**NHS ENGLAND SPECIALISED SERVICES**

# CLINICAL PANEL REPORT

Date: January 2022

Intervention: subcutaneous copper histidinate

Indication: presymptomatic neonates with classical Menkes disease

URN: 2105

Gateway: 2, Round 1

Programme: Women and Children

CRG: Metabolic Disorders

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**Information provided to the Panel**

Evidence Review completed by Solutions for Public Health

Policy Proposition

Blueteq™ Forms – Initiation and Continuation

Evidence to Decision Making Summary

Patient Impact Report

Equality and Health Inequalities Assessment (EHIA) Report

Clinical Priorities Advisory Group (CPAG) Summary report

Policy Working Group Appendix

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This Policy Proposition recommends the routine commissioning of copper histidinate for subcutaneous use in presymptomatic neonates with classical Menkes disease. 'Classical' Menkes disease presents soon after birth and is a life-limiting disease, with affected children suffering seizures, growth failure and a poor quality of life. It is a progressive disease, with an average life expectancy of 3 years without early treatment. It is caused by a defect in copper transportation in the gut. Treatment with subcutaneous copper histidinate injections can reduce the subsequent symptoms caused by copper deficiency.

There is a published Urgent Policy Statement for this treatment and condition. This is a policy proposition now with a full evidence review completed.

Clinical Panel members were presented with the evidence base supporting this proposition. Four papers were identified for inclusion. Two cohort studies, one prospective and one retrospective, compared children who received early copper histidinate prior to symptoms developing to children who received no early copper histidinate, but who did receive copper histidinate at a later stage. Two case series of patients who received early copper histidinate. No studies comparing children who received early copper histidinate with no copper histidinate at any stage were identified.

The evidence levels indicated very low certainty using GRADE methodology, with study limitations identified. There was evidence available for all the critical outcomes, which were survival, neurodevelopmental outcomes and clinical seizures. For late treatment, death at three years old was 50% compared to 28.6% in early treatment. By 6 years old, death in the late treatment group was 65.5%, whereas it is 40% in the early treatment group. Statistically

significant evidence reported in one study of neuro developmental outcome improvements in those receiving early (before the age of one month) vs later treatment. Frequency of seizures maybe less.

No evidence was identified for cost effectiveness.

The Panel considered there could be significant burden on carers regarding dosage implications as described in one fo the studies and so there is a need to ensure families are given adequate support.

Panel members discussed the age cut off and expressed concern at the use of this being so definitive as some patients may benefit after this. The Policy Working Group (PWG) should consider this and either put ‘around the age of 28 days’ or ‘before functional neurological symptoms.

The Clinical Panel examined the proposition.

EHIA – no additional comments received.

Patient Impact Report – no additional comments received.

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**Recommendation**

Clinical Panel recommends that this proposition progresses as proposed, with the amendments requested.

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**Why the panel made these recommendations**

Clinical Panel members considered that the proposition was written reflective of the evidence base.

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**Documentation amendments required**

Policy Proposition:

- The PWG should consider the age cut off and either rephrase to ‘around the age of 28 days’ or perhaps ‘before functional neurological symptoms’.
- PWG to consider the impact of pre-term babies and if this will make a difference to dosage.
- Proposed treatments page 4 - states ‘can’ cause kidney damage with long term use. Should it be ‘may’ instead of can. Clarify with the Policy Working Group (PWG).
- Inclusion criteria page 4 – family history confirmation – why state this and then potentially exclude those children who developed this condition sporadically and don’t have a family history? Check with PWG.
- Starting criteria page 5 – states renal ultrasound, echocardiology, electroencephalogram. Is this information relevant?
- Reassessment page 5 – outpatients follow up every 6 months. How has this been derived? Should this be worded to be more flexible regarding remote consultation? PWG to consider.
- Reassessment page 5 – the section regarding monitoring around the management of the disease rather than the drug. Consider removing.

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Declarations of Interest of Panel Members: None

Panel Chair: James Palmer, National Director, Specialised Services

Post panel note

1. '*The PWG should consider the age cut off and either rephrase to 'around the age of 28 days' or perhaps 'before functional neurological symptoms'*

   The policy was amended so that the inclusion criteria states that

   'Neonates will be evaluated for the capacity to benefit from treatment under this policy proposition if they meet all of the following inclusion criteria:

   - Family history of classical Menkes disease
   - Confirmed classical Menkes disease by the finding of a pathogenic mutation on ATP7A[1]
   - Around 28 days or younger at the time of commencing treatment '

2. *PWG to consider the impact of pre-term babies and if this will make a difference to dosage.* The PWG considered that no change in dosage for pre term babies was required.
3. *Proposed treatments page 4 - states 'can' cause kidney damage with long term use. Should it be 'may' instead of can.* The PWG agreed the change from 'can' to 'may'.
4. *Inclusion criteria page 4 – family history confirmation – why state this and then potentially exclude those children who developed this condition sporadically and don't have a family history? Check with PWG.*
   The PWG retained the reference to family history. The complexities in diagnosis including that there is no screening at birth for this disease, are discussed in the section about the condition. These factors mean it is very unlikely that baby would be diagnosed in time for treatment to be initiated.
5. *Starting criteria page 5 – states renal ultrasound, echocardiology, electroencephalogram. Is this information relevant?* This information has been removed.
6. *Reassessment page 5 – outpatients follow up every 6 months. How has this been derived? Should this be worded to be more flexible regarding remote consultation? PWG to consider.* Twice yearly is the standard monitoring offered to stable patients with such major illnesses. Metabolic services offer virtual consultations where clinically appropriate.
7. *Reassessment page 5 – the section regarding monitoring around the management of the disease rather than the drug*. *Consider removing.* This section has been removed.



[1] In certain cases, it may be appropriate to make a diagnosis by biochemical means where the family index case has not previously had genetics testing.