Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2824

mercaptamine gastro-resistant hard capsules (Procysbi®)

Chiesi

10 October 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a third resubmission assessed under the orphan equivalent medicine process

mercaptamine (Procysbi®) is accepted for use within NHSScotland.

Indication under review: treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.

A phase III, open-label, crossover study demonstrated that extended-release mercaptamine (Procysbi®) was non-inferior to immediate-release mercaptamine in control of white blood cell cystine levels in patients with nephropathic cystinosis who were previously controlled on mercaptamine therapy.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Within lysosomes, mercaptamine (cysteamine) participates in a reaction (thiol-disulphide exchange) that converts cystine to cysteine and cysteine-cysteamine, which can both then exit the lysosome. This reduces the lysosomal accumulation of cystine that characterises cystinosis. The dose of mercaptamine gastro-resistant hard capsules (Procysbi®) is titrated to an assay-dependent target (detailed in the summary of product characteristics [SPC]). The daily-targeted maintenance dose for newly diagnosed patients is 1.3 g/m^2 and the maximum dose is 1.95 g/m^2 given orally in two doses, 12 hours apart. Patients transferring from an immediate-release mercaptamine formulation, should maintain the same total daily dose.[1]

1.2. Disease background

Cystinosis is a rare genetic (autosomal recessive) disorder of metabolism in which cystine transport from the lysosomes is reduced or absent leading to accumulation of cystine and formation of crystals that damage organs. The kidneys are particularly affected, and patients develop Fanconi syndrome and progressive kidney failure. Cystinosis can affect other systems (for example, brain, cornea, conjunctiva, bone marrow, lymph nodes and leucocytes) with additional symptoms including growth failure, rickets and photophobia.[2] The estimated prevalence is 1 in 100,000.[3]

1.3. Treatment pathway and relevant comparators

Currently, an immediate-release formulation of mercaptamine hard capsule (Cystagon®), with the same indication as mercaptamine (Procysbi®) is used to treat patients with nephropathic cystinosis. It is administered as four doses each day (6 hours apart).[4]

1.4. Category for decision-making process

Eligibility for a PACE meeting

Mercaptamine gastro-resistant hard capsules (Procysbi®) meets SMC orphan equivalent criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The main comparative evidence was provided by the randomised RP103-03 study described in Table 2.1.[5, 6] This was supported by the comparative, non-randomised RP103-07 study[7, 8] and the non-comparative studies, RP103-04 and RP103-08 detailed in Section 2.3.2.[9-11]

Table 2.1. Overview of relevant studies

Criteria	RP-103-03[5, 6]
Study design	Open-label, phase III crossover.
Eligible patients	≥6 years of age and ≥21 kg with nephropathic cystinosis taking a stable dose (≥3 weeks) of mercaptamine (Cystagon®) that maintained WBC cystine level at ≤2.0 nmol hemicystine/mg protein. They had eGFR > 30mL/min/1.73m^2.
Treatments	Mercaptamine (Cystagon®) stable dose every 6 hours Mercaptamine (Procysbi®) every 12 hours, with daily dose about 70% of patient's prior daily dose of mercaptamine (Cystagon®) which could be increased if WBC cystine levels were higher than run-in or previous crossover period under

	mercaptamine (Cystagon®). Following an amendment, the initial dose of mercaptamine (Procysbi®) was changed to 80% (or up to 100%, if required) of the patient's usual dose of mercaptamine (Cystagon®).
Randomisation	After a 2-to-3-week run-in period where patients received their usual dose of mercaptamine (Cystagon®), patients were randomised equally to either mercaptamine (Cystagon®) for 3 weeks followed by crossover to mercaptamine (Procysbi®) for 3 weeks or the reverse sequence. Randomisation was stratified by WBC cystine level in run-in period (≤1.0 or >1.0 nmol hemicystine/mg protein).
Primary outcome	Peak WBC cystine levels measured every morning over 3 consecutive days at the end of each 3-week treatment crossover period.
Secondary outcomes	Pharmacokinetic parameters.
Statistical analysis	Primary analysis was non-inferiority in per protocol population at a margin of 0.3 for upper limit of 95.8% confidence interval. No formal testing of other outcomes.

