Clinical Priorities Advisory Group Summary Report

Agenda item	4.5
Date of Meeting	11/05-13/05/2026
Title of the Proposition	Delayed-release mercaptamine bitartrate for patients with nephropathic cystinosis (Age >1 years)
Unique Reference Number	2338
Programme of Care	Internal Medicine
Clinical Reference Group	Renal Services
Service/treatment status	Highly Specialised Service

Action requested

Support the adoption of the policy proposition

Recommended its relative prioritisation.

Summary of the proposition:

Delayed-release (DR) mercaptamine bitartrate is recommended to be available as a routine commissioning treatment for nephropathic cystinosis within the criteria set out in the policy proposition.

Nephropathic cystinosis is a rare, life-long incurable autosomal recessive genetic disease that leads to accumulation of the amino acid cystine in cells in the body. This reduces life expectancy and can notably lead to chronic kidney disease often requiring dialysis or transplant in adulthood. Extra-renal complications include poor growth, ocular involvement, hypothyroidism, bone disease and diabetes.

While there is no cure for nephropathic cystinosis, a medication, referred to as cystine-depleting therapy, can be used to reduce the accumulation of cystine in the cells. This improves symptoms and delays the complications of this condition. Currently, the only available commissioned cystine-depleting therapy is immediate-release (IR) mercaptamine bitartrate which is a capsule taken with food every 6 hours. This means that patients and/or carers must wake during the night to take this medication, as well as disrupt their school and/or work hours, as well to sleep during the night for both patients and carers. This could improve adherence to treatment for patients, delay the complications of cystinosis and improve quality of life for patients.

Clinical Panel recommendation:

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

Assurances

The committee is asked to receive the following assurance:		
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of developmental and governance steps.	
2.	The Deputy Director of Acute Programmes confirms the proposition is supported by the following documentation (please tick the box where applicable)	
	Draft Clinical Commissioning policy proposition	☒
	Evidence Review	☒
	Public Health Evidence Report	☐
	Evidence to Decision Making (EtD) Summary	☒
	Equalities and Heath Inequalities Assessment (EHIA)	☒

	Prior Approval Form	☒
	Engagement Report	☒
	13Q Assessment and Patient & Public Voice Assurance	☒
	Clinical Panel Report	☒
	Policy Working Group membership	☒
	Other (please state if required)	☐
3.	The Deputy Director of Finance (Specialised Commissioning) confirms that the Impact Assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.	
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the Service and Operational Impact Assessments have been completed.	
5.	The Deputy Director of Quality and Nursing (Specialised Commissioning) confirms that the proposed quality indicators have been adequately defined (where applicable).	

Evidence Review Summary

In people with nephropathic cystinosis what the clinical effectiveness and safety of is delayed-release mercaptamine bitartrate compared to current standard care?[1]

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Disease response **Certainty of evidence:** Very low to low	This outcome is important to patients because it reflects how effective the treatment is at preventing disease progression. One three week crossover RCT, one prospective single-arm study [long-term follow-up to the crossover RCT], one prospective cohort study, and one prospective case series provided evidence relating to disease response in patients with nephropathic cystinosis. Disease response was defined as WBC/leukocyte cystine levels (nmol hemicystine/mg protein) in all four papers. The single-arm follow-up study, cohort study, and case series also provided evidence on the proportion of patients or study visits where WBC/leukocyte cystine levels were <1nmol hemicystine/mg protein[2] during treatment with DR mercaptamine bitartrate. The follow-up durations ranged from three weeks to 24 months. WBC/leukocyte cystine levels (nmol hemicystine/mg protein) *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* **At three week crossover** One three week crossover RCT (Langman et al 2012; n=41) showed that mean WBC cystine levels remained optimal (i.e. ≤1 nmol hemicystine/mg protein) in patients with nephropathic cystinosis when treated with DR cysteamine bitartrate and IR cysteamine bitartrate (LSM [SEM]: 0.70 [0.19] and 0.97 [0.19]

