis set (FAS; all randomised patients/eyes receiving at least one treatment)**			
Effect estimate (mean difference between groups)	3.84 (0.84) (95% CI 2.11 to 5.56)		<0.0001
	vCH (0.55%) eye drops	**CH (0.10%) eye drops**	**P-value**
	n=18 eyes	**n=15 eyes**	
Primary outcome: Reduction in corneal cystine crystal density as assessed by in vivo confocal microscopy (IVCM) mean (SD) **Per protocol set (PPS) eye population of the FAS who did not meet any major protocol deviations**			
Absolute change in IVCM from baseline at 90 days follow-up (total score)	-4.29 (2.96)	-0.82 (3.43)	P=0.0002
	n=18 eyes	n=14 eyes	
Relative change in IVCM from baseline at 90 days follow-up (percentage score)	-40.0% (16.5)	-2.59% (34.9)	
Effect estimate (mean difference between groups)	3.48 (95%CI 1.67 to 5.29)		P=0.0002
Secondary outcome: clinician assessed photophobia mean (SD) **(FAS; all randomised patients/eyes receiving at least one treatment)**			
	n=30 eyes	n=32 eyes	
Effect estimate (mean difference between groups)	0.69 (95%CI 0.23; to 1.14)		P<0.0048
	n=22 eyes	n=24 eyes	
Responder analysis (number of eyes with photophobia at baseline whose photophobia score reduced with at least 1 or 2 points on a 0-5 point scale)	19 % reduced by 2 points 35% reduced by 1 point	0 % reduced by 2 points 7% reduced by 1 point	Not reported
Secondary outcome: Patient rated photophobia mean (SD) **(FAS; all randomised patients/eyes receiving at least one treatment)**			
	n=30 eyes	n=31 eyes	
Absolute change from baseline at Day 90	-0.27 (0.58)	0.23 (0.72)	Not reported
Abbreviations: vCH viscous cysteamine hydrochloride aCH aqueous cysteamine hydrochloride			

Labbé et al. (2014) OCT-1 (Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis)

	aCH 0.1% eye drops (Run in period day -30[a]; Month -1)	vCH 0.55% eye drops Day 1 (baseline-Month 0)	vCH 0.55% eye drops (Month 48)
Corneal crystal density:(IVCM total score; µm) mean (SD) at each visit			
IVCM total score	11.38 (3.30) Range 6-16	11.38 (2.94) Range 7-18	8.13 (4.15) Range 5 to 15
Crystal thickness (CCCS) mean (SD) at each visit			
CCCS total score	2.94 (0.11) Range 2.75 to 3	2.91 (0.13) Range 2.75 to 3	2.75 (0.32) Range 2.25 to 3
Depth/ thickness of corneal crystal deposits (OCT) mean (SD) at each visit			
OCT Depth of crystal deposition	301.4 (105.1) Range 202 to 545	306.4 (98.9) Range 200 to 531	265.1 (119.3) Range 173 to 568
OCT central corneal thickness	538.3 (22.2) Range 510 to 571	543.1 (28.6) Range 502 to 580	552.8 (27.3) Range 501 to 577
Photophobia scores mean (SD) at each visit			
Clinician assessed photophobia	2.8 (1.1) Range 1 to 4	2.5 (0.9) Range 1 to 4	1.6 (1.0) Range 0 to 3
Best corrected visual acuity (logMAR) mean (SD) at each visit			
VA (logMAR)	0.1 (0.1) Range -0.0 to 0.3	0.1 (0.1) Range -0.1 to 0.3	0.1 (0.1) Range -0.1 to 0.3
Intraocular pressure (IOC- mmHg) mean (SD) at each visit			
IOP (mm Hg)	10.8 (2.0) Range 8 to 14	11.8 (2.5) Range 8 to 16	14.8 (2.3) Range 12 to 18
Number of applications of daily eye drops mean (SD) at each visit			
Number of instillations per day	4.0 (0.5) Range 3 to 5	4.0 (0.5) Range 3 to 5	3.0 (0.9) Range 1 to 4
Safety outcomes			
	• 7 out of 8 patients reported a total of 44 adverse events during 48 month study follow-up • No serious adverse events or significant adverse events were related to the treatment • All patients reported some symptoms at instillation during the first 24 months. • Stinging was reported in 55%; blurred vision in 25% and burning after instillation in 19% of people • Pain at instillation (measured by a 0-100 visual analogue scale) was 27 mm higher in the 0.55 vCH instillations than 0.1% CH formulation, but decreased and remained <10mm at month 48 • In the last 30 days (of the 48 month period) 2 patients had stinging after instillation		

[a] Patients received aqueous cysteamine eye drops at usual frequency
Abbreviations: vCH viscous cysteamine hydrochloride; CH aqueous cysteamine hydrochloride; IVCM in vivo confocal microscopy; CCCs corneal cystine crystal score; OCT optical coherence tomography; IOP intra ocular pressure

Table 10 OCT-1 (Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis) data reported in EPAR only

	vCH 0.55% eye drops (Month 60)
Corneal crystal density:(IVCM total score; µm) mean (SD) at each visit	
IVCM total score	7.9 (4.4) Range not reported
Absolute change from baseline	-3.4 (2.8) Range not reported
percentage change from baseline	-32.7 % (25.4) Range and p value not reported
Crystal thickness (CCCS) mean (SD) at each visit	
CCCS total score	Not reported
Depth/ thickness of corneal crystal deposits (OCT) mean (SD) at each visit	
OCT Depth of crystal deposition	Not reported
OCT Central corneal thickness	Not reported
Photophobia scores mean (SD) at each visit	
Clinician assessed photophobia	1.6 (0.9) Range not reported
Best corrected visual acuity (logMAR) mean (SD) at each visit	
VA (logMAR)	Not reported
Intraocular pressure (IOC- mmHg) mean (SD) at each visit	
IOP (mm Hg)	Not reported
Number of applications of daily eye drops mean (SD) at each visit	
Number of instillations per day	Not reported
Safety outcomes	
Stinging n=7 (87.5%); Blurred vision n= 6 (75%); Burning n= 4 (50%); Discomfort n=2 (25%) Itching 2 n= (25%); Sticky eyes n=2 (25%) Irritation n= 1 (12.5%); Irritation eyelid n= 1 (12.5%) Redness n=1 (12.5%); Watering n= 1 (12.5%)	
Abbreviations; vCH; viscous cysteamine hydrochloride; CH aqueous cysteamine hydrochloride	
Abbreviations: vCH viscous cysteamine hydrochloride; IVCM in vivo confocal microscopy; CCCs corneal cystine crystal score; OCT optical coherence tomography; IOP intra ocular pressure	

Appendix 5 Grading of the evidence base

[NHS England has requested that NICE use the following system for grading the evidence:]

Each study is assigned one of the following codes:

NSF-LTC Categories of research design

Primary research-based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research-based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	**Criteria**
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.