Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2374

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

Chiesi Limited

6 August 2021

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 resubmission assessed under the orphan medicine process

mercaptamine (Procysbi®) is not recommended for use within NHSScotland.

Indication under review: For the treatment of proven nephropathic cystinosis.

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.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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

The submitting company has indicated their intention to make a resubmission.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of proven nephropathic cystinosis. Mercaptamine 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.[1]

Dosing Information

The dose of mercaptamine (Procysbi®) is dependent on whether the patient is an adult or child, and on whether they have previously been receiving the immediate release formulation of mercaptamine, please see the summary of product characteristics (SPC) for further details. Mercaptamine therapy must be initiated promptly once the diagnosis is confirmed (i.e., increased WBC cystine) to achieve maximum benefit.

Mercaptamine should be administered every 12 hours. The determination of WBC cystine and/or plasma cysteamine must be obtained 12.5 hours after the evening dose the day before, and therefore 30 minutes after the following morning dose is given. See the SPC for details on monitoring the dose according to white blood cell (WBC) cystine level. Mercaptamine should not be administered with food rich in fat or proteins, or with frozen food like ice-cream. Patients should try to consistently avoid meals and dairy products for at least one hour before and after Procysbi® dosing. See the SPC for detailed information concerning administration by opening the capsule and sprinkling capsules on food or fruit juice for young children at risk of aspiration, or for administration through a feeding tube.

Mercaptamine treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.[1]

Product availability date

November 2017

Mercaptamine (Procysbi®) was designated an orphan medicine by the European Medicines Agency (EMA) on 20 September 2012 and orphan designation was maintained at the time of granting of the marketing authorisation (EU/3/10/778).

Summary of evidence on comparative efficacy

Cystinosis is a rare, autosomal recessive lysosomal storage disease that results in accumulation of cystine crystals in the lysosomes of cells, accelerating cell death. It is typically diagnosed in infancy as nephropathic cystinosis, which is severe and progressive, resulting in renal failure and extra-renal effects including growth retardation, hypothyroidism, diabetes mellitus, ocular effects and osteomalacia. Within lysosomes, mercaptamine is involved in a thiol-disulfide interchange reaction which converts cystine to cysteine and cysteamine mixed disulfide which can both leave the lysosome. This results in reduced accumulation of lysosomal cystine.[1]

The submitting company has requested that SMC consider mercaptamine (Procysbi®) as a second-line option for patients who are not well-controlled on immediate-release mercaptamine, due to issues regarding compliance, tolerance or administration. The target cystine level in white blood cells (WBC) at which a patient's cystinosis would be considered to be well controlled is <1nmol hemicystine/mg protein.[1]

The key evidence is from a phase III open-label, randomised, controlled, crossover study (RP103-03) and its long term extension study (RP103-04). Study RP103-03 recruited adults and children aged at least 6 years with a documented diagnosis of nephropathic cystinosis and were taking a stable dose (for at least three weeks) of Cystagon® considered by the investigator to be adequately maintaining their WBC cystine level at ≤2.0nmol hemicystine/mg protein. Patients had to be able to swallow Cystagon® capsules intact; were required to have their own kidneys, with an estimated glomerular filtration rate (GFR) >30mL/min per 1.73m^2 body surface area and have had no significant change in liver or renal function tests in the last six months.[2] There were 24 male and 19 female patients aged from 6 to 26 years; 63% (27/43) were children aged 6 to 12 years; 35% (15/43) were aged 13 to 21 years one patient was 26 years old.[3]

Following a two to three-week run-in period in which patients received their current dose regimen of Cystagon®, patients were randomised to continue treatment with Cystagon® every 6 hours or to switch to Procysbi® every 12 hours for 3 weeks (+/- 3 days); and then to swap over to the alternative treatment for 3 weeks (+/- 3 days).[3] During Cystagon® treatment, proton pump inhibitor (PPI) use was at the discretion of the patient and/or the study physician, during Procysbi® treatment, patients were asked to discontinue PPI, although they were allowed to continue or restart them in case of intolerable adverse events.[4]

The primary outcome was a non-inferiority comparison between Procysbi® and Cystagon® of peak WBC cystine levels measured on each of three consecutive mornings at the end of each 3 week treatment crossover period.[4] In the primary analysis in the per protocol population (n=39), WBC cystine levels, least squares (LS) mean (standard error [SE]), were 0.51 (0.05) versus 0.44 (0.05) nmol hemicystine/mg protein in the Procysbi® and Cystagon® treatment groups respectively; mean difference 0.08 (95.8% confidence interval [CI]: 0.01 to 0.15; p<0.0001). The upper limit of the 95.8% CI of the difference between Procysbi® and Cystagon® was less than the pre-specified non-inferiority margin of 0.3, therefore non-inferiority was achieved. The corresponding results in the ITT population (n=41) were 0.53 (0.14) versus 0.74 (0.14) nmol hemicystine/mg protein; mean difference -0.21 (95.8% CI: -0.48 to 0.06; p<0.001).[3] Pharmacokinetics was assessed as a secondary outcome and there was no difference in the mean peak plasma concentration between the two formulations.[2]