	nmol hemicystine/mg protein, respectively), although three patients treated with IR cysteamine bitartrate had a mean WBC cystine level >2 nmol hemicystine/mg protein and were considered *"not well controlled"*. The difference between treatment groups was *statistically significant* (LSM [SEM; 95.8% CI]:[3] -0.27 nmol hemicystine/mg protein [0.36; -0.63 to 0.09]; p<0.001) and indicated greater benefit with DR cysteamine bitartrate[4]. **(LOW)** *DR mercaptamine bitartrate vs no comparator* **At 12 months follow-up** One prospective cohort study (Gaillard et al 2021; n=17) showed an increase in leukocyte cystine levels from baseline to 12 months follow-up during treatment with DR cysteamine bitartrate in patients with nephropathic cystinosis (median: 0.3 nmol hemicystine/mg protein [range 0.1 to 2.5] to 1.1 nmol hemicystine/mg protein [range 0.3 to 2.7], respectively), with the median follow-up result being greater than the optimal target of ≤1 nmol hemicystine/mg protein. No statistical measures were reported. **(VERY LOW)** **At study exit (timeframe not clear)**[5] One prospective case series (Vaisbich et al 2022; n=13) reported that DR cysteamine bitartrate resulted in a *"clinically meaningful*" decrease (i.e. improvement) in WBC cystine levels from baseline to study exit in children with nephropathic cystinosis (mean: 3.2 nmol hemicystine/mg protein [SD 3.0] to 0.8 nmol hemicystine/mg protein [SD 0.8], respectively). The definition of a clinically meaningful effect size was not reported, but the change from baseline was *statistically significant* (p=0.04). **(VERY LOW)** **At 24 months follow-up** One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that WBC cystine levels *"were maintained under optimal control (<1 nmol hemicystine/mg protein)"* from baseline to 24 months follow-up during treatment with DR cysteamine bitartrate (mean: 0.43 nmol hemicystine/mg protein [SD 0.15] to 0.55 nmol hemicystine/mg protein [SD 0.34], respectively) in patients with nephropathic cystinosis. The change from baseline was *not statistically significant* (p=0.38). **(VERY LOW)** <u>Proportion of visits or participants with WBC/leukocyte cystine levels ≤1 nmol hemicystine/mg protein</u> *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* No evidence was identified for this outcome. *DR mercaptamine bitartrate vs no comparator* **At 12 months follow-up** One prospective cohort study (Gaillard et al 2021; n=17) reported that for each patient with nephropathic cystinosis, the median proportion of visits with leukocyte cystine levels ≤1 nmol hemicystine/mg protein[6] was 60% (range 0% to 100%) during 12 months follow-up with DR cysteamine treatment. No statistical measures were reported. **(VERY LOW)** **At study exit (timeframe not clear)** One prospective case series (Vaisbich et al 2022; n=13) reported that the proportion of children with nephropathic cystinosis who reached optimal WBC cystine levels (i.e. <1.0 nmol hemicystine/mg protein) increased from 20.0% (three of 15 children) at baseline to 76.9% (10 of 13 children) at study exit. No statistical measures were reported. **(VERY LOW)** **At 24 months follow-up** One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that *"mean WBC (cystine) remained below 1*

	nmol ½ cystine/mg protein during the entire study"[7] in patients with nephropathic cystinosis who were treated with DR cysteamine bitartrate. No further details were reported. **(VERY LOW)** **DR mercaptamine bitartrate vs IR mercaptamine bitartrate:** **One three week crossover RCT provided low certainty evidence that mean WBC cystine levels remained optimal (i.e. ≤1 nmol hemicystine/mg protein) in patients when they were treated with DR cysteamine bitartrate and when they were treated with IR cysteamine bitartrate, but there was a *statistically significant* difference between treatment groups which indicated greater benefit with DR cysteamine bitartrate.** **DR mercaptamine bitartrate vs no comparator:** **One prospective single-arm follow-up study, one prospective cohort study, and one prospective case series provided very low certainty evidence showing mixed findings. One prospective cohort study showed that WBC/leukocyte cystine levels increased from baseline to 12 months follow-up, with the median follow-up results being greater than the optimal target of ≤1 nmol hemicystine/mg protein, but no statistical measures were reported. One prospective case series reported a *"clinically meaningful"* decrease (i.e. improvement) in WBC cystine levels from baseline to study exit (timeframe not clear and the definition of a clinically meaningful effect size was not provided), and one prospective single-arm follow-up study reported that WBC cystine levels *"were maintained under optimal control (<1 nmol hemicystine/mg protein)"* from baseline to 24 months follow-up. These three studies also reported that WBC/leukocyte cystine levels were optimal (i.e. ≤1 nmol hemicystine/mg protein) at follow-up for a median of 60% of visits for each patient, or for 76.9% or 100% of patients, respectively.**
Treatment adherence **Certainty of evidence:** Very low	Treatment adherence is important to patients as it provides an indication of how well the treatment is tolerated. Effective treatment of nephropathic cystinosis requires good compliance to reduce cystine-crystal accumulation in cells. Good adherence can postpone time to developing renal failure requiring dialysis or transplant. One prospective cohort study provided comparative and non-comparative evidence on treatment adherence in patients with nephropathic cystinosis. Two different scores were used to measure adherence at 12 months follow-up; objective measures (i.e. electronic caps) were used to compare adherence to treatment with DR cysteamine versus SA cysteamine, while subjective measures (i.e. self-reported) were used to assess adherence to DR cysteamine for all patients (i.e. including the four patients who initially received SA cysteamine). Adherence score[8] [0 to 2[9]], measured using electronic caps (MEMs®)[10] *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* **At 12 months follow-up** One prospective cohort study (Gaillard et al 2021; n=17) reported higher adherence scores at 12 months follow-up when patients with nephropathic cystinosis were treated with DR cysteamine (median score: 1.8 [range 0.1 to 2.0; n=17, including the four patients initially receiving SA cysteamine)[11] compared to initial treatment with SA cysteamine (median score: 0.5 [range 0.3 to 1.0]; n=4). No statistical measures were reported. **(VERY LOW)** *DR mercaptamine bitartrate vs no comparator* evidence was identified for this outcome. Adherence level,[12] measured using electronic caps (MEMs®) *DR mercaptamine bitartrate vs IR mercaptamine bitartrate*

