Health Technology Briefing
December 2023

Mexiletine hydrochloride for treating myotonia in children and adolescents with myotonic disorders

Company/Developer	Lupin Limited

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30808	NICE ID: Not Available	UKPS ID: 669281, 669313, 669314

Licensing and Market Availability Plans

Currently in phase III clinical development

Summary

Mexiletine is currently in clinical development for the treatment of children and adolescents with myotonic disorders. Myotonic disorders comprise both myotonic dystrophy (DM1 and DM2) and non-dystrophic myotonia (NDM). A common symptom of both conditions is myotonia, during which muscles relax slowly and with difficulty after a voluntary contraction. Muscles affected can include those in the hands, arms, legs, eyelids, face and jaw and muscles in the neck. For patients with symptoms of myotonia, they can appear anytime between the first decade of life and old age. Myotonic disorder patient symptoms may include muscle stiffness (myotonia) pain, weakness, clouding of the eye lens, a slow and irregular heartbeat, slurred speech, problems with swallowing, behavioural and personality problems and excessive sleepiness or tiredness. Life expectancy can vary for people with DM1 and 2; while some have a normal life expectancy, those with more severe congenital forms present from birth might die at a very young age. With NDM, life expectancy is not impaired. There is a medical need for a novel therapy in treatment of children and adolescents with myotonic disorders.

Mexiletine is orally administered to patients and acts mostly on active muscle fibres subject to repeated discharges (such as skeletal muscles). It improves myotonic symptoms by decreasing muscle stiffness through reducing the delay in muscle relaxation. If licensed, mexiletine will offer a novel treatment option for the symptomatic treatment of myotonia in children and adolescents.

Proposed Indication

The treatment of children and adolescents with myotonic disorders.[1]

Technology

Description

Mexiletine (Namuscla) is a sodium channel blocker and works by blocking channels in muscle cells that allow sodium ions (electrically charged particles) to pass in and out. These sodium channels play a role in the contraction and relaxation of muscles and are hyperactive in patients with myotonic disorders, causing excessive contractions and stiffness. By blocking them, the medicine helps to reduce the stiffness that occurs when the contractions are prolonged.[2] Mexiletine is, therefore, mostly active on muscle fibres subject to repeated discharges (such as skeletal muscles). It improves myotonia by decreasing muscle stiffness through reducing the delay in muscle relaxation.[3]

Mexiletine is currently in clinical development for the treatment of myotonia in children and adolescents with myotonic disorders. In the phase III clinical trial (NCT04624750) mexiletine is administered to subjects starting at an age-appropriate dose based on body weight once daily and up-titrated every 14 days for 4 weeks followed by a 4 weeks' maintenance period.[1]

Key Innovation

Currently there are no licensed medicines in the UK for the symptomatic treatment of myotonia in children and adolescents. Hence there is a need for a novel therapy for the treatment of the condition in this population group. Mexiletine has been found to be safe, well-tolerated and efficacious in randomised controlled trials, mainly for adult patients with myotonic disorder.[4,5]

If licensed, mexiletine will offer a novel treatment option for the treatment of children and adolescents with myotonic disorders.

Regulatory & Development Status

Mexiletine has a marketing authorization in the EU/UK for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.[3]

Mexiletine has an orphan drug designation in the EU in 2014 for the treatment of myotonic disorders.[2]

Mexiletine is currently not in any phase II/III clinical development for other indications.[6]

Patient Group

Disease Area and Clinical Need

Myotonic disorders are a heterogeneous group of conditions linked by a common clinical symptom of myotonia and characteristic electro-diagnostic features. Caused by muscle ion channel dysfunction, myotonia may produce stiffness, cramping or an aching sensation in affected muscles.[7] Patients with myotonia often report pain, fatigue and weakness and an inability to relax their muscles after a voluntary contraction.[8] Myotonic disorders (DM) can be either classified as dystrophic (DM1 and DM2) or as non-dystrophic myotonias (NDMs).[7] Patient symptoms of myotonia can appear anytime between the first decade of life and old age.[9] Myotonic disorder patient symptoms may include muscle stiffness (myotonia),

pain, weakness, clouding of the eye lens, a slow and irregular heartbeat, slurred speech, problems with swallowing, behavioural and personality problems and, excessive sleepiness or tiredness.[10] Life expectancy can vary for people with myotonic dystrophy. While some have a normal life expectancy, those with the more severe congenital form present at birth may have a fatal outcome at a very young age.[10]