Abbreviations: eGFR = estimated glomerular filtration rate; WBC = white blood cell.

Mercaptamine (Procysbi®) was non-inferior to mercaptamine (Cystagon®) for control of white blood cell (WBC) cystine levels in the primary analysis in the per protocol population and in the intention-to-treat population, as detailed in Table 2.2. Pharmacokinetic parameters were secondary outcomes and there appeared to be no difference in mean peak plasma concentration of mercaptamine between the two formulations.[2, 5]

Table 2.2 End-of-treatment White Blood Cell Cystine Levels in Study RP103-03.[2]

	Per protocol (n=39)		**Intention-to-treat (n=41)**	
	Procysbi®	**Cystagon®**	**Procysbi®**	**Cystagon®**
LSM WBC cystine level[a]	0.51	0.44	0.53	0.74
Difference (95.8% CI)	0.08 (0.01 to 0.15), p<0.001		-0.21 (-0.48 to 0.06), p<0.001	

a = measured in nanomole/mg protein over three days at the end of the three-week treatment period; CI = confidence interval; LSM = least square mean; WBC = white blood cell.

2.2. Health-related quality of life outcomes

In RP103-03, health-related quality of life was assessed using the Pediatric Quality of life Inventory (PedsQL) or, in the three adults in the study, the 36-item short form health survey (SF-36). Due to the small number of patients evaluated, data were difficult to interpret. It was noted by the regulator that improvements in quality of life had been seen by some patients.[2]

2.3. Supportive studies

RP103-07

An open-label phase IIIb study (RP103-07) recruited 41 patients ≥12 years with cystinosis who had a stable dose of mercaptamine (Cystagon®) for ≥3 weeks and had WBC cystine level > 1 nmol hemicystine/mg protein on average over at least two measurements during prior two years. All patients continued mercaptamine (Cystagon®) for the first three months and then switched to mercaptamine (Procysbi®) for four months. The primary analysis, which compared within-patient (Cystagon® versus Procysbi®) daily variation in WBC cystine level, was difficult to interpret due to differences in timing of measurements. Adherence was assessed via medication diary. [7, 8]

RP103-04

An open-label, single-arm, phase III study (RP103-04) recruited 40 patients who had completed RP103-03 plus an additional 20 patients: 14 children aged 1 to 6 years and 6 patients with a renal transplant, who had been on a stable dose of mercaptamine (Cystagon®) for at least 21 days. All

patients received mercaptamine (Procysbi®) dosed twice daily to achieve WBC cystine levels < 1 nmol hemicystine/mg protein. In patients who remained in the study, the proportion who achieved this varied .[2, 9]

RP103-08

An open-label, single-arm, phase IIIb study (RP103-08) recruited 17 patients, results were presented for 15 treatment-naïve patients <6 years old with nephropathic cystinosis. They all received mercaptamine (Procysbi®), with the dose adjusted to achieve WBC cystine levels < 1 nmol hemicystine/mg protein. At baseline, mean WBC cystine was 3.2 nmol hemicystine/mg protein and this was reduced at all subsequent assessments, with study exit mean of 0.8 nmol hemicystine/mg protein in 13 patients with measurements. At 12 months, 77% (10/13) of patients with assessments had cystine levels <1 nmol hemicystine/mg protein.[10, 11]

CrYSTobs (NCT02012114)

A prospective cohort study recruited patients with nephropathic cystinosis, at least 5 years of age, treated with oral mercaptamine. At inclusion, 4 of the 17 patients were receiving mercaptamine (Cystagon®) and 3 of them continued this for less than a month (26 to 29 days) before switching to mercaptamine (Procysbi®), with the other patient switching at 91 days; the other 13 patients received mercaptamine (Procysbi®) throughout. Adherence was measured using electronic caps (medication event monitoring [MEMs®]), and there were different definitions for Cystagon® and Procysbi®, with good adherence being daily intakes of 4 or 2 doses, and delays ≤1 or ≤2 hours, respectively. At the 12-month analysis, which included both mercaptamine (Cystagon®) and mercaptamine (Procysbi®) treatment periods, median percentage of days with good adherence was 2% (range 0 to 22%) and 88% (range 1% to 99%), respectively.[12] At the 24-month analysis, using data from mercaptamine (Procysbi®) treatment period only, there was a reduced rate of good adherence, 65% (range 1% to 99%). Median self-reported adherence (out of 10) had declined from 10 at baseline (range 7 to 10) to 8.4 (range 4 to 10) at 24 months.[13]

