Engagement Report

Topic details

Title of policy or policy statement:	Delayed-release mercaptamine bitartrate for patients with nephropathic cystinosis (Age >1 years)
Programme of Care:	Internal Medicine
Clinical Reference Group:	Renal Services
URN:	2338

1. Summary

This report summarises the feedback NHS England received from engagement during the development of this policy proposition, and how this feedback has been considered.

2. Background

Nephropathic cystinosis is a rare autosomal recessive genetic disease affecting 1 in every 100,000 to 200,000 live births. It is an incurable condition that results in accumulation of the amino acid cystine which forms crystals within almost any cell in the body. This reduces life expectancy and is associated with significant morbidity throughout childhood and adult life. The physical manifestations of nephropathic cystinosis include renal involvement, with children often presenting with Fanconi syndrome (meaning kidneys are not absorbing salts and minerals), developing into chronic kidney disease often requiring dialysis or transplant in adulthood. Extra-renal complications include poor growth, ocular involvement, and hypothyroidism in children, with adults subsequently becoming more likely to have diabetes mellitus, hepatic involvement, bone disease and central nervous system involvement.

Whilst this condition is life-long, it is generally diagnosed in early childhood, usually before the age of two. This reduces life-expectancy and is associated with significant morbidity throughout childhood and adult life due to the development of renal and extra-renal complications.

Whilst there is no cure for nephropathic cystinosis, a medication, referred to as cystine-depleting therapy, can be used to reduce the accumulation of cystine in the cells. Cystine-depleting treatment can improve symptoms and delay problems with the kidneys and other parts of the body. It is considered best practice to start cystine-depleting treatment as soon after diagnosis as possible. Currently, the only available commissioned cystine-depleting therapy is immediate-release (IR) mercaptamine bitartrate which is a capsule taken with food every 6 hours. This means that patients

and/or carers must wake during the night to take this medication, as well as disrupt their school and/or work.

The proposed intervention is delayed release (DR) mercaptamine bitartrate, which can be taken as a capsule every 12 hours The active ingredient is the same as the currently available IR mercaptamine bitartrate, but the formulation allows for twice daily dosing. This extended dosing regimen minimises disruption during school and/or work hours, as well as to sleep during the night for both patients and carers. Moreover, DR mercaptamine is associated with a reduction in intolerable side effects including halitosis and body odour.

3. Engagement

NHS England has a duty under Section 13Q of the NHS Act 2006 (as amended) to 'make arrangements' to involve the public in commissioning. Full guidance is available in the Statement of Arrangements and Guidance on Patient and Public Participation in Commissioning. In addition, NHS England has a legal duty to promote equality under the Equality Act (2010) and reduce health inequalities under the Health and Social Care Act (2012).

The policy proposition underwent a four-week stakeholder testing between the 7th October 2024 and 21st October 2024 with registered stakeholders from the following Clinical Reference Groups:

- Specialised Paediatric Renal Services
- Specialised Paediatric Endocrinology
- Specialised Paediatric Gastroenterology
- Metabolic Disorders
- Renal services

Respondents were asked the following consultation questions:

- Do you support the proposal for routine commissioning based on the evidence review and within the criteria set out in the proposal?
- Do you believe that there is any additional information that we should have considered in the evidence review?
- Do you believe that there are any potential positive and/or negative impacts on patient care as a result of making this treatment option available?
- Do you support the Equality and Health Inequalities Impact Assessment?
- Does the Patient Impact Summary present a true reflection of the patient and carers lived experience of this condition?
- Do you have any further comments on the proposal?
- Please declare any conflict of interests relating to this document or service area.

The comments have then been shared with the Policy Working Group (PWG) to enable full consideration of feedback and to support a decision on whether any changes to the proposition might be recommended.

A 13Q assessment has been completed following stakeholder testing.

The Programme of Care has decided that the proposition offers a clear and positive impact on patient treatment, by potentially making a new treatment available which widens the range of treatment options without disrupting current care or limiting patient choice, and therefore further public consultation was not required. This decision has been assured by the Patient Public Voice Advisory Group.

4. Engagement Results

The policy proposition received 12 stakeholder responses:

- 2 Clinicians
- 3 Paediatric Nephrology Centres
- 5 Charities
- 2 Pharmaceutical companies

Given the rarity of both nephropathic cystinosis, this was deemed a very good response and there was a range of wide range of NHS and private stakeholders represented.

How has feedback been considered?

Responses to engagement have been reviewed by the Policy Working Group. The following themes were raised during engagement.