	At 12 months follow-up One prospective cohort study (Gaillard et al 2021; n=17) reported that at 12 months follow-up, a greater proportion of patients with nephropathic cystinosis had a good adherence score (of 2) when treated with DR cysteamine (median: 88% [range 1% to 99%]; n=17, including the four patients initially receiving SA cysteamine) compared to initial treatment with SA cysteamine (median: 2% [range 0% to 22%]; n=4). No statistical measures were reported. **(VERY LOW)** One prospective cohort study (Gaillard et al 2021; n=17) reported that at 12 months follow-up, a greater proportion of patients with nephropathic cystinosis had a partial or good adherence score (of 1 or 2) when treated with DR cysteamine (median: 91% [range 5% to 99%]; n=17, including the four patients initially receiving SA cysteamine) compared to initial treatment with SA cysteamine (median: 43% [range 27% to 78%]; n=4). The authors reported that three of four patients initially receiving SA cysteamine reported higher partial or good adherence scores when receiving DR cysteamine (74%, 75% and 92%) compared to SA cysteamine (27%, 52% and 78%). The fourth patient had similar adherence scores during DR and SA cysteamine treatment (40% and 35%, respectively). No statistical measures were reported. **(VERY LOW)** *DR mercaptamine bitartrate vs no comparator* evidence was identified for this outcome. Self-reported adherence [VAS score][13] *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* evidence was identified for this outcome. *DR mercaptamine vs no comparator* **At 12 months follow-up** One prospective cohort study (Gaillard et al 2021; n=17) reported high levels of self-reported adherence at 12 months follow-up in patients with nephropathic cystinosis (median score: 9 [range 4 to 10]). **(VERY LOW)** **DR mercaptamine bitartrate vs IR mercaptamine bitartrate:** **One prospective cohort study provided very low certainty evidence showing greater adherence to treatment (scored using objective measures) at 12 months follow-up when patients were treated with DR cysteamine compared to initial treatment with SA cysteamine, but no statistical measures were reported.** **DR mercaptamine bitartrate vs no comparator:** **One prospective cohort study provided very low certainty evidence showing high self-reported adherence (scored using subjective measures) at 12 months in patients with nephropathic cystinosis treated with DR cysteamine treatment.**
Progression of cystinosis associated renal disease **Certainty of evidence:** Very low	This outcome is important, as a goal of effective treatment would be to postpone the physical health consequences of cystinosis such as renal failure requiring dialysis or transplant which would have negative mental and physical health consequences to patients. One prospective single-arm study [long-term follow-up to the crossover RCT], one prospective cohort study, and one prospective case series provided non-comparative evidence relating to progression of cystinosis associated renal disease in patients with nephropathic cystinosis. These three studies provided evidence on eGFR during treatment with DR mercaptamine bitartrate from two weeks to 24 months follow-up. The prospective single-arm follow-up study also reported the number of patients needing renal transplant or renal dialysis at 24 months follow-up.