An open-label extension study (RP103-04) evaluated the long term effects of Procysbi® in patients who completed study RP103-03 (n=40), paediatric patients aged ≤6 years (n=14) and patients who received a kidney transplant (n=6).[5, 6] Clinical laboratory assessments, physical examination and vital signs, ECG, body weight, body mass index, body surface area, and an age appropriate quality of life questionnaire (Pediatric Quality of Life Inventory, PedsQL) were made at monthly (first 6 months) and quarterly visits. For patients who completed study RP103-03, mean WBC cystine levels were maintained at <1nmol hemicystine/mg protein over the course of the study (average

treatment duration of 4.4 years). For patients ≤6 years (average treatment duration 3.5 years) and for renal transplant patients (average treatment duration 3.3 years), mean WBC cystine levels were similar to or lower than that on day 1 at the majority of study visits.[5] Over the course of the study, in which 50% of patients had received Procysbi® for more than 5 years, stable renal function was maintained across the groups.[5]

Upon entering the extension study (RP103-04), improvements were observed in measures of social function, school function and total function measures of the PedsQL. After two years of extended release mercaptamine, these changes persisted and there was no significant loss of quality of life in the other two measures (physical and emotional).[6] Baseline results indicated that many of the patients already had reasonably good functionality upon entering study RP103-03.[5]

Supportive evidence was available from a retrospective observational cohort study (n=12)[7] of patients who switched from mercaptamine immediate release to mercaptamine extended release; the main reason for switching was difficulty with night-time administration. The company also provided information about a pharmacokinetic study of children aged ≥6 years.[8, 9] In both studies WBC cystine levels were maintained in patients who switched from Cystagon® to Procysbi® and there was no deterioration in renal function.

Summary of evidence on comparative safety

In study RP103-03 treatment emergent adverse events (TEAE) occurred in 58% (25/43) of patients receiving Procysbi® and in 32% (13/41) of patients receiving Cystagon®. The following TEAE (incidence ≥5.0%) were reported in patients receiving Procysbi® compared with Cystagon®: nausea (19% versus 12%); vomiting (16% versus 7.3%); abdominal pain (9.3% versus 0); hypokalaemia (7.0% versus 0) and headache (9.3% versus 0).[3] Serious adverse events were reported in six patients receiving Procysbi® and in one patient receiving Cystagon®. One serious adverse event was considered to be possibly treatment related; abdominal discomfort in a patient receiving Procysbi® which led to the patient missing two days of treatment.

The incidence of gastrointestinal adverse events was higher with Procysbi® than with Cystagon® in study RP103-03 and this may be due to fact that more patients in the Cystagon® group than the Procysbi® group received concurrent PPI.[4]

Summary of clinical effectiveness issues

There is no cure for cystinosis and treatment is focused on preventing or delaying renal and extra-renal complications and prolonging life expectancy. Early treatment and adherence to mercaptamine is critical to slowing the progression of the disease and improving prognosis.[3, 10] . Mercaptamine is, however, associated with unpleasant side effects such as gastrointestinal adverse effects and body and breath odour. The immediate release formulation (Cystagon®) requires dosing every six hours, including a night time dose. The frequent dosing and unpleasant adverse effects may impact on tolerability and compliance with therapy. Procysbi® is a delayed

release formulation of mercaptamine that is administered every 12 hours, avoiding the need for night time dosing.[3] Clinical experts consulted by SMC considered that Procysbi® fills an unmet need in this therapeutic area, namely due to reduced dosing frequency. Mercaptamine meets SMC orphan criteria. The submitting company has requested that SMC consider Procysbi® as a second-line treatment option, reserved for those patients whose condition is not well controlled on immediate release mercaptamine (Cystagon®) due to issues regarding compliance, tolerance or administration. Procysbi® is not intended for patients who are well controlled under a current Cystagon® regimen.