Keys themes in feedback	NHS England Response
Relevant Evidence	
Most stakeholders agreed that the relevant evidence had been identified in the independent evidence review. One stakeholder commented that the use of homecare and NHSE VAT savings need to be considered. Two stakeholders referenced research indicating that patients on DR mercaptamine have improved quality of life. These were a patient survey, and a poster submitted to an international conference. One stakeholder referenced a published paper on the	Noted. Cost saving considerations are assessed as part of the financial impact assessment and at Clinical Priorities Advisory Group (CPAG). Posters and unpublished data cannot be considered as part of evidence base in line with the published NHS England Methods: National Clinical Policies. The evidence review noted statistically significant improvements in measures of quality of life, including in relation to social and school functioning (Langman et al 2012; Langman et al 2014). The independent evidence review noted that patients on DR mercaptamine have a higher rate of adverse events, notably gastrointestinal adverse events, compared to IR mercaptamine. It is stated under the starting criteria in the policy proposition, that patients should be aware of the special warning and precautions of DR mercaptamine as outlined in the Summary of Product Characteristics. This includes the

risk of fibrosing colonopathy with DR cysteamine bitartrate and highlighted that the policy should make clinicians aware of this warning. One stakeholder commented that the EPAR states that DR mercaptamine is not taken with food, whereas IR mercaptamine can be given with or without food. One stakeholder commented that there lacked evidence into the impact of a missed dose with the DR mercaptamine compared to IR mercaptamine, and that the data on adherence was limited.	risk of fibrosing colonopathy, which is outlined under Section 4.4 of SmPC page for DR mercaptamine (https://www.medicines.org.uk/emc/product/2080/smpc) and the Safety Checklist for prescribing clinicians. This policy proposition offers the choice of DR mercaptamine bitartrate to patients and carers. If the dietary restrictions of DR mercaptamine bitartrate lead to tolerability concerns for patients and/or carers, patients should be switched back to IR mercaptamine bitartrate as outlined in the stopping criteria of the policy. In the independent evidence review, Gaillard et al 2021 was the only study to report on treatment adherence and found that adherence was greater in patients taking DR mercaptamine, compared to when they were initially taking short-acting mercaptamine. The PWG acknowledges that there is limited evidence, however in their clinical experience a twice daily regime will reduce pill burden for patients, and this will correlate with improved adherence. The stopping criteria states that patients should be stopped if there is no improved adherence, which includes patients who are missing doses regularly.
Policy Proposition	
Most stakeholders supported the policy proposition and noted that the policy would have a positive impact on patients. Multiple stakeholders commented that the reduced side effect profile of DR mercaptamine should be noted in the policy. They commented that DR mercaptamine is associated with a lower rate of symptoms such as halitosis and body odour due to the extended dosing compared to IR mercaptamine.	No further action required. The independent evidence review noted that DR mercaptamine was associated with a higher frequency of adverse events, notably gastrointestinal side effects, compared to IR mercaptamine (Langman et al 2012). Therefore, the suggested inclusion of patients having less side effects with DR mercaptamine was not made in line with the evidence base. The independent evidence review reported a higher rate of adverse events with DR mercaptamine, compared to IR mercaptamine with the most common side effect being gastrointestinal side effects. Patients are monitored regularly as outlined in the monitoring

One stakeholder noted that DR mercaptamine is associated with a three-fold increase in GI side effects.	section of the proposal to monitor these adverse events, and patients with concerns about adverse events should stop DR mercaptamine as mentioned in the stopping criteria. The PWG have noted in the evidence to decision summary that gastritis can be mitigated or treatment with proton pump inhibitors when indicated as this is current practice for IR mercaptamine bitartrate.
Impact Assessment	
Multiple stakeholders commented that the PIA could benefit from more detail, especially in the first section.	The purpose of the Patient Impact Assessment (PIA) is to provide a brief overview of the impact of the condition on patients and carers' lives. There is a 150-word limit on the PIA and the first section of the PIA, the PWG choose from categorical values (no/slight/moderate/severe problems) to grade the condition on each activity of daily living. Further detail cannot be provided in this section.
Stakeholders commented that the PIA needed to emphasise: • The progressive and multisystem nature of the disease • The complications of non-adherence • The impact of nephropathic cystinosis on sleep, mental health, personal relationships and social settings, and family life	The PIA was reviewed by the clinical lead and patient public representative who addressed these suggestions in the free-text section. The grading of the impact of nephropathic cystinosis on 'mobility' and 'ability to provide self-care' was changed from moderate to severe.
One stakeholder commented that the reduced side effects of DR mercaptamine compared to IR mercaptamine should be noted.	The independent evidence review reported a higher rate of adverse events with DR mercaptamine, compared to IR mercaptamine.
Current Patient Pathway	
One pharmaceutical company did not support the policy as they commented that the evidence did not support the proposed treatment	The patient pathway has been developed by clinical experts in cystinosis and recognises the role of the patient and/or carer alongside the multidisciplinary team to monitor and review tolerability, adherence and quality of life.

