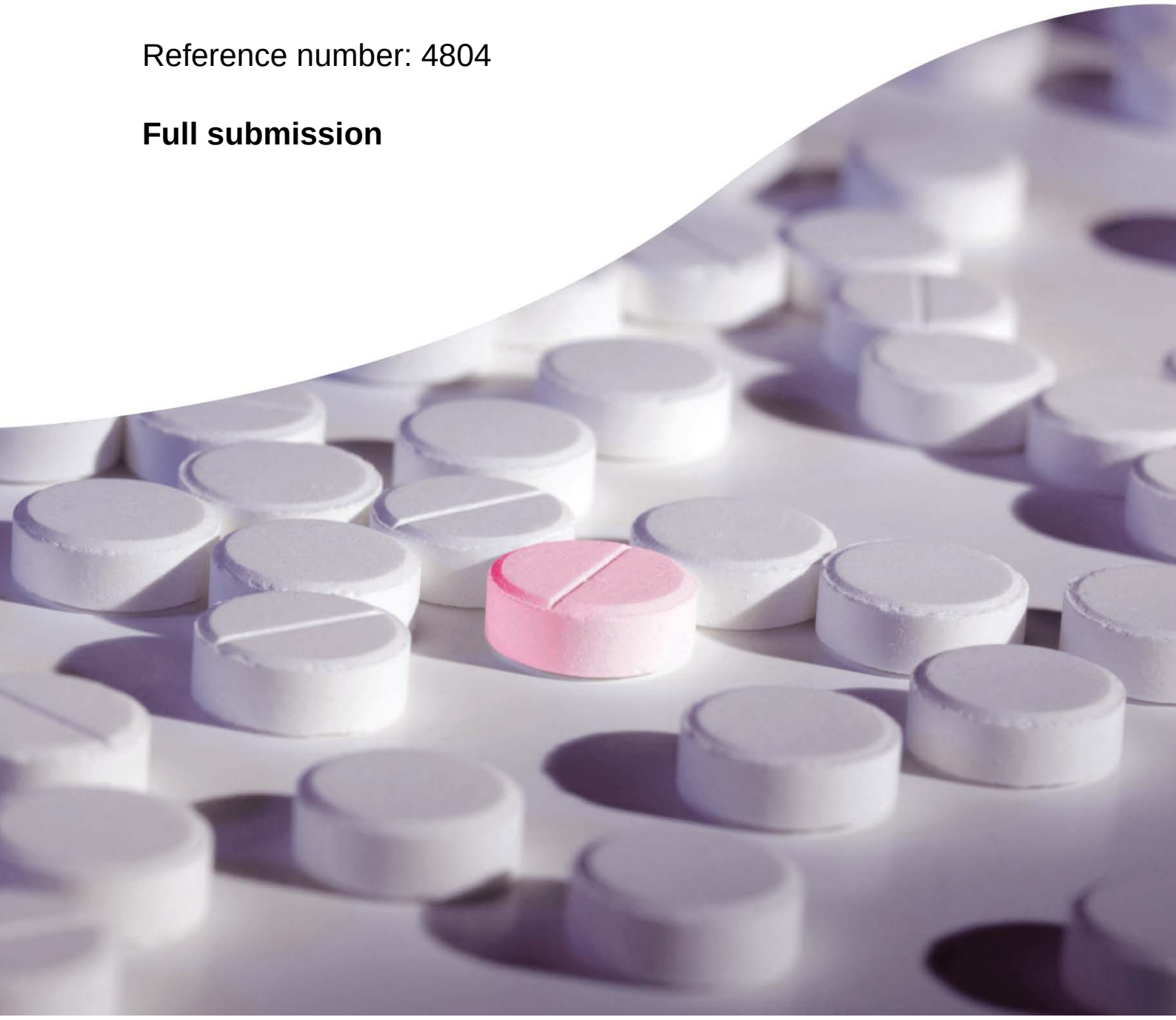
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Mercaptamine bitartrate (Procysbi®)
25 mg and 75 mg gastro-resistant hard capsules

Reference number: 4804

Full submission



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

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This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report
Mercaptamine bitartrate (Procysbi®) 25 mg and 75 mg gastro-resistant hard capsules

