NHS ENGLAND SPECIALISED SERVICES

CLINICAL PANEL REPORT

Date: 21 August 2024

Intervention: delayed release mercaptamine bitartrate

Indication: nephropathic cystinosis (age >1 years)

URN: 2338

Gateway: 2, Round 1

Programme: Internal Medicine

CRG: Renal services

Information provided to the Panel

Policy Proposition

Title Change Report

Evidence Review completed by Solutions for Public Health

Clinical Priorities Advisory Group (CPAG) Summary Report

Evidence to Decision (EtD) Summary

Equalities and Health Inequalities (EHIA) Assessment

Patient Impact Assessment

Blueteq® Form – initiation and continuation

Policy Working Group (PWG) Appendix

This Policy Proposition recommends the use of delayed release mercaptamine bitartrate in patients with nephropathic cystinosis (age >1 years). Nephropathic cystinosis is a rare genetic disease 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. 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 therapy is currently only available in an immediate release (IR) formulation, known as IR mercaptamine bitartrate which needs to be taken every 6 hours. This policy proposition is for a delayed-release formulation taken every 12 hours for patients who have difficulty adhering or tolerating the current 6-hour regimen. This indication is within the marketing authorisation of the medicine.

An evidence review was completed which included four studies: a three-week cross over randomised controlled trial (RCT), a prospective single arm follow up study to the RCT, a prospective cohort study, and a prospective case series.

Outcomes that were considered critical and important to decision making were presented to Panel members. The evidence was of very low to low certainty for all reported outcomes mainly due to: the small numbers of patients included, heterogeneous population, risk of bias due to study design, and a lack of comparators for most outcomes. A statistical significant difference

was seen in disease response when compared with IR formulation although it was acknowledged that treatment duration was short. A statistically significant improvement was shown in two quality of life scores within the single arm study when compared to previous IR treatment. One study reported a clinically meaningful decrease in cystine levels from baseline, although clinically meaningful effect size was not defined. Self-reported greater adherence to treatment was reported at 12 months follow up. Most common reported adverse events were gastrointestinal disorders.

The proposition and the supporting documentation were presented to Clinical Panel members. A few points were debated and it was agreed some amendments were required.

EHIA – no amendments requested.

PIA – no amendments requested.

Recommendation

Clinical Panel recommends that this proposition proceeds as a routine commissioning policy proposition, once amendments have been made and approved through Chairs action in consultation with the presenter.

Why the panel made these recommendations

Panel members agreed that, taking into consideration the limitations of the studies, the evidence base, does demonstrate clinical benefit and improved compliance to treatment as it is only taken twice a day rather than four times.

Documentation amendments required

Policy Proposition:

- Page 3 – 'About' section – should refer to a capsule rather than a tablet.
- Inclusion criteria – page 4, 3rd bullet point – wording needs clarification. Does this mean anyone with high cystine levels?
- Dosing – typo – the 2 in the 2nd line needs to be superscript.
- Monitoring –
  - the requirement is for a minimum of an annual review. It was considered by Panel members that more frequent monitoring of compliance would be needed within the first year. This needs to be clarified whether the annual review refers to the highly specialised service and more frequent monitoring would take place in a local service.
  - Monitoring of blood counts and liver function should be included.
- Pathway – pages 6 and 7. Reference to those under 1 years old and continuing on IR formulation. An addendum should be considered for inclusion to enable a step for re-evaluation as to whether they should be considered for DR.

Declarations of Interest of Panel Members: One received due to clinical practice.

Panel Chair: Anthony Kessel, Deputy Medical Director, Specialised Services

Policy Proposition		
Panel Comment	**Amendment**	**Page number (if applicable)**
About section – should refer to a capsule rather than a tablet.	Tablet changed to capsule throughout document	Page 3
Inclusion criteria – 3rd bullet point – wording needs clarification. Does this mean anyone with high cystine levels?	The clinical lead clarified that to be eligible for treatment, patients do not necessarily have to have high cystine levels. Patients are eligible for treatment if there are concerns about adherence, tolerability or quality of life with white cell cysteine levels < 1nmol hemicystine/mgprotein). This has also been changed on the patient pathway on pages 6 and 7.	Page 4
Dosing section - the 2 in the 2nd line needs to be superscript.	Noted and changed.	Page 5
Monitoring – the requirement is for a minimum of an annual review. It was considered by Panel members that more frequent monitoring of compliance would be needed within the first year. This needs to be clarified whether the annual review refers to the highly specialised service and more frequent monitoring would take place in a local service.	The monitoring section has been reviewed so that within the first year, it is suggested that patients receive a minimum of a three-monthly review at their specialist centre within the first year of starting DR mercaptamine. After the first year, patients should be reviewed every 6-12 months.	Page 5
Monitoring of blood counts and liver function should be included.	This has been added to the monitoring section and the clinical lead has recommended that these are done every 3 months for the first year and 6-12 monthly after this. White blood cell cystine levels should also be measured at these timepoints.	Page 5
Pathway – Reference to those under 1 years old and continuing on IR formulation. An addendum	The patient pathways have been amended so that if the patient turns 1, white blood cell cystine levels rise above 1	Page 6 + 7

should be considered for inclusion to enable a step for re-evaluation as to whether they should be considered for DR.	nmol hemicystine/mg protein or there are concerns about tolerability, adherence or quality of life, they should be re-evaluated for potential DR mercaptamine.	