	eGFR (ml/min/1.73m^2) *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* evidence identified for this outcome. *DR mercaptamine bitartrate vs no comparator* **At two weeks follow-up** One prospective case series (Vaisbich et al 2022; n=NR[14]) showed an increase (i.e. improvement) in eGFR from baseline to two weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m^2 [SD 22.43] to 57.62 ml/min/1.73m^2 [SD 19.35], respectively). No statistical measures were reported. **(VERY LOW)** **At six weeks follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed that eGFR was similar at baseline and six weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m^2 [SD 22.43] to 55.43 ml/min/1.73m^2 [SD 17.41], respectively). No statistical measures were reported. **(VERY LOW)** **At 10 weeks follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed a decrease (i.e. decline) in eGFR from baseline compared to 10 weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m^2 [SD 22.43] to 53.83 ml/min/1.73m^2 [SD 17.72], respectively). No statistical measures were reported. **(VERY LOW)** **At six months follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase (i.e. improvement) in eGFR from baseline compared to six months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m^2 [SD 22.43] to 61.27 ml/min/1.73m^2 [SD 15.47], respectively). No statistical measures were reported. **(VERY LOW)** **At nine months follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase (i.e. improvement) in eGFR from baseline compared to nine months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m^2 [SD 22.43] to 61.71 ml/min/1.73m^2 [SD 23.43], respectively). No statistical measures were reported. **(VERY LOW)** **At 12 months follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase (i.e. improvement) in eGFR from baseline compared to 12 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m^2 [SD 22.43] to 60.92 ml/min/1.73m^2 [SD 25.63], respectively). No statistical measures were reported. **(VERY LOW)** One prospective cohort study (Gaillard et al 2021; n=15) reported that the median eGFR at baseline was 61.5 ml/min/1.73m^2 (range 7.9 to 132.2) in patients with nephropathic cystinosis and that *"GFR remained stable over the year in our cohort of patients"*. No further details were reported and no statistical measures were presented. **(VERY LOW)** **At 18 months follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase (i.e. improvement) in eGFR from baseline compared to 18 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m^2 [SD 22.43] to 67.20 ml/min/1.73m^2 [SD 31.17], respectively). No statistical measures were reported. **(VERY LOW)** **At study exit (timeframe not clear)**

	One prospective case series (Vaisbich et al 2022; n=14) showed an increase in eGFR from baseline compared to study exit in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m^2 [SD 22.43] to 63.79 ml/min/1.73m^2 [SD 21.44], respectively). The mean change from baseline to study exit was 8.14 ml/min/1.73m^2 (SD 15.48), but no statistical measures were reported. **(VERY LOW)** **At 24 months follow-up** One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that there was *no statistically significant* difference in eGFR from baseline to 24 months follow-up in patients with nephropathic cystinosis (mean: 63 ml/min/1.73m^2 [SD 25] to 57 ml/min/1.73m^2 [SD 25], respectively; p=0.32). **(VERY LOW)** <u>Number of patients needing renal transplant</u> *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* No evidence was identified for this outcome. *DR mercaptamine bitartrate vs no comparator* **At 24 months follow-up** One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT; n=40) reported that one patient treated with DR cysteamine bitartrate for nephropathic cystinosis underwent renal transplant at 17 months. **(VERY LOW)** <u>Number of patients needing renal dialysis</u> *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* No evidence was identified for this outcome. *DR mercaptamine bitartrate vs no comparator* **At 24 months follow-up** One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that one patient treated with DR cysteamine bitartrate for nephropathic cystinosis withdrew from the study at 21 months due to a decline in eGFR and need for renal dialysis. **(VERY LOW)** **DR mercaptamine bitartrate vs IR mercaptamine bitartrate:** **No evidence was identified for progression of cystinosis associated renal disease.** **DR mercaptamine bitartrate vs no comparator:** **One prospective single-arm follow-up study, one prospective cohort study, and one prospective case series provided very low certainty evidence relating to progression of cystinosis associated renal disease in patients with nephropathic cystinosis treated with DR mercaptamine bitartrate. One prospective cohort study reported that *"GFR remained stable over the year in our cohort of patients",* but no further details were reported. One prospective case series reported an increase (i.e. improvement) in eGFR from baseline up to study exit (timeframe not clear), but no statistical measures were reported. The prospective single-arm follow-up study reported that there were *no statistically significant* differences in eGFR from baseline to 24 months follow-up, although one patient each underwent renal transplant or renal dialysis.**
Important outcomes	
Quality of life	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in

