**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technologies Evaluation**

# OTL-200 for treating metachromatic leukodystrophy

**Final scope**

## Remit/evaluation objective

To evaluate the benefits and costs of OTL-200 within its marketing authorisation for treating metachromatic leukodystrophy for national commissioning by NHS England.

## Background

Metachromatic leukodystrophy (MLD) is an autosomal recessive genetic disorder, caused by a deficiency in the enzyme arylsulfatase-A (ARSA). This deficiency prevents the nerves from functioning properly and leads to neurological problems. MLD is a progressive disease where symptoms worsen over time. It is a chronically disabling and life-limiting condition. Disease with an earlier onset is associated with quicker progression and a reduced life expectancy compared with disease with an onset later in life, although all subtypes are associated with substantially reduced quality of life and life expectancy. The course of disease can be broadly divided into a pre-symptomatic stage with normal motor and cognitive development, followed by the onset of symptoms and a period of developmental plateau, which is short in early onset forms and longer and more variable in late onset forms.

MLD includes 3 main subtypes based on the age of onset. The late infantile type (the subtype with the earliest onset) is the most common and the most rapidly progressing. The 3 subtypes have different symptoms:

- Late infantile type, (40-60% of cases), has an onset between 6 months and 4 years[1]. Symptoms include peripheral neuropathy, muscle weakness, sight and hearing loss, difficulty walking, loss of speech, cognitive decline, and seizures[1,2,3]. Late infantile type progresses fairly rapidly and over a few years the child will lose awareness of their surroundings. Death normally occurs between the ages of 5 and 8[2].
- Early juvenile type (20-35% of cases), has an onset between 4 and 16 years[1]. Symptoms include impairment in fine motor skills and concentration, behavioural problems, difficulties with movement, slurred speech, incontinence, and seizures. The disease progression is less rapid than for late infantile MLD[1]. As the disease progresses, children develop more motor symptoms such as tremor and muscle rigidity, and eventually lose the ability to walk[3]. Death normally occurs within 10 to 20 years of onset[1].
- Adult type (15-25% of cases[1]) is the rarest subtype and has an onset after 16 years[3]. Symptoms include a decline in performance at school or work, cognitive decline, personality changes and lapses in memory. The decline can be slow and almost imperceptible. Without intervention, movement can become clumsy, people may become


 

incontinent and their arms and legs may be paralysed[3]. Death normally occurs within 5 to 20 years of onset[1].

The prevalence of MLD is estimated at around 1-9 in 1,000,000[4]. The incidence of MLD is estimated at around 1.1 cases per 100,000 live births in the European Union. The incidence in the UK is estimated at 1 in 40,000 live births.[2] It is possible that the incidence may prove to be higher with more modern diagnostic tools[3].

Treatment for late infantile MLD is usually palliative and supportive, because treatment such as stem cell transplant is ineffective even at a pre-symptomatic stage[1]. Children with early juvenile MLD who have a diagnosis before they have symptoms (usually if an older sibling has been diagnosed with MLD) or who have only recently started having symptoms may be able to have umbilical cord blood or stem cell transplant, although this is rare in the UK. People with adult onset MLD may also be able to have a stem cell transplant if they have no or mild symptoms[3]. Stem cell transplant carries risks and the long-term outcomes are unknown[1].

**The technology**

OTL-200 (brand name unknown, Orchard Therapeutics) is a gene therapy. The mechanism of action of OTL-200 in the central nervous system is thought to be by transduced cells migrating into the brain and engrafting, which then synthesise and secrete arylsulfatase A (ARSA). This enzyme is taken up by oligodendrocytes and neurons in the central nervous system, allowing the breakdown of harmful sulfatides, preventing further demyelination and atrophy.

OLT-200 does not currently have a marketing authorisation in the UK for treating MLD. It has been studied in single arm clinical trials in children under 7 with pre-symptomatic late infantile MLD and pre-symptomatic or early-symptomatic early juvenile MLD. It is administered intravenously.

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| **Intervention** | OTL-200 |
| **Population** | People with MLD |
| **Comparators** | Established clinical management without OTL-200, including but not limited to:<br>• Stem cell transplant<br>• Best supportive care |
| **Outcomes** | The outcome measures to be considered include:<br>• change in gross motor function<br>• change in neurological function, for example |


 

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| | speech and swallowing<br>• change in neurocognitive function<br>• change in arylsulfatase (ARSA) activity<br>• stability of nerve conduction<br>• age and time at severe motor impairment or death<br>• mortality<br>• adverse effects of treatment<br>• health-related quality of life (for patients and carers) |
| **Nature of the condition** | • disease morbidity and patient clinical disability with current standard of care<br>• impact of the disease on carer's quality of life<br>• extent and nature of current treatment options |
| **Clinical Effectiveness** | • overall magnitude of health benefits to patients and, when relevant, carers<br>• heterogeneity of health benefits within the population<br>• robustness of the current evidence and the contribution the guidance might make to strengthen it<br>• treatment continuation rules (if relevant) |
| **Value for Money** | • Cost effectiveness using incremental cost per quality-adjusted life year<br>• Patient access schemes and other commercial agreements<br>• The nature and extent of the resources needed to enable the new technology to be used |
| **Impact of the technology beyond direct health benefits** | • whether there are significant benefits other than health<br>• whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services<br>• the potential for long-term benefits to the NHS of research and innovation<br>• the impact of the technology on the overall delivery of the specialised service |


 

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| | • staffing and infrastructure requirements, including training and planning for expertise. |
| **Other considerations** | • Guidance will only be issued in accordance with the marketing authorisation.<br>• Guidance will take into account any Managed Access Arrangements<br>• If the evidence allows, the following subgroups may be considered<br>  ○ pre-symptomatic MLD<br>  ○ early-symptomatic MLD |
| **Related NICE recommendations and NICE Pathways** | None. |
| **Related National Policy** | NHS England (2013) 2013/14 NHS Standard Contract for Metabolic Disorders (Laboratory Services): Particulars, Schedule 2 - The Services, A. Service Specifications. Ref: E06/S/c |

**References**


1. Wang RY, Bodamer OA, Watson MS et al. on behalf of the ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases (2011) Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals. Genetics in Medicine 13(5): 457-484.
2. Great Ormond Street Hospital Metachromatic leukodystrophy late infantile form [online, accessed October 2019]
3. MLD Support Association UK About MLD [online, accessed October 2019]
4. Orpha.net Metachromatic Leukodystrophy [online, accessed October 2019]