Study RP103-03 demonstrated that Procysbi® was non-inferior to Cystagon® in control of WBC cystine at therapeutic target levels.[2] An extension study showed this effect was maintained up to four years and renal function remained stable in patients who continued Procysbi® treatment for up to four years.[4]

Small patient numbers and the open-label design of study RP103-03 made interpretation of quality of life data difficult. Longer term outcomes on renal function were explored in the extension study but there is no direct evidence comparing the two formulations of mercaptamine on long term health outcomes. Evidence on subjective outcomes including halitosis was only available from a small retrospective observational study.[7]

The company provided some observational evidence that supported the proposed position. There is no comparative evidence in the patient population included in the company's positioning, study RP103-03 only included patients who were controlled on immediate release mercaptamine (Cystagon®). There is no evidence that patients on Procysbi® had improved adherence to treatment compared with Cystagon®.

Clinical experts consulted by SMC considered that mercaptamine (Procysbi®) is a therapeutic advancement due to the reduced dosing frequency that may improve compliance. The availability of Procysbi® may benefit patients and carers in avoidance of a night time dose and have a possible beneficial effect on adherence due to reduced dosing frequency required compared with Cystagon®. The number of capsules of Procysbi® required may be greater than that required for an equivalent dose of Cystagon® due to the lower drug content per capsule.

Patient and clinician engagement (PACE)

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

The key points expressed by the group were:

- 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.

- In addition to the huge burden of care is the fact that this has to be managed on, at best, a six hour overnight sleep routine as current treatment with the Cystagon® formulation necessitates a dose during the night, thereby interrupting the sleep of both patients and carers. Coping with constant tiredness adds to the stress.

- The long-acting Procysbi® formulation of mercaptamine would allow a full night's restorative sleep for patients and their carers; which would have an extremely beneficial impact on their physical, psychological and emotional quality of life, helping them to cope with the devastating consequences of nephropathic cystinosis.

- Procysbi® could be especially helpful for patients/families who have great difficulty in complying with Cystagon® treatment. Not needing to take a dose of mercaptamine during the night or in the middle of the school/working day is a huge advantage.

- Adherence to Cystagon® treatment declines in young adults compared with children as the parents' role in administering medication diminishes and this poses a massive challenge. Fewer missed doses may translate into better overall disease control and reduced morbidity.

Additional Patient and Carer Involvement

We received a joint patient group submission from Cystinosis Foundation UK and Metabolic Support UK, which are both registered charities. Cystinosis Foundation UK has not received any pharmaceutical company funding in the last two years. Metabolic Support UK has received 45% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Cystinosis Foundation UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis that evaluated Procysbi® in patients who do not meet a <1 nmol therapeutic level of hemicycstine/mg protein in WBCs due to Cystagon® failure. In the model the possibility that such patients may continue on Cystagon® therapy is not considered, so that the comparator is no-treatment. 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 state permutations (plus death). All event probabilities are estimated independently. A lifetime horizon was adopted.

The sources of clinical data used in the model primarily included a published study by Brodin-Sartorius et al [11], and clinical expert opinion. The Brodin-Sartorius paper provided Kaplan-Meier plots for each complication and mortality, with results presented for 'no treatment', Cystagon® initiated before 5 years old and Cystagon® initiated after 5 years old. No patients within the study received Procysbi®. The Kaplan-Meier plots were extrapolated using Weibull or Gompertz functions for each event in order to generate risks of complications and death over the lifetime horizon of the model. Expert clinical opinion was then used to estimate the efficacy of Procysbi®by upwardly adjusting the survival estimates of Cystagon (initiated before 5 years old) from Brodin-Sartorius.[11]

Median age at mortality for no-treatment was estimated at approximately 23 years in the base case (using a Weibull function), and assumed to be 50 years for Procysbi®, with ESRD, diabetes, and NMD at 9, 15, and 27 years, compared to 20, 40 and 45 years, for no treatment (Cystagon® failure) and Procysbi® respectively.

Body surface area (BSA) for Procysbi® dosing was based on data from the Horizon RP103-03 study.[4] The average mercaptamine equivalent target dose was derived as 1,083 mg/m^2/day (compared to the SPC target dose of 1,300 mg/m^2/day), and this was applied in the economic model. 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. No account was taken of costs relating to treatment of potential adverse events.

A baseline estimate of health related quality of life, or utility, was derived from PedsQL data collected in Langman et al[6], mapped to EQ-5D using a published algorithm, with decrements for each modelled complication. Adverse events were not reflected in the QALY calculations. The analysis estimated an initial baseline utility of 0.87, however, this value was increased to 0.95 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 Dale et al[12], and Kobelt et al.[13] These are applied as multiplicative decrements to the baseline utility. The latter decrement may have been over-estimated; given that independence of complications and mortality, and the marked extension in survival assumed in the model, this may have the effect of increasing Procysbi®'s cost-effectiveness ratio compared to analyses with lesser decrements.