Metabolic Support UK Digital Survey

A digital survey undertaken by Metabolic Support UK and funded by Chiesi had usable responses from 28 patients taking mercaptamine (Cystagon®), dosed 4, 3, 2 and 1 times a day for 68%, 11%, 18% and 3% of patients, respectively, and 11 patients taking mercaptamine (Procysbi®) twice daily. For the respective treatments, overall 75% (Cystagon®) and 73% (Procysbi®) never forgot or only forgot a dose once a month (21% and 46% never forgot, 54% and 27% forgot once a month), while 25% and 27% forgot a dose at least once a week. The proportions of the respective groups who experienced minimal or no impact from (a) bad breath were 54% and 64%; and (b) body odour was 71% and 73%.[14, 15]

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In RP103-07, within the open-label, four-month mercaptamine (Procysbi®) phase, compared with the three-month mercaptamine (Cystagon®) phase, there were higher rates of adverse events, 93% (38/41) versus 76% (31/41), which were considered treatment-related in 49% versus 9.8%. Serious adverse events were reported by 15% and 12% of patients, respectively. In particular,

there were higher rates of gastrointestinal adverse events, including: nausea, 37% versus 10%; vomiting, 27% versus 4.9%; diarrhoea 24% versus 10%; upper abdominal pain, 15% versus 4.9%; abdominal pain, 7.3% versus 2.4%; and constipation, 4.9% versus 0.[7, 8]

In the open-label study RP103-03, adverse events rates were higher during the three-week phase when patients received mercaptamine (Procysbi®) compared with mercaptamine (Cystagon®): 58% (25/43) versus 32% (13/41). There appeared to be higher rates of the following adverse events in the mercaptamine (Procysbi®) group compared with mercaptamine (Cystagon®): vomiting (19% versus 12%); nausea (16% versus 7.3%); abdominal pain (9.3% versus 0); headache (9.3% versus 0); and hypokalaemia (7.0% versus 0). Serious adverse events were reported in six patients receiving mercaptamine (Procysbi®) and in one patient receiving mercaptamine (Cystagon®). One serious adverse event was considered possibly treatment related: abdominal discomfort in a patient receiving mercaptamine (Procysbi®), which led to the patient missing two days of treatment.[2, 6]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In a phase III study (RP103-03), mercaptamine (Procysbi®) demonstrated non-inferiority to mercaptamine (Cystagon®) for controlling WBC cystine levels. The extension study (RP103-04) provided evidence that suggests the effects were maintained over the longer term (up to four years).[2, 6, 9]
- Mercaptamine (Procysbi®) has a less demanding and disruptive 12-hourly dosing schedule compared with mercaptamine (Cystagon®), which has a strict six hourly dosing schedule.[1, 4]

4.2. Key uncertainties

- The studies in the clinical trial programme (RP103-03, -04, -07 and -08)[5-11, 16] and the supportive studies were open-label, which may have little impact on WBC cystine levels, the primary endpoint in RP103-03 and RP103-07 and only outcome analysed inferentially. However, this limits assessment of subjective outcomes such as quality of life, safety and adherence. The supporting studies[12-27] including real-world evidence, were additionally limited by very small sample sizes and often by retrospective, observational design. Small sample sizes are expected due to the rarity of the condition.
- It remains unclear whether switching from mercaptamine (Cystagon®) to mercaptamine (Procysbi®) substantially improves adherence or that any potential improvement is associated with benefits in clinical outcomes, such as renal function. Available data is too limited to confirm whether switching to mercaptamine (Procysbi®) is associated with reduced length of hospital stays.
- In RP103-03 and RP103-07, the incidence of gastrointestinal adverse events was higher with mercaptamine (Procysbi®) than with mercaptamine (Cystagon®). In RP103-03, it was suggested that this may be due to a difference in concomitant proton pump inhibitors, with many patients discontinuing these prior to the mercaptamine (Procysbi®) phase in accordance with the study protocol. However, in RP103-07, this was not the case. [2, 6, 7]