1.0 Key facts

Assessment details	Mercaptamine bitartrate (Procysbi®) for the treatment of proven nephropathic cystinosis. Mercaptamine bitartrate (also known as 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. Procysbi® provides a delayed-release formulation administered every 12 hours. It is presented as gelatine capsules filled with enteric coated beads.
Current clinical practice	The only treatment currently available is immediate-release mercaptamine bitartrate (Cystagon®) which is administered every six hours. The applicant company suggests Procysbi® (which contains the same active substance as Cystagon®) is to be used as an additional treatment option for patients with nephropathic cystinosis, either in newly diagnosed patients or for those patients who are not well-controlled on Cystagon® due to issues regarding adherence, tolerance or administration.
Clinical effectiveness	Results from a phase III study demonstrated non-inferiority of Procysbi® compared to Cystagon® in control of white blood cell cystine levels for a treatment period of three weeks. Long-term data demonstrated that Procysbi® controlled cystine levels and maintained stable renal function for up to four years but no long-term comparison versus Cystagon® was available.
Cost-effectiveness	A cost-utility analysis compares delayed-release mercaptamine bitartrate (Procysbi®) as an alternative treatment option for proven nephropathic cystinosis to immediate-release mercaptamine bitartrate (Cystagon®) in newly diagnosed patients two years of age and older or for patients who are not well-controlled on Cystagon® due to issues regarding adherence, tolerance or administration. The company base case suggests that Procysbi® is [commercial in confidence figure removed] more costly and produces an additional 6.04 quality-adjusted life-years (QALYs) compared to Cystagon® over the 100-year horizon with an incremental cost-effectiveness ratio

	(ICER) of [commercial in confidence figure removed] per QALY gained. This ICER estimate includes carer disutility. When carer disutility is removed from the analysis this produces an ICER of [commercial in confidence figure removed] per QALY gained. While the model structure appears robust to sensitivity and scenario analyses provided by the company, there is a lot of uncertainty around data inputs, with ICER estimates for Procysbi® ranging from [commercial in confidence figures removed] per QALY gained. The ICER is most sensitive to the dose of Procysbi®, acquisition cost of Procysbi®, baseline utility scores and disutility associated with Cystagon®, and the time to complications onset/mortality. AWTTC considers the plausible range of ICERs to be [commercial in confidence figures removed].
Budget impact	The company suggests that [commercial in confidence figure removed] patients would receive treatment with Procysbi® in Wales in Year 1, increasing to [commercial in confidence figure removed] by Year 5. The company estimates that introducing Procysbi® (with displacement of Cystagon®) would lead to an overall net cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5 with an overall budget impact over the 5-year period of [commercial in confidence figure removed]. Basic sensitivity analysis undertaken by the company suggests budget impact to be in the range from [commercial in confidence figures removed] over the 5-year time horizon. Whilst the budget impact analysis is subject to uncertainty AWTTC-sought clinical expert opinion and prescribing data for Cystagon® suggest the company's estimates are broadly reasonable.
Additional factors to consider	The European Medicines Agency designated Procysbi® as an orphan product in 2013; this designation expires in September 2023. The company and AWTTC consider Procysbi® eligible to be considered as an ultra-orphan medicine.

This assessment report is based on evidence submitted by Chiesi Limited and an evidence search conducted by AWTTC on 16 November 2021.

2.0 Background

2.1 Condition and clinical practice

Cystinosis is a rare, autosomal recessive congenital error of metabolism, in which transport of cystine across the lysosomal membrane is reduced or absent[1,2]. Cystine accumulates within cells, forming crystals that damage various organs: in particular, the kidneys, leading to progressive glomerular failure (renal Fanconi syndrome)[2]. Without specific treatment most children with cystinosis develop kidney failure before the age of ten, requiring dialysis or a kidney transplant[1]. Patients with cystinosis also suffer from growth failure, rickets, photophobia (due to cystine deposit in the cornea)[2], diabetes mellitus, hypogonadism, pulmonary dysfunction, muscle weakness, epilepsy, dementia and cerebral atrophy[3].

Cystinosis is diagnosed usually before the age of two[1]. Based on a prevalence of 1 in 100,000 there would be around 32 people living with cystinosis in Wales[4]. However, clinical expert opinion sought by the company reports 13 cystinosis patients in Wales[5].

There is no known cure for cystinosis and the aim of current treatment is to delay disease progression[5]. Mercaptamine bitartrate (also known as cysteamine) is currently the only cystine-depleting therapy[5]. Cystagon® is an immediate-release formulation of mercaptamine bitartrate licensed in the EU since 1997[6]. Treatment with Cystagon® must be initiated promptly after confirmation of the diagnosis of nephropathic cystinosis to achieve maximum benefit[6]. The maintenance dose of Cystagon® should be divided into four doses and has to be given strictly every six hours including a night time dose[6] as the cellular cystine level returns to the original high level after six hours[3]. Monitoring of the cystine concentration is required to adjust the dose[3] and the medicine must be taken life-long[7].