Certainty of evidence: Very low	activities of daily living. Measurement of quality of life can help inform patient-centred decision making. One prospective single-arm study [long-term follow-up to the crossover RCT] provided evidence on quality of life in patients with nephropathic cystinosis up to 24 months follow-up, measured using the PedsQL[15]. Percentage change in PedsQL - intercept[16] *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* **Unclear follow-up [from three week crossover RCT to enrolment in the follow-up study)** One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that there was a *statistically significant* improvement in two of four PedsQL subscale scores and the total score in patients with nephropathic cystinosis when comparing scores assessed during previous treatment with IR cysteamine (in the three week crossover RCT) to treatment with DR cysteamine in the single-arm follow-up study: social function (p=0.049), school function (p=0.004), and total function (p=0.048), but there was *no statistically significant* difference in the subscale scores for physical function (p=0.160) and emotional function (p=0.136). **(VERY LOW)** *DR mercaptamine bitartrate vs no comparator* No evidence identified for this outcome. Percentage change in PedsQL - slope[17] *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* evidence identified for this outcome. *DR mercaptamine bitartrate vs no comparator* **At 24 months follow-up** One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that there were *no statistically significant* differences in any PedsQL subscale score or total score from baseline to 24 months follow-up in patients with nephropathic cystinosis treated with DR cysteamine: physical function (p=0.054), emotional function (p=0.890), social function (p=0.201), school function (p=0.126), and total function (p=0.072). **(VERY LOW)** **DR mercaptamine bitartrate vs IR mercaptamine bitartrate:** **One prospective single-arm follow-up study provided very low certainty evidence that there was a *statistically significant* improvement in two of four paediatric quality of life subscale scores and the total score in patients with nephropathic cystinosis when comparing scores during previous treatment with IR cysteamine (in the three week crossover RCT) to treatment with DR cysteamine during the single-arm follow-up study.** **DR mercaptamine bitartrate vs no comparator:** **One prospective single arm follow-up study provided very low certainty evidence that when patients were treated with DR cysteamine there was *no statistically significant* change in any of the paediatric quality of life subscale scores or total score from the follow-up study baseline to 24 months follow-up.**
Growth measurements	Growth measurements such as weight and height are important outcomes to patients and their carers as they can be a marker of treatment success. This is particularly valued by the paediatric patient cohort. One prospective single-arm study [long-term follow-up to the crossover RCT], and one prospective case series provided evidence on growth measures in patients with

Certainty of evidence: Very low	nephropathic cystinosis. Growth measurements included height, weight, BSA, and BMI, mainly measured using Z-scores, and results were reported at two weeks to 24 months follow-up. Z-score (height)[18] *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* evidence identified for this outcome. *DR mercaptamine bitartrate vs no comparator* **At two weeks follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in height Z-score from baseline to two weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to -2.9 [SD 1.5], respectively). No statistical measures were reported. **(VERY LOW)** **At 12 weeks follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in height Z-score from baseline to 12 weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to -2.5 [SD 1.5], respectively). No statistical measures were reported. **(VERY LOW)** **At six months follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in height Z-score from baseline compared to six months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to -2.0 [SD 1.7], respectively). No statistical measures were reported. **(VERY LOW)** **At 12 months follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in height Z-score from baseline compared to 12 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to -1.1 [SD 1.9], respectively). No statistical measures were reported. **(VERY LOW)** **At 18 months follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in height Z-score from baseline compared to 18 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to 0.1 [SD 2.1], respectively). No statistical measures were reported. **(VERY LOW)** **At study exit (timeframe not clear)** One prospective case series (Vaisbich et al 2022; n=15) showed an increase in height Z-score from baseline compared to study exit in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to 0.1 [SD 2.0], respectively). The authors stated that the increase was "*clinically meaningful*", but the definition of a clinically meaningful effect size was not provided and no statistical measures were reported. **(VERY LOW)** **At 24 months follow-up** One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that there was *no statistically significant* difference in height Z-score in patients with nephropathic cystinosis from baseline (mean: −1.15 [SD −0.93]) to 24 months follow-up (mean: -1.21 [SD -0.96]; p=0.46). **(VERY LOW)** Z-score (weight)[29] *DR mercaptamine bitartrate vs IR mercaptamine bitartrate*