- It is uncertain whether switching from mercaptamine (Cystagon®) to mercaptamine (Procysbi®) is associated with improvements in halitosis or body odour. In the pivotal study, RP103-03, and the 7-month switching study, RP103-07, halitosis or body odour were not listed in the common adverse events reported in ≥5% of patients.[2, 6, 7] The supporting evidence from digital surveys or switching studies is limited by small sample size and open-label design, with differing outcomes across patients within the samples and across the studies.[14-19, 25] There is no pharmacokinetic or pharmacodynamic rationale for a difference between the two formulations.

*Other data were also assessed but remain confidential.**

4.3. Clinical expert input

Clinical experts consulted by SMC considered that mercaptamine (Procysbi®) may be a therapeutic advancement for a small number of patients who struggle to take mercaptamine (Cystagon®), which would continue to be prescribed to patients in the first instance.

4.4. Service implications

No major service implications are anticipated with the delivery of mercaptamine (Procysbi®) treatment.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of mercaptamine (Procysbi®), as an orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Nephropathic cystinosis is a rare, progressive, multi-organ, life-limiting condition with a heavy burden of morbidity throughout childhood and adult life. Care is extremely complex, time-consuming and demanding for the whole family, with consistent adherence difficult to achieve.
- The current treatment, mercaptamine (Cystagon®) is administered every 6 hours, requiring a dose during the night and during school or work, which disrupts sleep and daily routine. Mercaptamine treatment is associated with predictable post-dose side effects such as gastrointestinal upset, halitosis and body odour, that may be particularly distressing for children, teenagers and young adults and can be associated with social issues such as isolation and bullying. It can prevent young people from gaining independence; they remain reliant on caregivers to wake them for night-time doses. There is an unmet need for a greater choice of treatments with improved dosing schedules and tolerability.
- An alternative mercaptamine formulation provides patients with greater choice. Mercaptamine gastro-resistant capsules (Procysbi®) is administered every 12 hours, allowing a full night's restorative sleep and no dosing during school or work. PACE participants considered that twice daily dosing reduce the incidences of post-dose side effects. It is expected to increase treatment adherence and thereby disease control, while improving quality of life, social interactions, education and career development, resulting

in an overall positive impact on patients' and families' mental health. Patients report that its impact on overall disease management is life changing.

- Management of cystinosis is complex and involves other medications (including electrolyte replacement). Therefore, mercaptamine (Proscysbi®) whilst allowing a 12-hour break and sleep at night would not necessarily mean a complete break from all medications during the day. PACE participants considered that other medicines prescribed during the day do not have the same impact on the patient as mercaptamine.

Additional Patient and Carer Involvement

We received a joint patient group submission from Cystinosis Foundation UK, Metabolic Support UK and Kidney Research UK, which are all registered charities. Cystinosis Foundation UK has received 50% pharmaceutical company funding in the past two years, including from the submitting company. Metabolic Support UK has received 46.7% pharmaceutical company funding in the past two years, including from the submitting company. Kidney Research UK has received 3.32% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three patient groups participated in the PACE meeting. The key points of the joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

An economic case was presented and is summarised in table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime
Population	Treatment of proven nephropathic cystinosis. This includes patients who are treatment naïve or previously treated with mercaptamine (Cystagon®).
Comparators	mercaptamine (Cystagon®)
Model description	The company submitted a hybrid Markov-based model. Patients enter the model at risk of mortality and complications including end stage renal disease (ESRD), diabetes, and neuromuscular disorder (NMD). Incident probabilities are assigned for each complication to surviving patients, resulting in eight health states (plus death). All event probabilities were estimated independently. No discontinuation or treatment waning was included in the model.
Clinical data	The sources of clinical data used in the model primarily included a published retrospective cohort study by Brodin-Sartorius et al, and clinical expert opinion. The Brodin-Sartorius study[28] provided Kaplan-Meier curves which were digitised to provide pseudo individual patient datasets for each of the modelled complications (ESRD, diabetes and NMD) and mortality, to which parametric models were then fitted in order to generate risk of complications and death over the model time horizon. No patients within the study received mercaptamine (Procysbi®).
Extrapolation	For each of the modelled complications, goodness of fit statistics (AIC and BIC) were calculated to assess model fit with the long-term model predictions validated by visual inspection and expert opinion. The log-normal was judged the best-fitting curve for the extrapolation of time to complication onset for ESRD, NMDs and mortality and the gamma curve selected for diabetes. Expert clinical opinion was then used to estimate the efficacy of mercaptamine (Procysbi®) by upwardly adjusting the survival estimates of mercaptamine