When adherence is consistent, mercaptamine can reduce cystine levels by 95%, preserve renal and extra-renal organ function, and improve overall survival[8]. However, Cystagon® has side effects such as bad breath, abnormal skin odour and gastrointestinal discomfort[2], which, together with the four times daily dosage regime, can interfere with patients' adherence to the treatment accelerating the disease's progress[5]. Adherence with Cystagon® is often insufficient to achieve a stable cystine level below the recommended therapeutic target value[3]. In a study it was reported that approximately 14% of patients did not tolerate treatment due to strong nausea and vomiting. In tolerant patients only 23% complied with the strict medication schedule, with 17% of patients taking medication only during the day[3]. Despite the severity of the disease and efficacy of mercaptamine adherence reduces with time particularly in adolescents and adults[8].

2.2 Medicine

Mercaptamine bitartrate (Procysbi®) is presented as a gelatine capsule, filled with enteric coated beads containing the same active substance as Cystagon®[2]. Procysbi® provides a delayed-release formulation (licensed September 2013[9]) for the treatment of proven nephropathic cystinosis. The goal of therapy is to maintain a white blood cell (WBC) cystine level < 1 nmol hemicystine/mg protein

when measured using the mixed leukocyte assay[9]. The dose of Procysbi® depends on whether the patient is an adult or child, and on whether they have previously received Cystagon®; please see the summary of product characteristics for further details[9].

Similarly to Cystagon®, treatment with Procysbi® must be initiated promptly, but the maintenance dose should be divided into two doses and be given every 12 hours, eliminating the need for night-time and midday administration[9]. For patients that have difficulties swallowing capsules, the beaded formulation allows the content of the capsules to be mixed with food or liquids[2]. The granules have a gastro-resistant coating so that the prolonged-release advantage is maintained. Procysbi® is released in the duodenum, which may reduce the potential for halitosis[5].

The applicant company suggest Procysbi® is to be used as an additional treatment option for patients with nephropathic cystinosis, either in newly diagnosed patients or for those patients who are not well-controlled on Cystagon® due to issues regarding adherence, tolerance or administration[5].

2.3 Comparators

The comparator included in the company's submission is mercaptamine bitartrate (Cystagon®).

2.4 Guidance and related advice

- Emma F, Nesterova G, Langman C, et al. Nephropathic cystinosis: an international consensus document. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association (2014)[10].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a Statement of Advice for the use of mercaptamine bitartrate (Procysbi®).

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, mercaptamine bitartrate (Procysbi®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

3.0 Clinical effectiveness

The company submission included evidence from one pivotal phase III crossover study (RP103-03)[7] that evaluated the non-inferiority of Procysbi® compared with Cystagon® in patients with nephropathic cystinosis, and its long-term follow-up study (RP103-04)[11]. The company also provided evidence from two long-term open-label single-arm studies (RP103-07[12] and RP103-08[13]) and from three real-world observational studies[14-16]. These studies were supportive but did not provide new information regarding the comparative efficacy of Procysbi® and are not discussed further.

3.1 Study RP103-03

RP103-03 was a multicentre, open-label, randomised, controlled, crossover study to assess the steady-state WBC cystine levels of delayed-release Procysbi® every 12 hours compared to immediate-release Cystagon® every 6 hours[2,7]. At the end of a two-week run-in period where patients were treated with Cystagon® at their current dose regimen, 43 eligible patients (average age 11.7 years, standard deviation 4.2 years[7]) were randomised to one of two treatment sequences; three weeks treatment with Cystagon® every 6 hours followed by crossover to three weeks of Procysbi® (mean daily dose 82% of the Cystagon® dose) every 12 hours or the reverse sequence (Procysbi® followed by crossover to Cystagon®)[2]. Patients were included in the study if they were six years of age or older, were on a stable dose of Cystagon® considered sufficient to maintain their WBC cystine level at ≤ 2.0 nmol hemicystine/mg protein, and had an estimated glomerular filtration rate (eGFR) > 30 ml/minute/1.73 m^2 body surface area[2].

The primary outcome was a non-inferiority comparison of peak WBC cystine levels between Procysbi® and Cystagon® measured every morning over three consecutive days at the end of each of the corresponding three-week treatment crossover periods[2,7]. Results demonstrated non-inferiority of Procysbi® compared to Cystagon® in the per protocol population; the upper limit of the 95.8% confidence interval (CI) of the difference (0.08 nmol hemicystine/mg protein) was less than the 0.3 non-inferiority margin[2] (See Table 1 for results).

