mercaptamine gastro-resistant hard capsules (Procysbi®)

Chiesi

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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 second resubmission assessed under the orphan medicine process

mercaptamine (Procysbi®) is not recommended 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.

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.

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 suffer Fanconi syndrome and progressive glomerular 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]

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 nephrotic cystinosis. It is administered as four doses each day (6 hours apart).[3]

1.4. Category for decision-making process (if appropriate)

Eligibility for a PACE meeting
Mercaptamine gastro-resistant hard capsules (Procysbi®) meets SMC orphan 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.[4, 5] This was supported by the comparative, non-randomised RP103-07 study[6, 7] and the non-comparative studies, RP103-04 and RP103-08 detailed in Section 2.3.[2, 8-10]

Table 2.1. Overview of relevant studies

Criteria	RP-103-03[4, 5]
Study design	Open-label, phase III crossover
Eligible patients	≥6 years of age 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	Mercapatmine (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

	mercatpamine (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 mercapatmine (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.

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. Pharmacokinetics parameters were secondary outcomes and there appeared to be no difference in mean peak plasma concentration of mercaptamine between the two formulations.[2, 4]

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 received a stable dose of mercaptamine (Cystagon®) for ≥3 weeks prior to screening and had WBC cystine level > 1 nmol hemicystine/mg protein on average over at least two measurements during two years prior to screening. All patients continued their stable dose of mercaptamine (Cystagon®) for the first three months and then switched to mercaptamine (Procysbi®) for four months. After this, 38 of 40 patients who completed both phases opted to continue mercaptamine (Procysbi®) in a long-term extension study, with median duration of treatment 2.4 years (range 30 days to 3.7 years).[6]

The primary efficacy analysis of RP103-07 compared mean within-patient (Cystagon® phase paired with Procysbi® phase) differences in daily variation in log WBC cystine level, that is: non-morning minus morning. [6]

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 <1.0 nmol hemicystine/mg protein. In patients who remained in the study, the proportion who achieved this varied. [2]

RP103-08

An open-label, single-arm, phase IIIb study (RP103-08) recruited 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, 80% (10/13) of patients with assessments had cystine levels <1 nmol hemicystine/mg protein.[9]

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

3. Summary of Safety Evidence

In RP103-07, within the 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.[6, 7]

In 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®): nausea (19% versus 12%); vomiting (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, 5]

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, 5, 8]
- 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, 3]

4.2. Key uncertainties

- 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 (PPI), with many patients discontinuing these prior to the mercaptamine (Procysbi®) phase in accordance with the study protocol. [4-7]
- There is no direct, prospective comparative evidence of benefit for mercaptamine (Procysbi®) over mercaptamine (Cystagon®) in terms of quality of life or adherence.
- The Real World studies[11-15] presented by the company do not provide robust evidence for benefit in adherence as they have several limitations in design and patient numbers. For example, CrYSTobs, recruited 17 patients: only four patients entered the study while receiving mercaptamine (Cystagon®) but switched to mercaptamine (Procysbi®) after 26 to 91 days. The other 13 patients received mercaptamine (Procysbi®) from entry and throughout the 12-month study. The time interval to define non-adherence was 1 hour for mercaptamine (Cystagon®) but 2 hours for mercaptamine (Procysbi®).[11]
- The evidence to support the assertion that mercaptamine (Procysbi®), compared with mercaptamine (Cystagon®) is associated with lower rates of halitosis or breath odour is from analyses of dimethylsulphide in the breath of 4 and 20 patients in two studies.[16, 17] It is not possible to estimate clinically relevant halitosis from these. In the two studies that included both mercaptamine (Cystagon®) and mercaptamine (Procysbi®) phases, halitosis or breath odour were not reported as adverse events in ≥5% of patients.[2, 6]
- There are no comparative data on long-term outcomes such as renal failure as all longer-term studies were uncontrolled.[8, 18]
- All of the studies (PR103-03, -04, -07 and -08) were open-label, which may have little impact on WBC cystine levels (the main efficacy outcome). However, this limits the assessment of subjective outcomes such as quality of life, safety and adherence.[4, 5, 8-10, 18]
- Apart from the primary outcome in RP103-03 and RP103-07 (WBC cystine levels), all outcomes in these studies and in the RP103-04 and RP103-08 studies were analysed descriptively.[4, 5, 8-10, 18]

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

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

5. 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, 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 47.5% pharmaceutical company funding in the past two years, including from the submitting company. Kidney Research UK has received 6% 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 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

