CLINICAL PRIORITIES ADVISORY GROUP
6th September 2023

Agenda Item No	2.1
National Programme	Women and Children's Programme of Care
Clinical Reference Group	Metabolic
URN	2105

Title
Subcutaneous copper histidinate injections for presymptomatic neonates with classical Menkes disease.

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
For routine commissioning. There is a published urgent policy statement currently in place for this intervention and indication. This policy proposition replaces that. Menkes disease is an inherited disorder of copper transport, which mainly affects males. '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. Current treatment focuses on treating the symptoms of the disease, as there is no cure. Copper injections delivered under the skin are thought to reduce symptoms and treat the condition, as patients with Menkes disease cannot absorb copper normally from their diet. These injections are delivered twice a day for the first year and then once a day and are a lifelong treatment. These injections are expected to be delivered by the child's carers. For the treatment to be effective, it must be started before or around 28 days after birth.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progresses as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

No	*Metric*	*Summary from evidence review*
1.	Survival Certainty of evidence Very low	This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. Without treatment, life expectancy is usually less than three years. In total, three studies[(1)] (one prospective cohort study, one retrospective cohort study and one case series) provided evidence relating to survival with follow-up of up to six years for children with classical Menkes disease treated with subcutaneous copper histidinate. The two cohort studies compared children who received early copper histidinate delivered prior to symptoms developing with children who did not receive any early copper histidinate but did receive copper histidinate at a later stage. No

		studies compared early copper histidinate with no copper histidinate at any stage. At three years: • One prospective cohort study (Kaler 2014) reported death by three years old in ten of 35 children (28.6%) who received early copper histidinate and 11 of 22 children (50.0%) who received later copper histidinate. No statistical comparison reported. (VERY LOW) At follow-up of up to six years: • Two studies (one retrospective cohort study and one case series) reported survival with follow-up of up to six years. • One retrospective cohort study (Gu et al 2014) reported death by the time of the study for children who received early and later copper histidinate. Mean follow-up not reported. No statistical comparison reported. (VERY LOW) only (n=7) or oral plus other feeding (n=22). Mean (± SD) age at death was 59 ± 10 months (n=3) and 46 ± 22 months (n=16) respectively (range not reported). Mean (± SD) age of survivors was 100 ± 44 months (n=4) and 21 ± 10 months (n=6) respectively (range not reported). • One case series (Kaler et al 2010) reported that nine of 24 children (37.5%) who received early treatment with copper histidinate died during the study. Mean follow-up not reported. Age at death ranged from 5.5 months to 2.6 years. (VERY LOW). These studies provided very low certainty evidence that survival for children receiving early treatment with copper histidinate ranges from 28.6% for death by three years old to 40.0% for death at a follow-up period of up to six years. For children who received copper histidinate later, death by three years old was 50.0% and death at a follow-up period of up to six years was 65.5%. No statistical comparison was reported comparing early to later treatment. • Two of five children (40.0%) who received early copper histidinate died. The mean (± SD) age at death was 53.5 ± 43.1 months (range 23 to 84). The mean (± SD) age of the three survivors at last follow-up was 55.7 ± 25.4 months (range 35 to 84). • Nineteen of 29 children (65.5%) who received later copper histidinate died. Mean age at death and mean age of survivors was reported separately for children who received oral feeding.

2.	Neurodevelopmental outcomes Certainty of evidence: Very low	Neurodevelopmental outcomes are important to patients as they are a marker of the development of the brain and the child's ability to meet milestones such as smiling, crawling, walking. These may be measured by tools such as the Denver Developmental Screening Test. In total, three studies (one prospective cohort study, one retrospective cohort study and one case series) provided evidence relating to neurodevelopmental outcomes with follow-up of up to six years for children with classical Menkes disease treated with subcutaneous copper histidinate. The two cohort studies compared children who received early copper histidinate delivered prior to symptoms developing with children who did not receive any early copper histidinate but did receive copper histidinate at a later stage. No studies compared early copper histidinate with no copper histidinate at any stage. At follow-up of up to three years: • One prospective cohort study (Kaler 2014) reported neurodevelopmental level achieved by three years old or time of death using the Denver Developmental Screening Test2 (mean follow-up not reported). (VERY LOW) • For gross motor function, children treated with early copper histidinate achieved a statistically significantly better neurodevelopmental level in months than children who received later copper histidinate ($p<0.0001$). Early copper histidinate (n=35) mean (SD; range) 13.743 (12.200; 1 to 36) compared to later copper histidinate (n=22) 2.455 (2.154; 1 to 10) • For fine motor-adaptive, children treated with early copper histidinate achieved a statistically significantly better neurodevelopmental level in months than children who received later copper histidinate ($p<0.0001$). Early copper histidinate (n=35) mean (SD; range) 16.200 (12.762; 1 to 36) compared to later copper histidinate (n=22) 2.409 (1.652; 1 to 8) • For personal-social, children treated with early copper histidinate achieved a statistically significantly better neurodevelopmental level in months than children who received later copper histidinate ($p<0.0001$). Early copper histidinate (n=35) mean (SD; range) 17.657 (13.482; 1 to 36)