Table 1. Results of white blood cell cystine level in study RP103-03[2]

	Per Protocol population (n = 39)		Intention to Treat population (n = 41)	
	Cystagon®	**Procysbi®**	**Cystagon®**	**Procysbi®**
WBC cystine level (LS mean ± SE) in nmol hemicystine/mg protein	0.44 ± 0.05	0.51 ± 0.05	0.74 ± 0.14	0.53 ± 0.14
Treatment effect (LS mean ± SE; CI 95.8%; *p*-value)	0.08 ± 0.03; 0.01 to 0.15; < 0.0001		−0.21 ± 0.14; −0.48 to 0.06; < 0.001	
CI: confidence interval; LS: least square; SE: standard error; WBC: white blood cell.				

3.2 Study RP103-04

RP103-04 was an open-label follow-up extension study to RP103-03 to assess the safety and tolerability of long-term repeat dosing of Procysbi® [11,17]. Forty of forty-one patients who completed study RP103-03 enrolled in RP103-04[11,17]. Twenty new patients were added to the study, including paediatric patients ≤ 6 years old (n = 14) and patients who received a kidney transplant (n = 6)[17]. For patients who had completed study RP103-03, WBC cystine levels remained < 1 nmol hemicystine/mg protein for an average treatment duration of 4.4 years[17]. This was achieved with a mean reduction in Procysbi® dosing over the same time interval from 43.5 (± 10.8) to 40.1 (± 13.1) mg/kg/day

($p = 0.05$)[11]. For patients ≤ 6 years old and patients who received a kidney transplant, mean cystine levels were similar to or lower than the baseline levels in the majority of visits[11]. In the study half of the patients received treatment for more than 5 years and stable renal function was maintained in all three subgroups[17].

The extension study assessed quality of life using the PedsQL tool in 39 patients (with fewer patients providing data at later timepoints) who had completed study RP103-03[11]. Upon entering the study as patients switched from Cystagon® to Procysbi® improvements were seen for social function, school function and total function. These improvements were maintained for two years of Procysbi® therapy. No significant change was seen for physical and emotional function scores[11].

3.3 Comparative safety

In study RP103-03 the most frequently reported adverse events (AEs) were gastrointestinal disorders such as vomiting, nausea or abdominal pain. More gastrointestinal AEs were reported during Procysbi® treatment than during Cystagon® treatment (30.2% versus 19.5%)[18]. Only one serious AE, abdominal discomfort in a patient receiving Procysbi®, was considered to be treatment-related. Patients receiving Procysbi® were asked to voluntarily stop use of proton pump inhibitors (PPIs) but could continue PPI use if they, the parent, carer or physician felt it was needed. Concomitant use of gastric acid inhibitors was almost seven times greater during Cystagon® treatment compared to treatment with Procysbi®[18]. The follow-up study RP103-04 confirmed that the long-term safety profile of Procysbi® was consistent with the findings from RP103-03 and with the known safety profile of Cystagon®[17]. The Committee for Medicinal Products for Human Use concluded that although the long-term safety data of Procysbi® are limited, the safety profile is expected to be similar to the well-established profile of Cystagon®[2].

3.4 Ongoing studies

- CrYSTobs: a French study in 17 patients with nephropathic cystinosis assessing adherence to mercaptamine treatment and WBC cystine levels. One-year results have been published[16] and a two-year follow-up is expected[5].
- [Commercial in confidence text removed].

3.5 AWTTC critique

- Non-inferiority of Procysbi® compared to Cystagon® was demonstrated over a period of three weeks of treatment in the pivotal study RP103-03. A long-term extension study showed that Procysbi® controls cystine levels and maintains stable renal function for up to four years. There is no long-term data comparing health outcomes for patients treated with Procysbi® versus Cystagon®.
- Clinical experts contacted by AWTTC highlighted that the administration of Cystagon® in the middle of the night is associated with major issues with compliance and difficulty for carers and patients in adhering to strict daily administration. The impact on lost sleep and attendance at school was highlighted by a clinical expert as being an issue with compliance with Cystagon®. The nausea and vomiting side effects were also raised

as affecting compliance with Cystagon®. There is therefore an unmet need for an alternative treatment involving less sleep disruption and reduced side effects.