Table 6.1 Description of economic analysis

<table>
<tr><th>Criteria</th><th>Overview</th></tr>
<tr><td>Analysis type</td><td>Cost-utility analysis</td></tr>
<tr><td>Time horizon</td><td>Lifetime</td></tr>
<tr><td>Population</td><td>Treatment of proven nephropathic cystinosis. This includes patients who are treatment naïve or previously treated with mercaptamine (Cystagon).</td></tr>
<tr><td>Comparators</td><td>mercaptamine (Cystagon®)</td></tr>
<tr><td>Model description</td><td>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.</td></tr>
<tr><td>Clinical data</td><td>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. [19] The Brodin-Sartorius study 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®).</td></tr>
<tr><td>Extrapolation</td><td>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 (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, mapped to EQ-5D using a published algorithm, with decrements for each modelled complication. [18] 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 0.92 on the basis of assumption. This adjustment was intended to account for the impact of</td></tr>
</table>

	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. An additional disutility of 0.132 was applied to mercaptamine (Cystagon®) treated patients to capture the quality of life impact of sleep disturbance due to the 6-hourly treatment regimen. The same disutility was also applied to carers but only in sensitivity analysis.
Costs and resource use	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®). Analysis using a dose of 1,200mg/m^2/day was provided in the sensitivity analysis. 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.
PAS	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.

6.2. Results

The results of the base case analysis estimated by the submitting company are presented in table 6.2 below.

Table 6.2 Base case results (list price)

	mercaptamine (Procysbi®)	**mercaptamine (Cystagon®)**
Total cost (£)	2,563,354	£408,720
QALYs	18.64	13.93
Incremental cost (£)	2,154,634	
Incremental QALYs	4.71	
ICER (£/QALY)	**457,527**	

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

6.3. Sensitivity analyses

Selected sensitivity analysis results are presented in table 6.3 below.

Table 6.3 Selected sensitivity analysis results (list price)

	Scenario	**Base case**	**ICER (£/QALY) at list prices**
	Base case		***457,527***
1	Increase dose of mercaptamine (Procysbi®) by 25% to 1,287mg/m^2/day	1,030mg/m^2/day	579,544

2	Dose based on RP103-03 clinical trial (mercaptamine (Procysbi®)steady-state dose was 82% of mercaptamine (Cystagon®))	1,030mg/m^2/day	564,440
3	Decrease utility at baseline to 0.69	Baseline utility of 0.92	610,092
4	Caregiver disutility of 0.132 applied to patients until age 16	No carer disutility	370,451
5	Caregiver disutility of 0.1	No carer disutility	388,405
6	Caregiver disutility of 0.17	No carer disutility	351,241
7	Decrease disutility applied to mercaptamine (Cystagon®) patients to 0.07	Disutility of 0.132	580,082
8	Remove disutility applied to mercaptamine (Cystagon®) patients	Disutility of 0.132	831,573
9	Reducing time to onset of complications and mortality with mercaptamine (Procysbi®) by 25%	As estimated by company clinical experts	898,163
10	No additional clinical benefit of mercaptamine (Procysbi®) over mercaptamine (Cystagon®) with QALY gain based only on improved QoL due to avoiding sleep disturbance	Additional benefit included based on assumed improved adherence to mercaptamine (Procysbi®)	874,229
Additional analyses provided post-NDC			
11	Scenarios 2 and 10 combined (no additional clinical benefit with Procysbi® and dose from RP103-03 trial)		1,076,890
12	Cost-minimisation analysis		**Incremental cost** of £1,851,850 with Procysbi®

QALY = quality adjusted life-year; ICER = incremental cost-effectiveness ratio; QoL = quality of life

6.4. Key strengths

- The model is relatively simple and focusses 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 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 or reduced the ICER increases significantly (scenarios 9, 10 and 11).
- The model applies a disutility (0.132) 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. There is some uncertainty with this estimate and sensitivity analysis requested from the company showed the results were sensitive to reducing this disutility value by 50% (scenario 7) and removing this disutility from the model (scenario 8).
- 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 1) and using the dose from the clinical study RP103-03 (scenario 2).
- The baseline utility value (0.92) is comparable with general population paediatric norms, which may lack face validity. Applying a lower utility value (scenario 3) had an upward impact on the ICER, although this scenario uses a much lower baseline value of 0.69.
- 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.

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

7. Conclusion

The Committee considered the benefits of mercaptamine in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as mercaptamine 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 mercaptamine for use in NHSScotland.

8. Guidelines and Protocols

No international or national 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 13 July 2023. Cost 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

The submitting company estimated there would be 23 patients eligible for treatment with mercaptamine (Procysbi®) in year 1 and 24 patients in year 5 estimates. The estimated uptake rate was 52% (12 patients) in year 1 rising to 100% (24 patients) in year 5.

The gross impact on the medicines budget was estimated to be £1.3m at list prices in year 1 rising to £3m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £1.2m in year 1 and £2.8m in year 5.

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

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This assessment is based on data submitted by the applicant company up to and including 21 September 2023.

*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.