<table>
<tr><td></td><td>(Cystagon®). Mortality and median time to onset of complications with mercaptamine (Cystagon®) and mercaptamine (Procysbi®) are summarised in the table below.

<table>
<tr><th rowspan="2">Event</th><th colspan="2">Median age at onset of event</th></tr>
<tr><th>mercaptamine (Cystagon®)</th><th>mercaptamine (Procysbi®)</th></tr>
<tr><td>ESRD</td><td>15 years</td><td>23 years</td></tr>
<tr><td>Diabetes</td><td>30 years</td><td>32 years</td></tr>
<tr><td>Neuromuscular disorders</td><td>32 years</td><td>42 years</td></tr>
<tr><td>Mortality</td><td>40 years</td><td>53 years</td></tr>
</table>

For ESRD and diabetes models, the under 5 data were used to model progression of complications. However, for NMDs and death data from the over-5 group were used as the under 5 data were limited.</td></tr>
<tr><td>Quality of life</td><td>A baseline estimate of health related quality of life was derived from PedsQL data collected in Langman et al,[16] mapped to EQ-5D using a published algorithm, with decrements for each modelled complication. The analysis estimated an initial baseline utility of 0.87, however, this value was increased to 0.92 on the basis of assumption. This adjustment was intended to account for the impact of complications present in the Langman population that are to be explicitly modelled with decrements applied for these. Estimates for complications are taken from separate published studies. These are applied as multiplicative decrements to the baseline utility.

Disutilities were included for the adverse events of halitosis, body odour and social isolation. Rates of halitosis and body odour varied by treatment arm and were according to a Metabolic Support UK survey[14] of patients treated with mercaptamine (Procysbi®) or mercaptamine (Cystagon®). Rates of social isolation were derived from the rates of halitosis and body odour by the company. The disutility of halitosis and body odour were assumed to be equal to that of periodontitis and social isolation disutility was from a systematic literature review.

An additional disutility of 0.24 was applied to mercaptamine (Cystagon®) treated patients to capture the quality of life impact of sleep disturbance associated with the 6-hourly treatment regimen.</td></tr>
<tr><td>Costs and resource use</td><td>The doses of mercaptamine (Procysbi®) and mercaptamine (Cystagon®) were based on a retrospective cohort study (O'Connell et al) where median doses were 1,030mg/m^2/day and 1,310mg/m^2/day for mercaptamine (Procysbi®) and mercaptamine (Cystagon®) respectively. This compares to the SPC target dose of 1,300 mg/m^2/day for mercaptamine (Procysbi®).

In both arms routine care comprising physician costs and blood tests was accounted for, with costs relating to modelled complications based on sources from the literature.</td></tr>
<tr><td>PAS</td><td>A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.</td></tr>
</table>

6.2. Results

Table 6.2 presents the base case results inclusive of the PAS discount for mercaptamine (Procysbi®). SMC is unable to present these results due to competition law issues.

Table 6.2 Base case results

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Procysbi	CIC	23.78	12.08	-	-	-	-
Cystagon	440,971	21.19	4.89	CIC	2.60	7.19	CIC

Abbreviations: CIC = commercial in confidence, ICER = incremental cost effectiveness ratio, LYG = life year gain, QALY = quality adjusted life year

6.3. Sensitivity analyses

The company provided probabilistic sensitivity analysis, deterministic sensitivity analysis (DSA) and scenario analysis. In the DSA, the parameters with the greatest impact on the estimates of cost effectiveness were the dose of mercaptamine (Procysbi®), the baseline utility of patients with nephropathic cystinosis and the disutility of sleep disruption.