		compared to later copper histidinate (n=22) 3.364 (3.499; 1 to 15) • For language, children treated with early copper histidinate achieved a statistically significantly better neurodevelopmental level in months than children who received later copper histidinate ($p<0.0001$). Early copper histidinate (n=35) mean (SD; range) 15.800 (12.034; 1 to 36) compared to later copper histidinate (n=22) 3.227 (2.943; 1 to 12) At follow-up of up to six years: • Two studies (one retrospective cohort study and one case series) reported neurodevelopmental outcomes with follow-up of up to six years. • One retrospective cohort study (Gu et al 2014) reported status at last follow-up or prior to death (mean follow-up not reported). Of five children who received early treatment with copper histidinate, four were described as “could lift head from a prone position, sit well unsupported, stand without help and walk” and one was described as “could lift head from a prone position and sit with support”. All 39 children who received later copper histidinate were described as “normalised scalp hair and capable of smiling back but could not lift head from a prone position”. No numerical data or statistical comparison reported. (VERY LOW) • One case series (Kaler et al 2010) reported neurodevelopmental status in 14 survivors who received early treatment with copper histidinate with data at last follow-up (mean follow-up not reported). Three children (21.4%) were described as having normal development, one (7.1%) was mildly delayed, three (21.4%) were moderately delayed and seven (50.0%) were severely delayed. Neurodevelopmental status was assessed using the Denver Developmental Screening test, however the categories were not further described. (VERY LOW) One study provided very low certainty evidence of statistically significantly better outcomes in four neurodevelopmental areas at up to three years follow-up for children receiving early treatment with copper histidinate compared to children who received later treatment. Two further studies provided narrative descriptions of children’s neurodevelopment at up to six years follow-up. One described outcomes ranging from normal to severely delayed for children who received early treatment with copper histidinate. In the other study, the

		descriptions given suggested that children who received copper histidinate later achieved fewer neurodevelopmental outcomes than children who received early treatment.
3.	Number of seizures Certainty of evidence: Very Low	The absence or reduction in the number of seizures is important to patients as they may develop drug-resistant seizures requiring hospital attendance and admission with status epilepticus. In total, two case series provided evidence relating to seizures with follow-up of up to six years for children with classical Menkes disease treated with early subcutaneous copper histidinate delivered prior to symptoms developing. No studies compared early copper histidinate with no copper histidinate. At follow-up of up to six years: • One case series (Kaler et al 2008) reported that two of 12 children (16.7%) who received early treatment with copper histidinate had clinical seizures. The study mean follow-up was 4.6 years (range 1.5 to 8.6 years). The timeframe for this outcome was unclear. (VERY LOW) • One case series (Kaler et al 2010) reported that three of 24 children (12.5%) who received early treatment with copper histidinate had clinical seizures. Patients were followed-up for up to six years. Mean follow-up was not reported. Mean age at first seizure was 20.3 ± 9.3 weeks (range 14 to 31). (VERY LOW) Two studies reported very low certainty evidence that clinical seizures occurred in 12.5% and 16.7% of children receiving early treatment with copper histidinate.
4.	Health-related quality of life Certainty of evidence: Not applicable	Quality of life is important to patients and their carers as it provides a holistic evaluation and indication of the patient's general health and their and their carer's perceived well-being. Quality of life for patients with classical Menkes disease can be measured with tools such as Peds-QL (Paediatric Quality of Life Inventory) or the EQ-5D-Y. No evidence was identified for this outcome.
5.	Growth measurements Certainty of evidence: Very low	Growth measurements such as weight, length and head circumference are important outcomes to patients and their carers as they can be a marker of treatment success.

