National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Mexiletine for treating symptomatic myotonia in adults with non-dystrophic myotonic disorders

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Lupin Healthcare (UK) Limited	Yes, it is appropriate that NICE reviews mexiletine (Namuscla). Non-Dystrophic Myotonia (NDM) is a group of ultra-rare, genetic disorders, with no current licensed pharmaceutical treatments. It is important that NICE reviews the evidence base for Namuscla to ensure it offers value for money to the NHS. Additionally, some patients do have access to unlicensed imported mexiletine, therefore national commissioning will ensure equity of patient access to Namuscla and avoid confusion of the imported, unlicensed versions of mexiletine. People with NDM see many experts before diagnosis and no national clinical guidelines exist; therefore, NICE technology appraisal guidance for Namuscla will optimise patient management, standardise and define the treatment care pathway.	Comment noted. No action required. Comment noted. At the scoping workshop it was noted that the existing service provision of mexiletine functioned well, and access to treatment was not an issue.
	The National Hospital for	Mexiletine has been used off-label and unlicensed as first-line treatment for non-dystrophic myotonia for at least 10 years. It is an anti-arrhythmic and sodium channel blocker. This group or type of medicine is well established	Comment noted. The extent to which the technology may or may

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	Neurology and Neurosurgery	and there is nothing specialist about the drug/technology. Its current cost to the NHNN (NHS) is relatively cheap at approximately £1600 per patient per year on maximal dose. The diseases are rare and most patients are likely to be seen either at our specialist centre or other neuromuscular services around the country. However prescribing is not limited to our specialist service and some patients do currently receive mexiletine from their local neurologist or even their GP. It should be noted that mexiletine is used in neurology for other indications e.g. pain and was originally licensed as an anti-arrhythmic so doctors outside of the HSS service for muscle channelopathies do have experience of prescribing it. The condition is genetic and thus chronic. Mexiletine once started is usually taken life-long if effective. Severity of disability is less in comparison to other neuromuscular disorders e.g. the majority of patients are employed and ambulant without aids. The condition is not life-limiting in the adult population.	not be innovative will be considered in any appraisal of the technology. Comment noted. At the scoping workshop it was noted that the existing service provision of mexiletine functioned well, and access to treatment was not an issue. Comment noted. At the scoping workshop the clinical expert noted that around half of people with non-dystrophic myotonia would have their life and daily activities limited in some way. They also noted that the condition would not have an impact on life expectancy.

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	Genetic Alliance UK	The small patient numbers mean that the technology appraisal programme is not best suited to evaluate this medicine. However, we would also not consider this medicine a priority for one of the limited number of slots in the highly specialised technology evaluation programme either, as the medicine is already widely used off label for this indication. This is a further example of the urgent need for an appraisal route suitable for medicines for rare diseases which do not meet the criteria for the HST programme.	Comment noted. After considering information received from consultation and comments from the scoping workshop it was agreed that the appropriate route for mexiletine was as a single technology appraisal.
	Muscular Dystrophy UK	We are aware that Mexiletine has been used off-label and unlicensed as a treatment for non-dystrophic myotonia for at least 10 years. This group or type of medicine is well established and there is nothing specialist about the drug/technology. We have been told by prescribing clinicians that the current cost of the treatment is relatively cheap at approximately £1600 per patient per year on maximal dose. The condition is genetic and thus chronic. Mexiletine once started is usually taken life-long if it is effective for the individual. Severity of disability is less in comparison to other neuromuscular disorders e.g. the majority of patients are employed and ambulant without aids. The condition is not life-limiting in the adult population.	Comment noted. The extent to which the technology may or may not be innovative and the nature of the condition will be considered in any appraisal of the mexiletine.
Wording	Lupin Healthcare (UK) Limited	Yes, but the remit should include the word “symptomatic” such that it is: “To appraise the clinical and cost effectiveness of mexiletine within its marketing authorisation for treating symptomatic myotonia in adults with non-dystrophic myotonic disorders.”	Comment noted. The wording of the remit has been amended in line with the suggested text.