The results of key scenario analyses are presented in table 6.3.

Table 6.3 Key scenario analyses

#	Parameter	Base case	Scenario	Incr. cost (£)	Incr. QALYs	ICER (£/QALY)
1	Clinical benefit in terms of time to complication and mortality	Included	Excluded	CIC	5.31	CIC
2	Caregiver disutility	Excluded	Including caregiver disutility until age 16 (1 per patient)	CIC	8.29	CIC
3			Including caregiver disutility until age 18 (1 per patient)	CIC	8.45	CIC
4	Procysbi dose	1,030mg/m^2	RP103-03 study dose	CIC	7.19	CIC
5			1,200mg/m^2	CIC	7.19	CIC
6			1,287mg/m^2	CIC	7.19	CIC
7	Sleep disruption disutility	0.24 derived from Chalet et al 2024[29] by subtracting sleep deprived utility scores from 1	0.092 from Chalet et al 2024 by subtracting from general population utility according to study demographics	CIC	4.05	CIC
8			0.193 from Chalet et al 2024 by subtracting from general population utility using mean age of Scottish cystinosis patients (age 14-years)	CIC	6.19	CIC
9	Mean baseline utility score	General population at 5-years	Langman et al[16] = 0.873	CIC	7.05	CIC

		of age = 0.92				
10	Analysis method	Cost utility analysis	Cost minimisation analysis	CIC	N/A	N/A
11	Adverse events (halitosis, body odour and social isolation)	Included	Excluded	CIC	7.68	CIC
12	Adverse event disutility methodology	Additive	Multiplicative	CIC	5.90	CIC
13	GI side effect disutilities	Excluded	Included	CIC	7.16	CIC
14	Revised base case – alternative approach to calculating disutilities	Sleep deprivation disutility = 0.24 Social isolation disutility = 0.356	Sleep deprivation disutility = 0.193 Social isolation disutility = 0.295	CIC	6.25	CIC
C1	Combined scenarios	Scenarios 1 + 7		CIC	2.18	CIC
C2		Scenarios C1 + 5		CIC	2.18	CIC
C3		Scenarios C2 + 11		CIC	CIC	CIC
C4		Scenario C3 + 2		CIC	3.06	CIC

Abbreviations: CIC = commercial in confidence GI = gastrointestinal, ICER = incremental cost effectiveness ratio, LYG = life year gain, N/A = not applicable, QALY = quality adjusted life year

6.4. Key strengths

- The model is relatively simple and focuses on the key complications associated with nephropathic cystinosis.
- The limitations of the clinical data to support any clinical benefits with mercaptamine (Procysbi®) are acknowledged and explored through more realistic sensitivity and scenario analyses.

6.5. Key uncertainties

- There are no robust clinical data to support the large quality-adjusted life-year (QALY) gain estimated by the model for mercaptamine (Procysbi®). The model predicts significant benefits with mercaptamine (Procysbi®) due to improved adherence to the treatment regimen compared to the 6-hourly regimen required with mercaptamine (Cystagon®), thus resulting in a later onset of complications and reduction in mortality. This improved clinical benefit is highly uncertain and is based largely on clinical expert opinion with some

attempts made to validate the estimates from a variety of literature sources. When the clinical benefit of treatment is removed the ICER increases (Scenario 1).