	evidence identified for this outcome. *DR mercaptamine bitartrate vs no comparator* **At two weeks follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in weight Z-score from baseline to two weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -3.9 [SD 2.1], respectively). No statistical measures were reported. **(VERY LOW)** **At 12 weeks follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in weight Z-score from baseline to 12 weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -3.3 [SD 2.1], respectively). No statistical measures were reported. **(VERY LOW)** **At six months follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in weight Z-score from baseline compared to six months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -2.8 [SD 2.3], respectively). No statistical measures were reported. **(VERY LOW)** **At 12 months follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in weight Z-score from baseline compared to 12 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -2.2 [SD 1.7], respectively). No statistical measures were reported. **(VERY LOW)** **At 18 months follow-up** One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in weight Z-score from baseline compared to 18 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -1.3 [SD 2.0], respectively). No statistical measures were reported. **(VERY LOW)** **At study exit (timeframe not clear)** One prospective case series (Vaisbich et al 2022; n=15) showed an increase in weight Z-score from baseline compared to study exit in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -1.1 [SD 1.8], respectively). The authors stated that the increase was *"clinically meaningful"*, but the definition of a clinically meaningful effect size was not provided and no statistical measures were reported. **(VERY LOW)** <u>BMI</u> *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* evidence identified for this outcome. *DR mercaptamine bitartrate vs no comparator* **At study exit (timeframe not clear)** One prospective case series (Vaisbich et al 2022; n=14) showed a slight decrease in BMI Z-score from baseline compared to study exit in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -1.0 [SD 1.1] to -1.2 [SD 1.3], respectively). No statistical measures were reported. **(VERY LOW)** **24 months follow-up**

	One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that there was *no statistically significant* difference in BMI in patients with nephropathic cystinosis from baseline (mean: 18.2 kg/m^2 [SD 3.1]) to 24 months follow-up (mean: 18.3 kg/m^2 [SD 3.2]; p=0.27). **(VERY LOW)** Z-score (BSA)[29] *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* evidence identified for this outcome. *DR mercaptamine bitartrate vs no comparator* **At study exit (timeframe not clear)** One prospective case series (Vaisbich et al 2022; n=14) showed an increase in BSA Z-score from baseline compared to study exit in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -1.8 [SD 1.1] to -1.3 [SD 1.1], respectively). The authors stated that the increase was *"clinically meaningful"*, but the definition of a clinically meaningful effect size was not provided and no statistical measures were reported. **(VERY LOW)** **DR mercaptamine bitartrate vs IR mercaptamine bitartrate:** **No evidence was identified on growth measurements.** **DR mercaptamine bitartrate vs no comparator:** **One prospective single-arm follow-up study and one prospective case series provided very low certainty evidence relating to growth measurements in patients with nephropathic cystinosis treated with DR cysteamine bitartrate. One prospective case series reported a *"clinically meaningful"* increase (i.e. improvement) in height, weight and BSA Z-scores from baseline to study exit (timeframe not clear and the definition of a clinically meaningful effect size was not provided), but no statistical measures were reported. One prospective single-arm study reported that there were *no statistically significant* differences from baseline to 24 months follow-up in BMI or height Z-score.**
Activities of daily living **Certainty of evidence:** Not applicable	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. No evidence was identified for this outcome.
Progression of non-renal cystinosis associated disease **Certainty of evidence:** Not applicable	This outcome is important, as a goal of effective treatment would be to postpone the physical health consequences of cystinosis such as diabetes, hypothyroidism, muscle wasting and central nervous system involvement. To postpone or reduce the development of these complications would be valuable to patients as it would indicate an improvement in their overall health. No evidence was identified for this outcome.
Safety	
Frequency of adverse events **Certainty of evidence:**	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.