- The clinical expert reported their experience of using the 12-hourly dosing for Procysbi® (versus 6 hourly dosing for Cystagon®) with one patient and reported it led to improved compliance, reduced gastrointestinal side effects, and resulted in better disease control and delayed progression of kidney disease. The medicine helped delay the need for kidney dialysis/transplantation.
- Procysbi® granules can be sprinkled on food or liquids which is considered an advantage over Cystagon® for children with swallowing difficulties or for use in younger children[2].
- Quality of life data measured in patients receiving Procysbi® in the extension study were difficult to interpret due to lack of a comparator arm.
- The Committee for Medicinal Products for Human Use concluded that Procysbi® may reduce but not completely eliminate some of the disadvantages (palatability, disrupted sleeping patterns, halitosis, reduced social participation) associated with Cystagon®[2].
- The reduction in PPI use during Procysbi® treatment in the pivotal study (RP103-03) may have been responsible for the increased incidence of gastrointestinal disorders versus Cystagon® treatment[18].

4.0 Cost-effectiveness

4.1 Context

The company submission[5] includes a cost-utility analysis (CUA) comparing Procysbi®; versus Cystagon® as treatments for proven nephropathic cystinosis in newly diagnosed patients or for patients who are not well-controlled on Cystagon® due to issues regarding adherence, tolerance or administration.

The CUA takes the form of a partitioned survival model using parametric survival equations to estimate the proportion of a cohort in each state, with one-year cycles, a 100-year lifetime horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are discounted at a rate of 3.5% where the time horizon exceeds one year. Survival outcomes are assumed to be directly related to treatment adherence which is assumed to be improved with Procysbi® based on a prospective cohort study comparing Cystagon® and Procysbi®[16]. Depending on their respective cystine level control, patients can develop one or several complications such as end-stage renal disease (ESRD), diabetes and neuromuscular disorder at different times. Patients suffering from nephropathic cystinosis enter the model at the age of two years and receive treatment with either Cystagon® or Procysbi®. They then move through the possible health states which include any combination of different complications with the risk of complications as reported in published literature[19] and adjusted according to clinical expert opinion. Relevant health state utilities and costs are then applied to each year in the model and outcome based on the treatment (Cystagon® or Procysbi®), complication rate and adverse events evaluated.

Complications and mortality for patients on Cystagon® treatment were taken from a retrospective, observational study carried out in two centres in France[19] with parametric functions fitted to reconstructed Kaplan-Meier survival data. Model inputs regarding complications and mortality for Procysbi® relied on clinical opinion, supported by published literature. The median age to ESRD was set to 15 years for the Cystagon® group as per the best-fitting parametric model for the published evidence[19] and was assumed to be 23 years in the Procysbi® group based on the mean age when five patients with excellent adherence developed ESRD in a published study[20] and clinical expert opinion. Time to onset of other complications (e.g. diabetes, neuromuscular disorders) was estimated based on published evidence[19] and clinical expert opinion. Median ages of death were set to 40 years for Cystagon® and 53 years for Procysbi®, respectively, based on discussions with clinical experts. Adverse events considered in the model include gastrointestinal side effects requiring the use of PPIs. Based on observations from the pivotal RP103-03 trial[7], 47% of patients on Cystagon® were assumed to be on PPIs versus 6% of patients on Procysbi®.

Costs considered in the model include treatment costs, routine care (i.e., GP visits and cystine blood tests) and management costs of complications. Daily dose for Procysbi® in the model is based on the body surface area (BSA) data from the RP103-03 study[7] assuming a dose of 1,255 mg/m^2 calculated as 82% of a patient's Cystagon® dose before they started on Procysbi®. Cystagon® doses at each age are then derived by assuming a 1.22 higher dose compared to Procysbi®. Routine care was costed using standard unit costs[21] and expert opinion. ESDR costs comprised of dialysis costs, cost of kidney transplant and cost of transplant maintenance. Unit costs for treatment of complications were obtained from standard sources[22] and published evidence[23-25] inflated to 2019/2020 prices.

Baseline utility scores were mapped from PedsQL questionnaire data collected as part of the RP103-04 study[11]. Published literature was used to obtain disutilities associated with treatment side effects for Cystagon®[26], and complications[27-31] applied in the model. The model base case also includes carer disutility[32].

Deterministic and probabilistic sensitivity analyses and scenario analyses were conducted to test the influence of the uncertainty of individual parameters on the model results.

4.2 Results

The results of the base case are detailed in Table 2. When compared with Cystagon®, Procysbi® is [commercial in confidence figure removed] more costly and produces an additional 6.04 quality-adjusted life-years (QALYs) over the lifetime horizon. The higher cost for Procysbi® is predominantly driven by the higher acquisition costs though this is slightly offset by lower cost for the management of ESRD and neuromuscular disorder.