- The model applies a disutility (0.24) for mercaptamine (Cystagon®) treated patients in order to capture the quality of life impact of sleep disturbance as a result of the 6-hourly treatment regimen. The approach taken by the company to calculate the disutility from the published literature was highly uncertain as it subtracted the reported quality of life from study participants with sleep deprivation from 1, which would imply the participants were in perfect health other than experiencing sleep deprivation. When an alternative approach was taken to derive a sleep deprivation disutility, by subtracting study participants reported quality of life from age and gender adjusted general population utility scores, using the source preferred by the company, this resulted in lower estimate of the sleep deprivation disutility (0.092). When this alternative disutility was used in the analysis this resulted in a higher estimate of cost effectiveness (Scenario 7).
- The model included adverse event disutilities for body odour and halitosis which varied by treatment arm according to rates observed in a digital survey conducted by Metabolic Support UK (MSUK) which was limited by small sample size and open-label design. This meant that there was uncertainty around whether these would reflect rates of these adverse events experienced by patients in Scottish clinical practice. The overall magnitude of difference in rates of these adverse events between the treatment arms was small as was the disutility associated with them. This resulted in the inclusion of adverse event disutility for body odour and halitosis having a minimal impact on the results of the cost effectiveness analysis.
- The model included an adverse event disutility for social isolation at rates per treatment arm which the company described as being derived from the rates of body odour and halitosis observed in the MSUK digital survey. The company did not provide sufficient explanation as to the methodology used to obtain the estimated proportion of patients experiencing social isolation per treatment arm which was a source of of uncertainty. One-way sensitivity analysis showed that this was not a key driver of the cost effectiveness results.
- The exclusion of gastrointestinal (GI) adverse events which favoured Cystagon in the RP103-07 and RP103-03 study was uncertain. A scenario analysis that explored including GI adverse events had a minimal impact on the estimate of cost effectiveness (Scenario 13).
- There is some uncertainty regarding the likely dose of mercaptamine (Procysbi®) that will be used in practice. The dose in the model was based on real world data which results in a lower dose than the target dose in the SmPC. Results were sensitive to a higher dose more aligned with the target dose (Scenario 5), using the dose from the clinical study RP103-03 (Scenario 4) or by increasing the base case dose by 25% (Scenario 6).
- The baseline utility value (0.92) may be high when compared with general population norms. Applying a lower utility value had an upward impact on the ICER (Scenario 9).

- No treatment discontinuation or treatment waning were included in the model, which may be an oversimplification given the modelled time horizon. The company noted that clinical expert opinion supported these assumptions. While it may have been more accurate to include these aspects in the model structure, it may also have been challenging to find any data to support the estimates and also increased the model complexity.
- When the clinical benefit of treatment with mercaptamine (Procysbi®) in terms of time to complications or mortality was removed and an alternative sleep deprivation disutility were combined this led to a much higher estimate of cost effectiveness (Scenario C1). The estimate of cost effectiveness became even higher when an alternative dose for mercaptamine (Procysbi®) was also considered in a combined scenario (Scenario C2) and when adverse event disutilities were also excluded (Scenario C3).

7. Conclusion

The Committee considered the benefits of mercaptamine (Procysbi®) in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as mercaptamine (Procysbi®) is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted mercaptamine (Procysbi®) for use in NHSScotland.

8. Guidelines and Protocols

No clinical guidelines were identified.

9. Additional Information

9.1. Product availability date

November 2017

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Mercaptamine (Procysbi®)	1.3 g/m^2 per day orally in two divided doses	32,612 to 163,058