Very low to low	One crossover RCT, one prospective single-arm study [long-term follow-up to the crossover RCT], one prospective case series provided evidence on the occurrence of AEs in patients with nephropathic cystinosis. The follow-up durations ranged from three weeks to 24 months. Total number of AEs *DR mercaptamine bitartrate vs IR mercaptamine bitartrate* **At three week crossover** One three week crossover RCT (Langman et al 2012; n=41) reported a greater number of AEs during treatment with DR cysteamine bitartrate compared to IR cysteamine bitartrate in patients with nephropathic cystinosis (69 versus 25 AEs, respectively). The most common AEs were gastrointestinal disorders (n=31 in the DR cysteamine bitartrate group [23 were considered treatment-related and eight not treatment-related], n=11 in the IR cysteamine bitartrate group [eight were considered treatment-related and three not treatment-related]). No statistical measures were reported. **(LOW)** *DR mercaptamine bitartrate vs no comparator* **At study exit (timeframe not clear)** One prospective case series (Vaisbich et al 2022; n=15) reported that all children (100%) with nephropathic cystinosis experienced an AE during treatment with DR cysteamine bitartrate, but it was unclear whether they were treatment-related. **(VERY LOW)** **At 24 months follow-up** One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that all 40 (100%) patients with nephropathic cystinosis experienced a treatment-related AE up to 24 months follow-up. The most commonly occurring AE was gastrointestinal disorders which were experienced by 35 (87.5%) patients. **(VERY LOW)** **DR mercaptamine bitartrate vs IR mercaptamine bitartrate:** **One three week crossover RCT provided low certainty evidence showing a greater number of AEs occurred when patients were treated with DR cysteamine bitartrate compared to when they were treated with IR cysteamine bitartrate. For the most common AE (gastrointestinal disorders), most were considered to be treatment-related in both treatment arms. No statistical measures were reported.** **DR mercaptamine bitartrate vs no comparator:** **One prospective single-arm follow-up study and one prospective case series provided very low certainty evidence that all patients experienced an AE during treatment with DR cysteamine bitartrate; it was unclear whether the AEs were treatment-related in the case series, but all AEs were treatment-related in the single-arm follow-up study.**
Frequency of grade 3 or 4 adverse events **Certainty of evidence:** Very low to low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. One crossover RCT and one prospective case series provided evidence on the occurrence of SAEs (grade ≥3) in patients with nephropathic cystinosis. The follow-up durations ranged from three weeks to at least 18 months. Total number of SAEs

	DR mercaptamine bitartrate vs IR mercaptamine bitartrate **At three week crossover** One three week crossover RCT (Langman et al 2012; n=41) reported a greater number of SAEs during treatment with DR cysteamine bitartrate compared to IR cysteamine bitartrate in patients with nephropathic cystinosis (six versus one, respectively). For DR cysteamine bitartrate, three SAEs were gastrointestinal disorders, with one considered treatment-related and two not treatment-related. One SAE was related to metabolic and nutrition disorders, but not considered to be treatment-related. The remaining two SAEs were injury or procedural related and not treatment-related. For IR cysteamine bitartrate, the one SAE (vascular disorder) was not considered treatment-related. No statistical measures were reported. **(LOW)** *DR mercaptamine bitartrate vs no comparator* **At study exit (timeframe not clear)** One prospective case series (Vaisbich et al 2022; n=15) reported that DR cysteamine bitartrate resulted in a total of 36 SAEs which occurred in 12 (80.0%) patients with nephropathic cystinosis at study exit. This included five patients with gastroenteritis, four patients each with dehydration or vomiting, two patients each with electrolyte imbalance or gastrostomy, and one patient with other SAEs who was hospitalised and died the next day.[19] None of the SAEs were considered to be treatment-related. **(VERY LOW)** **DR mercaptamine bitartrate vs IR mercaptamine bitartrate:** **One three week crossover RCT provided low certainty evidence showing a greater number of SAEs when patients were treated with DR cysteamine bitartrate compared to when they were treated with IR cysteamine bitartrate, with most not considered treatment-related. No statistical measures were reported.** **DR mercaptamine bitartrate vs no comparator:** **One prospective case series provided very low certainty evidence that the majority of patients experienced at least one SAE, including one patient who died, but none were considered to be treatment-related.**
Abbreviations ADLs: activities of daily living; AE: adverse event; BMI: body mass index; BSA: body surface area; CI: confidence interval; DR: delayed-release; eGFR: estimated glomerular filtration rate; IR: immediate-release; LSM: least squares mean; MEMs: medication event monitoring system; m: metre; mg: milligram; min: minute; ml: millilitre; N: number; NR: not reported; nmol: nanomole; PedsQL: paediatric quality of life inventory; RCT: randomised controlled trial; SA: short-acting; SAE: serious adverse event; SD: standard deviation; SEM: standard error of the mean; VAS: visual analogue scale; WBC: white blood cell.	

In people with nephropathic cystinosis, what is the cost effectiveness of delayed-release mercaptamine bitartrate compared to current standard care?

Outcome	Evidence statement
Cost-effectiveness	No evidence was identified for cost effectiveness.