A detailed population-based study conducted in the north of England found that the prevalence of dystrophic myotonias to be 10.6 per 100,000 people in 2007.[11] In England, in 2022-23, there were 547 finished consultant episodes (FCE) and 430 admissions for myotonic disorders (ICD-10 code G7.11) which resulted in 201 day cases and 2,154 FCE bed days.[12]

Recommended Treatment Options

There are no current NICE recommended treatment options for children and adolescents with myotonic disorders. Management of childhood DM is currently adapted from approaches to adult myotonic dystrophy; a multidisciplinary team approach is critical in providing supportive care to manage symptoms, reduce complications, optimise function and undertake health surveillance.[13]

Clinical Trial Information

Trial	NCT04624750: An open-label, non-comparative study to evaluate the steady-state pharmacokinetics, safety, and efficacy of mexiletine in adolescents and children with myotonic disorders. **Phase III**: Recruiting **Location(s):** France **Primary completion date:** March 2024	NCT04622553: Open-label extension study to evaluate the long-term safety and efficacy of mexiletine in paediatric patients with myotonic disorders who have completed the NCT04624750 study. **Phase N/A:** Recruiting **Location(s):** France **Primary completion date:** January 2026
Trial Design	Single group assignment, open label	Single group assignment, open label
Population	N=14 (estimated); male or female patients aged more than 6 years and less than 18 year with genetically confirmed diagnosis of NDM or DM	N=14 (estimated); male or female patients aged more than 6 years and less than 18 year with genetically confirmed diagnosis of NDM or DM who had previously completed NCT04624750 and tolerated mexiletine in the study.
Intervention(s)	Mexiletine	Mexiletine
Comparator(s)	No comparator	No comparator
Outcome(s)	Primary outcomes: • Number and frequency of adverse events (AEs)/serious adverse events (SAEs) [Time frame: baseline to day 56]	Primary outcomes: • Assess the long-term safety and tolerability of mexiletine by AEs [Time frame: approximately 24 months] • Assess the long-term safety and tolerability of mexiletine

	• Incidence of adverse events of special interest (AESI) [Time frame: baseline to day 56] • Changes in ECG assessments from baseline [Time frame: baseline to day 56] • Efficacy of Namuscla treatment on the clinical outcomes based on the following functional evaluations: mean change in visual analogue scale (VAS) for muscle stiffness, pain, weakness and fatigue. [Time frame: baseline to day 56] • Efficacy of Namuscla treatment on the clinical outcomes (change from baseline to days 14, 28, 42 and 56, respectively) based on the following functional evaluations. See trial record for full list of outcomes.	by hand relaxation [Time frame: approximately 24 months] • Assess the long-term safety and tolerability of mexiletine measurement of AESI [Time frame: approximately 24 months] • Assess the long-term safety and tolerability of mexiletine by changes in ECG [Time frame: approximately 24 months] • Assess the long-term safety and tolerability of mexiletine by muscle stiffness [Time frame: Approximately 24 months] See trial record for full list of outcomes.
Results (efficacy)	-	-
Results (safety)	-	-

Estimated Cost

Mexiletine is already marketed in the UK; 100 units of 167mg Mexiletine capsules is £5000.00.[14]

Relevant Guidance

NICE Guidance

There is currently no NICE guidance for the treatment of myotonic disorders in children and adolescents.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard contract for paediatric neurosciences – neurology. E09/S/b
- NHS England. 2013/14 NHS Standard Contract for Diagnostic Service for Rare Neuromuscular Disorders (All Ages). D04/S(HSS)/a

Other Guidance

- Johnson NE, et al. Consensus-based care recommendations for congenital and childhood-onset myotonic dystrophy type 1. 2019.[15]
- Kamsteeg EJ, et al. Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2. 2012.[16]

Additional Information

References

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