Costs from BNF online on 11 June 2025. Costs based on doses recommended in summary of product characteristics which range from 200 mg to 1000 mg twice daily. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. Chiesi Ltd. Mercaptamine gastro-resistant hard capsule (Procysbi®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 8 July 2024.
2. European Medicines Agency (EMA). European Public Assessment Report (EPAR) mercaptamine (Procysbi®) EMEA/H/C/002465, 27 June 2013.
3. European Medicines Agency (EMA). Committee for Orphan Medicinal ProductS recommendation for maintenance of orphan designation at the time of marketing authorisation, EMA/COMP/415414/2013, 7 October 2013.
4. Recordati Rare Diseases UK Ltd. Mercaptamine hard capsule (Cystagon®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 10 February 2025.
5. Langman CB, Greenbaum LA, Sarwal M, et al. A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety. Clinical journal of the American Society of Nephrology 2012; 7(7): 1112-1120.
6. Raptor Therapeutics. Clinical study report RP103-03, 29 December 2011.
7. Clinicaltrials.gov. Record for RP103-07, NCT01733316.
8. Horizon Pharma. Clinical study report RP103-07, 16 March 2018.
9. Horizon Pharma. Clinical study report RP103-04, 22 March 2018.
10. Vaisbich MH, Caires Ferreira J, Price H, et al. Cysteamine bitartrate delayed-release capsules control leukocyte cystine levels and promote statural growth and kidney health in an open-label study of treatment-naïve patients <6 years of age with nephropathic cystinosis. Journal of Inherited Metabolic Disease Reports 2022; 63(1): 66-79.
11. Horizon Pharma. Clinical study report RP103-08, 7 June 2017.
12. Gaillard S, Roche L, Lemoine S, et al. Adherence to cysteamine in nephropathic cystinosis: A unique electronic monitoring experience for a better understanding. A prospective cohort study: CrYSTobs. Pediatric nephrology 2021; 36(3): 581-589.
13. Grosyeux C, Gaillard S, Morin D, et al. Adherence to delayed-release cysteamine in nephropathic cystinosis over time: data from the prospective CrYSTobs cohort study. Pediatric nephrology 2025; 40: 2319-27.
14. Smith L, Carroll v, Krepelka P, Hutchison A, Railton A. The Impact of Different Cysteamine Formulations on the Lives of People Living with Cystinosis. Metabolic Support UK. 2024.
15. Chiesi Ltd. Data on File: Metabolic Support UK Cystinosis Survey Results, 2024.
16. Langman CB, Greenbaum LA, Grimm P, et al. Quality of life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate. The Journal of pediatrics 2014; 165(3): 528-533
17. Ariceta G, Santos F, López Muñiz A, et al. Switching from immediate-to extended-release cysteamine in patients with nephropathic cystinosis: from clinical trials to clinical practice. Clinical Kidney Journal 2024; 17(4): sfae049.
18. Chiesi. Study Protocol: RELUCIR. Effectiveness and Safety of Switching from immediate- to extended-release cysteamine in nephropathic cystinosis patients: A Retrospective real-life study. 2020.
19. Bjerre A, Aase SA, Radtke M, et al. The effects of transitioning from immediate release to extended release cysteamine therapy in Norwegian patients with nephropathic cystinosis: a retrospective study. Pediatric nephrology 2023; 38(11): 3671-79.
20. van Stein C, Klank S, Grüneberg M, et al. A comparison of immediate release and delayed release cysteamine in 17 patients with nephropathic cystinosis. Orphanet Journal of Rare Diseases 2021; 16(1): 387.

21. Maltseva V, Ananin P, Vashurina T, et al. Early cysteamine treatment for nephropathic cystinosis: renal outcome of Russian children. Abstract at Pediatric nephrology 2022; 37: EP-285.
22. Elkhateeb N, Selim R, Soliman NA, et al. Clinical and neurophysiological characterization of early neuromuscular involvement in children and adolescents with nephropathic cystinosis. Pediatric nephrology 2022; 37(7): 1555-66.
23. Veys K, Zadora W, Hohenfellner K, et al. Outcome of infantile nephropathic cystinosis depends on early intervention, not genotype: A multicenter sibling cohort study. Journal of inherited metabolic disease 2023; 46(1): 43-54.
24. Hohenfellner K, Nießl C, Haffner D, et al. Beneficial effects of starting oral cysteamine treatment in the first 2 months of life on glomerular and tubular kidney function in infantile nephropathic cystinosis. Molecular Genetics and Metabolism 2022; 136(4): 282-8.
25. Ahlenstiel-Grunow T, Kanzelmeyer N, Froede K, et al. Switching from immediate- to extended-release cysteamine in nephropathic cystinosis patients: a retrospective real-life single-center study. Pediatric nephrology 2017; 32(1): 91-97.
26. Askiti V, Zampetoglou A, Komianou F, et a. Nephropathic cystinosis – a single center experience. Pediatric nephrology 2023; 38: 197.
27. Dohil R, Gangoiti JA, Cabrera BL, et al. Long-term treatment of cystinosis in children with twice-daily cysteamine. Journal of pediatrics 2010; 156(5): 823-827.
28. Brodin-Sartorius A, Tete MJ, Niaudet P, et al. Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults. Kidney international. 2012; 81(2):179-189.
29. Chalet FX, Albanese E, Egea Santaolalla C, et al. Epidemiology and burden of chronic insomnia disorder in Europe: an analysis of the 2020 National Health and Wellness Survey. J Med Econ. 2024;27(1):1308-1319.

This assessment is based on data submitted by the applicant company up to and including 22 August 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the

operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.