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	The National Hospital for Neurology and Neurosurgery	Broadly yes.	Comment noted. No action required.
	Genetic Alliance UK	This is the standard wording.	Comment noted. No action required.
	Muscular Dystrophy UK	Yes.	Comment noted. No action required.
Timing Issues	Lupin Healthcare (UK) Limited	The timing is urgent. With the availability of licensed mexiletine (Namuscla) for the treatment of symptomatic myotonia in adults with NDM there are currently existing patients on imported, unlicensed mexiletine who require treatment. As per MHRA guidelines patients should receive a licensed medicine where one is available and therefore they should be transitioned to Namuscla. When patients stop mexiletine symptoms quickly return (Statland 2012; MYOMEX study sponsored by Assistance Publique-Hôpitaux de Paris (Lupin confidential, Myomex CSR, 2017) and therefore it is important patients do not experience interruptions to their treatment.	Comment noted. The choice of treatment will be made between the clinician and the patient based on what is the most appropriate.
	The National Hospital for Neurology and Neurosurgery	Mexiletine is current standard of care and we have approximately 100 patients at our service alone established on this drug. There are a number of others throughout the country who receive it from their GPs or local neurologist. Any urgency is related to these patients and how to ensure a continued prescription and supply once the licensed product is available.	Comment noted. The choice of treatment will be made between the clinician and the patient based on what is the most appropriate.
	Genetic Alliance UK	The Committee for Medicinal Products for Human Use of the European Medicines Agency has already adopted a positive opinion recommending the marketing authorisation of mexiletine for this indication back in mid-October,	Comment noted.

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		so if NICE wishes to meet its own timelines it would be appropriate for this appraisal to begin urgently.	
	Muscular Dystrophy UK	Mexiletine is current standard of care. Any urgency is related to guaranteeing that those patients currently benefiting from the treatment continue to do so and that there are no barriers preventing newly diagnosed patients from gaining access as a result of the appraisal.	Comment noted. Patients' access to the technology and need will be considered in the process. The existing funding arrangement for people currently treated with mexiletine will not be affected by any recommendation. For newly diagnosed patients, the choice of treatment will be made between the clinician and the patient based on what is the most appropriate.
Additional comments on the draft remit	The National Hospital for Neurology and Neurosurgery	We have met with representatives from NHSE to discuss the possibility of treatment for non-dystrophic myotonia with mexiletine being commissioned by them directly as part of the national HSS for skeletal muscle channelopathies, if the cost of mexiletine were to remain within tariff. We discussed this including the possibility of us recommending other "approved" prescribers as we are aware not all patients can afford to travel to the clinic in London or may have physical difficulty in doing so.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Lupin Healthcare (UK) Limited	The background information would benefit from more detail on NDM and the impact it has on people with NDM. The following text is suggested. NDM disorders are a group of ultra-rare, genetic disorders, caused by mutations in voltage-gated ion channels in skeletal muscle cell membranes and can be classified into chloride channelopathies (point mutations or deletions in the CLCN1 (Cl- ion channel, gene on chromosome 7q) and sodium channelopathies (point mutations in the SCN4A-gene (Nav1.4) on chromosome 17q23) (Lehmann-Horn, 2008). Symptom onset of the disease is often in infancy or childhood (Trivedi, 2013), and symptoms of myotonia not only persist throughout the entire life but are also likely to increase in severity as reported by patients (Trip, 2009). Patients with muscular expressed, pathogenetic channelopathies experience debilitating muscle stiffness and/or episodes of muscle paralysis (NHSE, 2013), very often accompanied by pain, cramping and fatigue (Trivedi, 2013; Trip, 2009). NDM can affect the upper and lower limbs, which can lead to stumbling, falling, and disability (MDC, 2007); affect the facial muscles which may impact the ability to speak or swallow; and in some cases (as observed in myotonia permanens) affect thoracic muscles causing severe respiratory complications by cramping (Ginanneschi, 2017; Trip, 2009; Matthews, 2010). Furthermore, [redacted] (Lupin confidential, Orphan Drug Maintenance Report 2018 ,). [redacted]	Comment noted. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. The nature of the condition will be considered in any appraisal of mexiletine. Scope unchanged.

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		[redacted] (Lupin confidential, Myomex CSR, 2017). NDM patients suffer a reduced ability to undertake daily tasks, have difficulty maintaining employment (Trivedi, 2013), and their quality of life significantly impacted in terms of independence, social relations and emotional wellbeing (Statland, 2012; MYOMEX (Lupin confidential, Myomex CSR2017). In a recent European patient survey (Lupin confidential, Orphan Drug Maintenance Report) patients describe their harm of not having an efficacious treatment of symptoms of myotonia as [redacted].	
	The National Hospital for Neurology and Neurosurgery	This is accurate.	Comment noted. No action required.
	Genetic Alliance UK	The background section, and indeed the entire scope, appears to suggest that the medicine is also being considered for myotonic dystrophy. We suggest a redrafting of the background focusing solely on non-dystrophic myotonic disorders. It could mention, for example, some of the conditions in this group and their variations and overlapping features. There is also no mention of the role of triggers and the warm up effect seen in some of these conditions.	Comment noted. The background section of the scope has been updated to focus on non-dystrophic myotonic disorders.
	Muscular Dystrophy UK	This is an accurate description of the condition and the current available treatment.	Comment noted. No action required.