Procysbi® has a list price of approximately £0.22 per mg. 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 simple discount was offered on the list price.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the list price results can be presented.

The base case results (Table 1) and key sensitivity analyses (Table 2) are presented below.

Table 1: Base case results (list price)

	Procysbi®	Cystagon® failure
Total cost (£)	3,007,779	269,320
QALYs	19.53	12.32
Incremental cost (£)	2,738,549	
Incremental QALYs	7.22	
ICER (£)	379,404	

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.

In sensitivity analyses, parameters were generally varied individually by +/-25%. A number of scenarios were provided by the company following the NDC draft advice, including the use of higher average Procysbi® doses, the removal of the baseline utility adjustment for Procysbi®,

inclusion of costs of Cystagon® for a proportion of patients (50%/75%/100%), removal of the assumed mortality benefit versus Cystagon®, and a scenario where patients remain on treatment with Cystagon® and achieve a limited benefit relative to no treatment. Due to the commercial-in-confidence nature of these results, SMC is unable to publish these, however they were considered by the Committee.

Table 2: Deterministic sensitivity analysis (list price)

		ICER (£)	
		Low	High
	Base case	379,404	
	Sensitivity analysis		
1.	Dose Procysbi®	290,345	468,035
2.	Baseline utility of cystinosis	505,873	360,434
3.	Disutility of neuromuscular disorder	372,317	386,767
4.	Time to complications or mortality (Procysbi®)	511,271	326,998
5.	Time to complications or mortality (comparator)	290,295	521,327

ICER: incremental cost-effectiveness ratio

The analysis was subject to a range of limitations, each of which is expected to reduce the reliability of the results or introduce varying degrees of upwards uncertainty in the ICER.

- The model design may suffer from some limitations relating to the independence of each health state from any other, with no means of exploring a greater weight of mortality following complications.
- A key limitation in the clinical evidence is the somewhat conjectural nature of the projections of complications and mortality for no-treatment, and the even greater uncertainty surrounding the survival projections for treatment with Procysbi®, which involve substantial gains compared to Cystagon® and no treatment based on clinical opinion rather than the RP103-03 non-inferiority study.
- Treatment effect waning and discontinuation are notable omissions from the model. The absence of any discontinuation may lead to an over-estimation of Procysbi® acquisition costs, but the impact this and any attenuation of treatment effect may have on patient outcomes has not been considered.
- The inflated baseline utility may overestimate health related quality of life and could substantially impact the incremental QALY results given the life expectancy advantage attributed to Procysbi®.
- No general treatment related utility decrement was included in the model for Procysbi® which may not be a conservative assumption for comparisons versus no treatment. A substantial decrement assigned to NMD is also a concern as the data appears to have been misinterpreted in estimating the multiplicative decrement, with the uncertainty surrounding this compounded by the model design.
- A key weakness regarding resource use and costs is that the doses used in the economic model did not match those recommended in the SPC. There is therefore some uncertainty as to how adequately the modelling captures drug acquisition costs that may be incurred in routine usage. Costs relating to management of adverse events are also omitted.

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

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept Procysbi® for use in NHSScotland.

Additional information: guidelines and protocols

No international or national clinical guidelines were identified during the literature search which made recommendations regarding the treatment of nephropathic cystinosis. A published consensus statement on the treatment of nephropathic cystinosis was identified. This statement provides an overview of the condition and guidance for its diagnosis and treatment. It notes that specific cysteine-depleting treatment with mercaptamine represents the mainstay of therapy and this should be initiated as early as possible and continued lifelong, since it dramatically improves the overall prognosis. Non-specific symptomatic treatment of the renal Fanconi syndrome is essential and additional treatments for extra-renal manifestations may be required. The statement acknowledged that mercaptamine (i.e. Cystagon®) is an effective treatment option but also highlights that there are issues with patient compliance associated with posology (i.e. six hourly doses) and side effects, specifically bromhidrosis and halitosis. Furthermore, the consensus document highlights that delayed release mercaptamine may address some of the issues associated with patient compliance with Cystagon®.[10]

Additional information: comparators

mercaptamine (Cystagon®)

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Mercaptamine gastro-resistant hard capsules (Procysbi®)	The targeted maintenance dose is 1.3 gram/m^2/day in two divided doses. According to table in SPC, based on surface area and body weight: (<5kg to >50kg) = 200mg to 1000mg twice daily	32,612 to 163,058

Costs from BNF online on 14/05/21. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be 4 patients eligible for treatment with Procysbi® each year.

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 impact with the PAS.

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

References

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This assessment is based on data submitted by the applicant company up to and including 21 July 2021.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.