		In total, two studies (one prospective cohort study and one retrospective cohort study) provided evidence relating to growth measurements with follow-up of up to six years for children with classical Menkes disease treated with subcutaneous copper histidinate. The two cohort studies compared children who received early copper histidinate delivered prior to symptoms developing with children who did not receive any early copper histidinate but did receive copper histidinate at a later stage. No studies compared early copper histidinate with no copper histidinate at any stage. At follow-up of up to three years: • One prospective cohort study (Kaler 2014) reported growth measurement (weight, length, occipitofrontal circumference) centiles at three years old or time of death (mean follow-up not reported). (VERY LOW) • For weight, there was no statistically significant difference between children treated with early copper histidinate and children who received later copper histidinate (p=0.8735). Early copper histidinate (n=35) mean (SD; range) centile 12.086 (19.589; 0 to 80) compared to later copper histidinate (n=22) 11.273 (17.097; 0 to 50) • For length, there was no statistically significant difference between children treated with early copper histidinate and children who received later copper histidinate (p=0.1453). Early copper histidinate (n=35) mean (SD; range) centile 8.286 (13.501; 0 to 25) compared to later copper histidinate (n=22) 15.455 (23.192; 0 to 75) • For occipitofrontal circumference, children treated with early copper histidinate had a statistically significantly better measurement than children who received later copper histidinate (p<0.0009). Early copper histidinate (n=35) mean (SD; range) centile 33.286 (27.060; 0 to 90) compared to later copper histidinate (n=22) 11.136 (14.551; 0 to 50) At follow-up of up to six years: • One retrospective cohort study (Gu et al 2014) reported growth measurement (body weight and height) percentiles based on national data, with follow-up of up to six years. The specific timepoints for which outcomes were reported varied and are specified below. For children who received later copper histidinate, body weight and height were reported separately for children who received oral feeding only or oral plus other feeding.

		All children who received early treatment with copper histidinate received oral feeding only. For body weight up to 12 months (VERY LOW): • At six to 12 months, three children who received early treatment were all <3rd percentile • At five to seven months, one of three children who received later copper histidinate and oral feeding only was between the 10th and 25th percentiles and the other two children were between the 50th and 75th percentiles • At four to seven months, three of eight children who received later copper histidinate and oral plus other feeding were between the 3rd and 10th percentiles, three were between the 10th and 25th percentiles, one was between the 75th and 90th percentiles and one was >97th percentile For body weight after 12 months (VERY LOW): • At 13 to 60 months, four children who received early treatment were all <3rd percentile • At 24 to 25 months, two children who received later copper histidinate and oral feeding only were both <3rd percentile • At 22 to 59 months, five children who received later copper histidinate and oral plus other feeding were all <3rd percentile For height up to 12 months (VERY LOW): • At six to 12 months, three children who received early treatment were all <3rd percentile • At five to seven months, one child who received later copper histidinate and oral feeding only was <3rd percentile • At four to seven months, one of six children who received later copper histidinate and oral plus other feeding was <3rd percentile, two were between the 3rd and 10th percentiles, one was 10th percentile, one was between the 25th and 50th percentiles and one was between the 75th and 90th percentiles For height after 12 months (VERY LOW): • At 13 to 60 months, three children who received early treatment were <3rd percentile and one child was <10th to 25th percentile • At 24 to 25 months, two children who received later copper histidinate and oral feeding only were both <3rd percentile • At 22 to 59 months, three of five children who received later copper histidinate and oral plus other

		feeding were <3rd percentile and the other two children were between the 3rd and 10th percentiles. One study provided very low certainty evidence that children receiving early treatment with copper histidinate had statistically significantly better growth measurements in terms of occipitofrontal circumference than children who received later treatment. There was no statistically significant difference between early and later treatment for weight and length in this study. A second study provided descriptive information about body weight and height percentiles at different ages for children who received early or later treatment.
6.	Number of hospital attendances/admissions Certainty of evidence: Not applicable	Patients with classical Menkes disease often require frequent admissions to hospital, including paediatric intensive care units. The reduction of hospital admissions is an important outcome for patients and their carers as it is a marker that treatment is working. No evidence was identified for this outcome.
7.	Requirement for anti-convulsant medication Certainty of evidence: Not applicable	Patients with classical Menkes disease often require anti-convulsant medication to help control their seizures. A reduction in the requirement of these medications is preferred by patients as they can have negative side effects. Increased requirement for anticonvulsant medication may also be an indicator of treatment resistance. No evidence was identified for this outcome.
8.	Development of bladder diverticulae Certainty of evidence: Not applicable	Not developing bladder diverticulae is an important outcome for patients as bladder diverticulae can cause an increased risk of infection, bladder stones, vesico-ureteric reflux and difficulty passing urine. No evidence was identified for this outcome.
10.	Safety Drug-related serious adverse effects Certainty of evidence: Very low	This can include kidney damage and cardiomyopathy. Kidney damage may be monitored by the use of urine beta-2 microglobulin or other markers for early renal tubular dysfunction. In total, one case series provided evidence relating to drug-related serious adverse effects for children with classical Menkes disease treated with early subcutaneous copper histidinate prior to symptoms developing. This involved measurement of levels of urinary β2-microglobuln (a sensitive marker of renal tubular damage) whilst children were receiving copper histidinate (up to three years). The reference range was stated as 0.0 to 0.3 mg/L. No studies

		compared early copper histidinate with no copper histidinate. • One case series (Kaler et al 2008) reported that 11 children (100%) who received early treatment with copper histidinate had increased levels of urinary β2-microglobuln. The median maximum measured concentration was 27.4 mg/L (range 1.2 to 60.9). (VERY LOW) One paper reported very low certainty evidence that all children receiving early treatment with copper histidinate had increased levels of a marker of renal tubular damage during treatment.