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The technology/ intervention	Lupin Healthcare (UK) Limited	The mode of action can to be more accurately described as follows: Mexiletine blocks sodium channels with a stronger potency in situations of excessive burst of action potentials (use-dependent block) and/or prolonged depolarization (voltage-dependent block), as occurring in diseased tissues, rather than on physiological excitability (resting or tonic block). Mexiletine is, therefore, mostly active on muscle fibres subject to repeated discharges (such as skeletal muscles). It improves myotonic symptoms by decreasing muscle stiffness through reduction of the delay of muscle relaxation (Lupin confidential, Namuscla, SPC). Despite the variability in pathophysiology of the different non-dystrophic myotonic disorders, mexiletine exhibits a similar mode of action in all subtypes.	Comment noted. The technology section of the scope has been updated.
	The National Hospital for Neurology and Neurosurgery	What is described is accurate although what is perhaps missing is that as well as efficacy being demonstrated in a phase 3 trial mexiletine has been used clinically in the UK for at least 10 years and already forms part of the standard of care for the treatment of non-dystrophic myotonia.	Comment noted. No action required.
	Muscular Dystrophy UK	What is described is accurate in terms of the demonstrated efficacy of the treatment. However, it should also be noted that the treatment already forms part of the standard of care for the treatment of patients with non-dystrophic myotonia and has done for over 10 years. This supports the argument for the effectiveness of the treatment.	Comment noted. No action required.
Population	Lupin Healthcare (UK) Limited	The population wording should be more accurately defined as: Adults with non-dystrophic myotonic disorders requiring treatment of symptomatic myotonia.	Comment noted. It was noted in the comments received at consultation and discussion at the scoping workshop that

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		There are no groups in this population that should be considered separately. It is inappropriate to subgroup NDM patients by genotype for instance as this would lead to inequity of access, especially in the context of a very rare disease. The MYOMEX study (Lupin confidential, Myomex CSR, 2017)) demonstrated a consistent treatment effect for mexiletine across chloride and sodium channelopathies of NDM patients, as did the Statland study (2012) and a recent study by Stunnenberg (2018). Similar findings were reported in a retrospective chart review of UK patients with genetically confirmed NDM prescribed mexiletine with a minimum of 6 months follow-up (Suetterlin, 2015).	only people with symptomatic myotonia would be treated and it was agreed that this should be represented in the population wording. The wording of the population in the scope has been updated.
	The National Hospital for Neurology and Neurosurgery	Yes point prevalence is accurate. There are no particular sub-groups that should be regarded separately amongst the adult population.	Comment noted. No action required.
	Genetic Alliance UK	We suggest the removal of the words 'symptomatic myotonia and', as adults with non-dystrophic myotonic disorders is an adequate description of this population by itself. Many individuals with non-dystrophic myotonic conditions have described a worsening of symptoms during pregnancy. Though pregnant women have been excluded from the clinical trials for this medicine, it is likely that they are a subgroup in whom the medicine may be more (or less) clinically and cost effective.	Comment noted. It was noted in the comments received at consultation and discussion at the scoping workshop that only people with symptomatic myotonia would be treated and it was agreed that this should be represented in the population wording. The wording of the population in the

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			scope has been updated.
	Muscular Dystrophy UK	The population is defined appropriately. There are approximately 400 adult patients in England who could benefit from this treatment and many of whom may be already receiving it. There are no particular sub-groups that should be regarded separately amongst the adult population.	Comment noted. It was noted during the consultation that the population eligible for treatment in England may have been under estimated because of the small sample size of the study from which the prevalence was estimated, and the genetic diagnosis required. The scope was updated to reflect this.
	National Congenital Anomaly and Rare Disease Register; Public Health England	The population description needs to be less ambiguous.	Comment noted. Following discussions at the scoping workshop, the population of the scope has been amended to be more specific to the population treated in clinical practice.