pathway and suggested that quality of life should not be a reason to switch patients from IR to DR mercaptamine bitartrate. One stakeholder commented that the second flowchart was a repetition to the first flowchart.	The patient flowchart has been amended to note it is for patients with a known diagnosis of nephropathic cystinosis who will be continued on IR mercaptamine or be switched to DR mercaptamine.
Potential impact on equality and health inequalities	
One stakeholder did not answer whether they agreed with the EHIA. All other stakeholders agreed with the EHIA. One stakeholder noted that the title of the policy on the EHIA did not align with the title on the policy proposition. One stakeholder commented that patients from ethnic minority backgrounds may wait longer for a renal transplant and that patients from low socioeconomic groups are more likely to develop and progress faster with chronic kidney disease. One stakeholder commented that in the 'pregnancy and maternity' section on page 4 of the EHIA, the guidance needs to align with the SmPC.	No further action required. The title has been amended to match the policy proposition. Patients who meet the eligibility criteria for DR mercaptamine are eligible for treatment regardless of race/ethnicity and socioeconomic status as noted on page 5 and 9 of the EHIA. The EHIA recommends that prescribing centres should make patients aware of NHS Healthcare Travel Costs Scheme to support patients from low socioeconomic groups. The guidance was reviewed, and the section was updated so that the pregnancy and maternity advice was in line with the SmPC.
Changes/addition to policy	
One stakeholder commented the frequency of blood tests under the monitoring section should be amended so that guidance is in line with	The SmPC and EMC guidance on monitoring was reviewed. The policy now advises that monitoring of white blood cell cystine levels, full blood count and liver function tests should happen monthly until a stable cystine level has been reached, and then three-monthly thereafter. Patients switching from IR to DR

information form SmPC and EMC. Two stakeholders commented that the policy should allow for all paediatric nephrology centres to prescribe DR mercaptamine, rather than just highly specialised centres.	mercaptamine should have their cystine levels measured after 2 weeks, and 3 monthly thereafter. As a high-cost drug, it is recommended that prescribing should be from a highly specialised cystinosis centre to ensure expert management of patients and ongoing monitoring in line with the monitoring recommendations in the policy document. After the first year, reviews reduce in frequency and should be coordinated between HSS annual reviews and local specialist renal centre reviews monitoring. Enabling of prescribing for paediatrics will be kept under review in line with these requirements to support access.

5. Has anything been changed in the policy proposition as a result of the stakeholder testing and consultation?

The following change(s) based on the engagement responses has (have) been made to the policy proposition:

- Policy proposition:
    - Page 2 ('About nephropathic cystinosis'): 'In adulthood' was removed as patients can require dialysis and transplant in childhood.
    - Page 2 ('About delayed-release mercaptamine bitartrate'): The following statement was added: "This could improve adherence to treatment for patients and delay the complications of cystinosis."
    - Page 3 ('Exclusion Criteria'): A hyperlink for PROCYSBI 75mg SmPC has been added to the exclusion criteria.
    - Page 4 ('Monitoring): The word monitoring was changed to reviews.
    - Page 4 ('Monitoring'): The frequency of blood tests has been amended under the monitoring section to be in line with SmPC and EMC guidance. The policy now states that white blood cell cystine levels, full blood count and liver function tests should happen monthly until a stable cystine level has been reached, and then three-monthly thereafter. Patients switching from IR to DR mercaptamine should have their cystine levels measured after 2 weeks, and 3 monthly thereafter.
    - Page 6: ('Patient pathway'): The patient flowchart has been amended to note it is for patients with a known diagnosis of nephropathic cystinosis who will be continued on IR mercaptamine or be switched to DR mercaptamine.

- PIA:
    - The grading of the impact of nephropathic cystinosis on ‘mobility’ and ‘ability to provide self-care' was changed from moderate to severe.

    - The free-text section of the PIA was reviewed by the clinical lead and patient public representative. The suggestions made by stakeholders to note the progressive and multisystem nature of the disease, the complications of non-adherence and the impact of the disease on sleep, mental health, personal relationships/social settings, and family life were incorporated within the 150 word limit.

- EHIA:
    - The title has been amended as follows to align with the policy proposition and other policy documents: “Delayed-release mercaptamine bitartrate for patients with nephropathic cystinosis (age >1 year) [URN 2338]”

    - Page 2: The impact of the halitosis and body odour because of IR mercaptamine on social and personal relationships has been noted

    - Page 4/5: The guidance on the use of DR mercaptamine on pregnancy and maternity has been changed to align with guidance from the SmPC.

    - Page 6: The impact of nephropathic cystinosis on male fertility has been noted.

6. Are there any remaining concerns outstanding following the consultation that have not been resolved in the final policy proposition?

No.