Table 2. Results of the base case analysis

	Procysbi®	Cystagon®	Difference
Medicine acquisition costs	¶¶	£195,377	¶¶
Administration costs	£0	£0	£0
Healthcare costs (including routine care, monitoring, complications management and adverse events)	¶¶	£248,980	¶¶
Total costs	¶¶	£444,356	¶¶
Total life years	23.78	21.19	2.60
Total QALYs*	18.64	12.60	6.04
ICER (£/QALY gained)	¶¶		

[Commercial in confidence text removed]
¶¶ Commercial in confidence figure removed.
*Base case QALY difference includes carer disutility.
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

In deterministic sensitivity analysis, the incremental cost-effectiveness ratios (ICERs) for Procysbi® compared to Cystagon® ranged from [commercial in confidence figures removed]. The discount rate, dose of Procysbi®, cost per mg of Procysbi®, baseline utility scores and disutility associated with Cystagon®, and the time to complications onset/mortality impacted most on cost-effectiveness results. The results of the scenario analyses are assessed in order of plausibility in Table 3.

Probabilistic sensitivity analyses indicate that Procysbi® has a [commercial in confidence figure removed] and [commercial in confidence figure removed] probability of being cost-effective at standard willingness to pay thresholds of £20,000 and £30,000, respectively. Considering the ultra-orphan medication status of Procysbi®, there is a [commercial in confidence figure removed] probability of being cost-effective at willingness-to-pay threshold of £100,000 per QALY gained.

Table 3. Results of scenario analyses

Scenarios	ICER	Plausibility
Patients maintain adequate adherence to Cystagon® until the age of 11 and then switch to Procysbi® at age 12	¶¶	This scenario is plausible as evidence suggests that adherence to Cystagon® drops when children reach teenage years[8].
Patients maintain adequate adherence to Cystagon® until the age of 8 and then switch to Procysbi®	¶¶	This scenario is plausible since many patients develop renal failure by the age of 8 or 9. This would suggest that adherence to the optimum Cystagon® regimen cannot be maintained in these patients by this age.
Caregiver disutility excluded	¶¶	This scenario is plausible as caregiver disutility would not normally be included in the base case. However, it can be considered under the AWMSG rare diseases appraisal process and the impact of its inclusion on the ICER is small.
No clinical benefit of Procysbi® over Cystagon® assumed	¶¶	Considering the large degree of uncertainty around long-term adherence to Procysbi® and its effects on complications and mortality, this scenario appears plausible.
¶¶ Commercial in confidence figure removed. ICER: incremental cost-effectiveness ratio		

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed and transparent account of the methods and data sources used in the analysis.
- The model is well presented and appears robust and well-structured.
- Reasonable justifications are provided for the assumptions applied in the model.
- The company has made an effort to use the best available data.

Limitations:

- The benefit of Procysbi® compared to Cystagon® found in the model is mainly driven by improved adherence which has been demonstrated to be the key factor in delaying disease progression[20]. While short-term evidence suggests better adherence rates with Procysbi®[16], no long-term comparative data exists and it is uncertain whether these improvements remain over longer periods of time. The company provided a scenario

analysis where no clinical benefit of Procysbi® on adherence is assumed. This increases the ICER to [commercial in confidence figure removed] as QALY gains are solely driven by the effect on Procysbi® dosing schedule on patients' and carers' sleep and associated quality of life[26,32].