1 Kaler et al 2008 also reported survival and neurodevelopmental outcomes. However, these were not extracted as all of the patients who received early treatment with copper histidinate in this study were also included in the Kaler 2014 study population.

No	Metric	Summary from evidence review
1.	Cost effectiveness	No evidence was identified for cost effectiveness.
2.	Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from early treatment with subcutaneous copper histidinate.
3.	Age at treatment	In Gu et al 2014 and Kaler 2014, children received early treatment with copper histidinate at less than one month old. Their age was not further defined. In Kaler et al 2008 and Kaler et al 2010 the mean ± standard deviation age at treatment initiation was 10 ± 4 days (range 5 to 22) and 11.8 ± 9.6 days (range -3.5 weeks to 42 days3) respectively. In Gu et al 2014, children were described as receiving later treatment with copper histidinate, starting after one month of age. Their age at the start of treatment was not further defined. However, their age at diagnosis was stated as 8.0 ± 2.8 months and 7.5 ± 3.4 months for children who received oral feeding only and oral plus other feeding respectively. In Kaler 2014 the age at treatment initiation of children receiving later treatment with copper histidinate was not specified, only that it was after the appearance of symptoms.

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility**: Patients are unable to walk about • **ability to provide self-care**: Patients are unable to wash or dress • **undertaking usual activities**: Patients are unable to do their daily activities

- **experience of pain/discomfort:** Patients have moderate/severe/extreme pain or discomfort
- **experience of anxiety/depression**: Unable to answer due to the average age of patients with this condition

Further details of impact upon patients:

Children living with Menkes experience the following symptoms: seizures, developmental delay and neurological regression, severe hypertonia, osteoporosis, gastroesophageal reflux, gastrostomy/PEG feeding (completely nil by mouth), gut dysmotility, dual bladder diverticula, urinary and bowel incontinence, excessive drooling and sleep apnoea. Children with Menkes Disease are often born with severe jaundice, wrinkly skin, brittle/sparse hair, and disordered temperature regulation. Due to the rarity of the condition these signs and symptoms are often missed.

Children receive care from a multidisciplinary team including: Community nurses, Neurologists, Physiotherapists, Osteopaths, Dieticians and Metabolic Consultants. The impact on patients is severe, patients are solely dependent on parent/carers to wash, dress, feed and help them mobilise. With a limited life expectancy, it is unclear what impact this condition may have on adolescents and adults. The severity of symptoms from Menkes Disease means the child generally has a poor quality of life, when compared to other children of similar ages.

Further details of impact upon carers:

Parents and Caregivers become full time carers to children diagnosed with Menkes disease. Many parents/caregivers find the diagnosis difficult to process, have fears about the future and struggle to cope with the unknowns.

The psycho-social impact of Menkes Disease on parents and carers is significant, ranging from sleep deprivation to dealing with the unknown life expectancy of a child. Parents/caregivers often experience mental health issues linked to sleep deprivation, worry and anxiety and the pressure of maintaining consistent care and feeding routines. This is emphasised by a lack of awareness of Menkes Disease in the medical profession and by the public. The 24-hour caring routine means parents and caregivers living with Menkes Disease also have an extremely poor quality of life.

Considerations from review by Rare Disease Advisory Group

The Rare Disease Advisory Group confirmed support for this policy proposition in 10th November 2022.

Pharmaceutical considerations
This clinical commissioning policy proposition recommends subcutaneous copper histidinate to treat neonates diagnosed with classical Menkes disease who are asymptomatic. Copper histidinate does not have marketing authorisation for Menkes disease so use in this condition is unlicensed. Copper histidinate is excluded from tariff. Use of copper histidinate is currently recommended in an NHS England Urgent Policy Statement '*Subcutaneous copper histidinate injections for presymptomatic neonates with classical Menkes disease (210507P) [URN 2104]*'.

Considerations from review by National Programme of Care
The proposal received the full support of the Women and Children's Programme of Care Board in March 2023