From the evidence selected, are there any subgroups of patients that may benefit from delayed-release mercaptamine bitartrate more than the wider population of interest?

Subgroup	Evidence statement
Patients with nephropathic cystinosis aged ≤11 years vs aged >11 years	One prospective cohort study (Gaillard et al 2021) reported subgroup results in patients with nephropathic cystinosis by age group ≤11 years versus >11 years for the critical outcome treatment adherence, defined as percentage of days with good adherence.[20] Adherence scores were during treatment with DR or SA cysteamine. **Critical outcomes** **Treatment adherence** One prospective cohort study (Gaillard et al 2021; n=17) reported that patients with nephropathic cystinosis aged ≤11 years experienced a greater percentage of days with a good adherence score (whether receiving DR or SA cysteamine) compared to patients aged >11 years (median [range]: 89% [80% to 99%] and 68% [1% to 99%], respectively); statistical measures were not reported. **One prospective cohort study reported that patients with nephropathic cystinosis aged ≤11 years experienced a greater percentage of days with a good adherence score compared to patients aged >11 years (whether receiving DR or SA cysteamine), but statistical measures were not reported.**
Abbreviations DR: delayed-release; N: number; SA: short-acting.	

Patient Impact assessment

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** Patients have severe problems in walking about • **ability to provide self-care:** Patients have severe problems in washing or dressing • **undertaking usual activities:** Patients are unable to do their daily activities • **experience of pain/discomfort**: Patients have moderate pain or discomfort • **experience of anxiety/depression:** Patients are severely anxious or depressed
Further details of impact upon patients: Living with cystinosis presents significant challenges. Patients must adhere to a 6-hour medication schedule with side effects including nausea, body odour and halitosis. The disease progresses to multi-systemic complications, namely renal failure, myopathy, bone problems, and reduced life expectancy. This is often accelerated as adherence is difficult. The demanding medication regimen can affect personal relationships and patients' mental health. A DR mercaptamine formulation will provide 12-hour dosing intervals. This will improve adherence, potentially delaying the renal complications of cystinosis and mitigating muscle and bone problems. The extended dosing interval will improve sleep, lessen fatigue and reduce intolerable side effects at school or work. **Further details of impact upon carers:**

Cystinosis is typically diagnosed in childhood. Carers face significant physical and mental exhaustion from the burden of administrating 6-hour medications and regular hospital appointments alongside the emotional strain of managing a progressive, life-limiting condition. Carers struggle to balance work, family life, and their own mental well-being.

Considerations

Equality and Health Inequalities Impact Assessment (EHIA)	
Summary of any potential impacts of the proposal	This proposition will advance equality of opportunity and/or reducing health inequalities. As demonstrated in this document, carers who are having to administer a medication every 6 hours are hugely impacted by the current available treatment regimen. A 12-hour dosing regimen will allow carers and patients to be able to sleep through the night, and reduce disruption during the day, reducing a burden on the entire family. The lack of sleep disruption will also improve the lives of adult patients. The difficulty adhering the current regimen can lead to renal failure more quickly. People from ethnic minority groups often wait a year longer for a transplant than Caucasian patients. People from minority groups are also more likely to have type B blood and with current low donation rates from these populations, adding to the difficulty in suitability for transplant. This policy proposition would benefit this protected characteristic, as improved adherence will postpone and reduce the need for transplant.
13Q Assessment	
PPVAG outcome	No consultation required
Were PPVAG assured of the level of stakeholder testing?	Yes
Rare Disease Advisory Group	
Yes The policy proposition was considered by RDAG by correspondence. Members supported the policy proposition progressing to CPAG prioritisation. RDAG were supportive of the proposition overall, noting in particular the extended time between doses and reduction of side effects.	

Pharmaceutical

Yes

This clinical commissioning policy proposition is for the use of a delayed-release (DR) formulation of mercaptamine bitartrate, which allows the reduced frequency of administration, twice daily, rather than four times a day dosing required with the currently commissioned immediate release formulation. The recommendations are aligned to the marketing authorisation for DR mercaptamine bitartrate, with the minor amendment to enable use in children aged 1 year and over. The marketing authorisation doesn't specify a younger age and includes dosing from 0kg. The age of 1 year in the policy proposition reflects the evidence review undertaken and the advice from the Policy Working Group.

Mercaptamine bitartrate is included on the NHS Payment Scheme Annex A, so is a high-cost drug.

National Programme of Care

The proposition received the full support of the Internal Medicine National Programme of Care (NPoC)