- In the absence of long-term clinical studies comparing Cystagon® and Procysbi®, the clinical outcomes of patients receiving Procysbi® in the model rely on assumptions based on underlying knowledge of the disease process, patient experience and some published evidence with small sample sizes validated by one clinical expert in Wales. Furthermore, hazard ratios used to derive Procysbi® values from Cystagon® outcomes for mortality and complications were assumed based on clinical expert opinion. This causes considerable uncertainty around the results of the CUA.
- The fits of the parametric functions fitted to survival and complication onset data are generally weak due to the small sample sizes of the datasets they are fitted against. This causes inconsistencies (e.g. onset of neuromuscular complications calculated to be 52 years which was deemed implausible) and a mixture of curve-fitted extrapolations and mean values from published literature were used to populate the model. This reliance on a variety of published data sources may introduce bias and uncertainty into the calculated ICERs.
- Risks of complications and mortality estimates of Cystagon® are based on the sub-group of patients who started treatment before the age of five of a retrospective, two-centre cohort study undertaken in France[19] with the published Kaplan-Meier curves digitised to reconstruct pseudo individual patient datasets using an iterative process. The lack of access to actual patient level data could therefore introduce substantial bias and uncertainty based on lack of generalisability and accuracy, small sample size and the amount of manipulation required.
- While there is long-term follow-up data for Cystagon®[19], significant loss to follow-up occurred between year 20 and year 30 in the under-five sub-group resulting in limited data to model neuromuscular complications and mortality which causes substantial uncertainty for extrapolations beyond the observed period.
- Baseline utilities were mapped from the PedsQL questionnaire available in the RP103-04 study[11] to EQ-5D. While a published mapping algorithm was used[33], this may introduce bias. Furthermore, disutilities for different complications were directly obtained from different publications. Any heterogeneity between study populations and methods will introduce bias.
- In addition, the disutility applied to patients receiving Cystagon® is based on a publication describing the effect of sleep disturbance on patient quality of life[26]. However, the RP103-04 study failed to demonstrate a significant improvement from baseline to after two years of Procysbi® therapy in the Emotional Functioning subscale of the PedsQoL which includes sleep. This could overestimate the improvement in quality of life attributed to Procysbi® which is one of the key drivers of its benefit over Cystagon®.
- Costs of managing complications were obtained from published evidence. Some of the studies used were dated and proxies had to be used in places (e.g. costs for treatment of mild multiple sclerosis as a

proxy for neuromuscular disorders). It is therefore unclear how accurately these costs reflect actual costs in Wales.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any studies relevant to the cost-effectiveness of Procysbi® as an additional treatment option for proven nephropathic cystinosis compared to Cystagon® in newly diagnosed patients or for patients who are not well-controlled on Cystagon® due to issues regarding adherence, tolerance or administration.

5.0 Budget impact

5.1 Context and methods

The company estimates that 13 patients currently have cystinosis in Wales according to clinical expert opinion[34]. New incidence is assumed to be one patient over five years applied in Year 4. This is based on a cystinosis incidence rate of 0.75 per 100,000 live births with nephropathic cystinosis accounting for approximately 95% of these[35] and 28,781 live births in Wales in 2020[36]. Mortality and population growth are not taken into account. The company estimates an uptake rate of [commercial in confidence figures removed] in Year 1, increasing to [commercial in confidence figures removed] from Year 3. Annual costs were assumed to increase as children grow and their body surface area increases.

The company provided basic sensitivity analysis, altering uptake rate by up to 20% and acquisition costs by +/-25%.

5.2 Results

The budget impact is presented in Table 4. The company estimates that introducing Procysbi® would lead to an overall cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5 with an overall budget impact over the five-year period of [commercial in confidence figure removed]. This estimate incorporates cost differences resulting from the displacement of Cystagon®. Basic sensitivity analysis undertaken by the company suggests budget impact to be in the range from [commercial in confidence figures removed] over the five-year time horizon.

Table 4. Company-reported costs associated with use of Procysbi® as an additional treatment option for proven nephropathic cystinosis compared to Cystagon® in newly diagnosed patients or for patients who are not well-controlled on Cystagon® due to issues regarding adherence, tolerance or administration

	Year 1	Year 2	Year 3	Year 4	Year 5
Sub-population of eligible patients (indication under consideration)	13	13	13	14	14
Uptake of new medicine (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving new medicine allowing for discontinuations	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without new medicine	£121,555	£134,850	£134,850	£159,541	£159,541
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs (savings/costs)	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence figure removed.					

The company estimates that net resource implications arising from the introduction of Procysbi® will lead to a saving of £175 in Year 1, increasing to £350 in Year 5. This is mainly a consequence of savings in the use of PPIs due to gastrointestinal adverse events in patients taking Cystagon®. These resource savings are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The submission gives a reasonable account of the methods and data sources used to estimate budget impact. The company has also factored increased surface area of patients as children grow into the calculations.
- AWTTC-sought prescribing volume data suggests between 4–10 patients currently receive Cystagon® in Wales, [commercial in confidence text removed]. AWTTC sought clinical expert opinion is that (if Procysbi® were recommended) all patients who wanted to switch would be treated with Procysbi® therefore uptake would be expected to be near 100% from year 1. Therefore, since these two factors will oppose each other, on balance AWTTC considers the company's estimated uptake of between

[commercial in confidence figures removed] patients per year and the resulting costs are broadly reasonable estimates.

- The dose of Procysbi® (and therefore the acquisition cost) depends on the individual patient's body surface area. The company used an average age of 14 years to calculate the budget impact. It is unclear why this age was chosen and whether this accurately reflects the patients in Wales.

6.0 Additional factors to consider

6.1 Medicines developed to treat rare diseases

The European Medicines Agency designated Procysbi® as an orphan product in 2013, this designation expires in September 2023[37]. The applicant company suggests that mercaptamine bitartrate oral gastro-resistant hard capsules (Procysbi®) should be considered as an ultra-orphan medicine.

AWTTC does consider mercaptamine bitartrate oral gastro-resistant hard capsules (Procysbi®) eligible to be appraised as an ultra-orphan medicine. The full license indication for Procysbi® includes proven nephropathic cystinosis only. The company states that prevalence of proven nephropathic cystinosis is estimated to be around 1 in 100,000 of the population[38,39] which would equate to 32 people living with cystinosis in Wales[4]. According to the company, clinical experts suggest that there are currently 13 patients in Wales with a diagnosis of cystinosis[5]. Based on prescribing data, AWTTC estimates that between 4 and 10 patients currently receive Cystagon® in Wales.

The New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 5) if they consider Procysbi® is a medicine developed to treat a rare disease.

Table 5. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
Severity of the disease	Nephropathic cystinosis is a progressive, extremely severe disorder characterised by renal and extra-renal damage or failure, and premature death[19]. No cure exists and the aim of treatment is to delay disease progression. Renal glomerular damage generally becomes apparent by 2 to 5 years of age and results in end-stage renal disease by 9 to 10 years of age unless cystine-depleting therapy with mercaptamine is initiated early in life[40]. Complications also include growth retardation, hypothyroidism, diabetes mellitus, ocular complications, rickets and osteopenia, muscular weakness and wasting, pulmonary dysfunction, gastrointestinal complications, swallowing difficulties, central nervous system dysfunction and cardiovascular disease death[19]. Survival into the third decade of

NMG/AWMSG considerations	AWTTC comments
	life without a renal transplant requires early initiation of and strict adherence to mercaptamine therapy[20]. According to a paediatric clinical expert in Wales, most patients in Wales have required a transplant or been on dialysis by the age of 10 despite the use of Cystagon®. However, even after transplant, complications resulting from long-standing kidney disease, such as renal osteodystrophy and extra-renal complications of cystinosis remain.
Unmet need	Treatment of nephropathic cystinosis with mercaptamine focuses on preventing or delaying renal and extra-renal complications and prolonging life expectancy[41]. Before the marketing authorisation of Procysbi®, Cystagon® was the only mercaptamine product approved for the treatment of nephropathic cystinosis. When adherence is consistent, mercaptamine can reduce cystine levels by 95%[19], preserve renal and extra-renal organ function, and improve overall survival[40]. However, strict dosing regimen (every 6 hours requiring middle-of-the-night administration) and adverse effects (such as substantial GI side effects, halitosis and sulphuric body odour) of Cystagon® pose a significant burden on patients and carers and hamper consistent adherence resulting in suboptimal clinical outcomes[42]. The company suggests that significant unmet need exists for new treatments that offer a more convenient dosing schedule than Cystagon® and a more tolerable side effect profile, both of which would significantly improve adherence, clinical outcomes, and QoL. The company state that Procysbi® addresses these significant unmet needs by providing an additional treatment option for patients with nephropathic cystinosis that is more convenient and clinically effective.
Innovative nature of the medicine	Procysbi® offers an alternative mercaptamine formulation which may improve adherence, QoL and long-term clinical outcomes compared with current treatment due to the longer dosing interval. Procysbi® has granules of different size that dissolve at different rates to ensure prolonged release of mercaptamine over an extended period[14].

NMG/AWMSG considerations	AWTTC comments
Societal impact on non-health benefits that may not adequately be captured in the QALY	Nephropathic cystinosis is a very severe, 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. The strict six-hourly Cystagon® regimen requires administration in the middle of the night which negatively impacts upon the sleep quality of both patients and caregivers. In addition, the administration schedule of Cystagon® in the daytime, possible GI side effects and body odour impact on patients' social life and employment integration. Halitosis and body odour result in considerable challenges in adolescence due to bullying and lack of social acceptance from peers which impacts on both QoL and adherence[14].
Does the medicine cure or reverse rather than stabilise the condition?	Procysbi® does not reverse or cure the condition.
Does the medicine bridge a gap to a definitive therapy?	No – continued use of mercaptamine is still required following a kidney transplant for prevention or reduction of extra-renal complications. Gene therapies for cystinosis are currently in development, including the stem cell gene therapy CTNS-RD-04 currently being investigated in a phase1/2 trial (NCT03897361)[43].
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; GI: gastrointestinal; QALY: quality-adjusted life-year; QoL: Quality of life.	

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