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Comparators	Lupin Healthcare (UK) Limited	The draft scope describes comparators as: "Established clinical management without mexiletine." Lupin believes the comparators should be more accurately described as: "Established clinical management for first line treatment without mexiletine". Namuscla will be the only licensed medicine for the symptomatic treatment of NDM disorders. Mexiletine does appear to be considered the standard first line therapy for the treatment of NDM disorders (Lupin data on file, 2018). Carbamazepine is listed as a treatment option as well as mexiletine by the National Hospital for Neurology and Neurosurgery in Queen Square, London even though the evidence base for carbamazepine is very sparse. Some antiarrhythmic (procainamide, tocainide) have been tried but found to have severe adverse effects e.g. in the case of tocainide, agranulocytosis which led to its withdrawal from the market. Flecainide only has in-vitro data reported and propafenone is based on one case study (Matthews, 2010). Antiepileptic medicines such as phenytoin and carbamazepine has only been reported in case studies with only lamotrigine having had a randomised trial recently reported (Andersen, 2017). However, lamotrigine is considered in the UK for some patients as only a second line who do not respond or are intolerant to mexiletine (Lupin confidential, data on file, 2018). This practice is in line with other European countries such as Germany who does have National Guidelines in place for management of dystrophic and non-dystrophic myotonia (German Society of Neurology guidelines, 2017), where lamotrigine has been recommended during an update the annual congress of the German Neurology society (Berlin, Oct 29-Nov 3) as second line treatment).	Comment noted. The marketing authorisation for mexiletine does not specify its use as a first line treatment. During the consultation and workshop, it was noted that lamotrigine is increasingly used as an alternative to mexiletine. The comparators section has been updated to account for this.

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		Therefore, Lupin believes there are no appropriate pharmacological comparators for mexiletine as first line treatment. Non-pharmacological strategies such as physiotherapy, lifestyle adaptations, mobility aids and occupational assistance can form part of the supportive care for NDM patients.	
	The National Hospital for Neurology and Neurosurgery	Mexiletine is currently first line treatment and standard of care for these disorders. There are other sodium channel blockers that are used however and it is inaccurate to say that the only comparator is management without mexiletine. Multiple agents have been reported to have efficacy based on in vitro data, clinical experience, case reports and small series – including but not limited to carbamazepine, flecainide, propafenone and ranolazine. More recently a RCT of lamotrigine demonstrated efficacy. At the national service we have used lamotrigine in a number of patients who either cannot tolerate or have failed to respond to mexiletine. We have seen a good response at doses lower than that used in the clinical trial. I know of colleagues in Scotland who have had a similar experience. There has been no head to head study of mexiletine versus lamotrigine in these disorders.	Comment noted. The marketing authorisation for mexiletine does not specify its use as a first line treatment. It was noted at the scoping workshop that lamotrigine is increasingly used as an alternative to mexiletine. The comparators section has been updated to account for this.
	Muscular Dystrophy UK	Mexiletine currently forms part of the standard of care for the treatment of patients with non-dystrophic myotonia and has done for over 10 years.	Comment noted. During the consultation, it was noted that lamotrigine is increasingly used as an

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		Clinicians have informed us that there are other sodium channel blockers that are used meaning it is inaccurate to say that the only comparator is management of the condition without mexiletine.	alternative to mexiletine. The comparators section has been updated to account for this.
Outcomes	Lupin Healthcare (UK) Limited	The outcomes listed in the draft scope will capture many of the relevant health related benefits. The following outcomes from the MYOMEX (Lupin confidential, Myomex CSR, 2017), Statland (2012) and Stunnenberg (2018) studies will be presented regarding the patient related benefit of mexiletine. These can include: - Patient reported stiffness with visual analogue scale or interactive voice response diary (IVR) - Functionality (mobility) with chair test: Time to stand up from chair, walk around and sit down - Clinical Myotonia Score (CMS): a myotonia severity scale based on clinical examination of the patient and a disability scale based on the patient's view of disability in activities of daily living. - Pain, weakness, tiredness (IVR) Quality of life: SF-36 and Individualised Quality of Life questionnaire for neuromuscular disorders (INQOL)	Comment noted. In response to comments received at consultation and discussion at the scoping workshop the outcomes section of the scope has been updated to include motor function and fatigue. The list of outcomes is not exhaustive, therefore information on those specific outcome measures can be submitted.
	The National Hospital for Neurology and Neurosurgery	Yes with the exception of mortality. Non-dystrophic myotonia is not usually life-limiting in the adult population (a premature death would be exceptional and I could only relate this to the risk of a fall with serious injury as opposed to any systemic complication). There is a subset of infants who can experience life-threatening myotonia of their respiratory muscles. This risk naturally subsides with development and	Comment noted. Mortality has been removed as an outcome from the scope.

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		age so does not apply in adulthood. Also this process only applies to the use of mexiletine in adults in line with the license obtained.	
	Genetic Alliance UK	We suggest removal of the reference to muscle wasting, as these are non-dystrophic myotonic conditions. We would also suggest the addition of fatigue and some mention of electrodiagnostic testing.	Comment noted. In response to comments received at consultation and discussion at the scoping workshop the outcomes section of the scope has been updated to remove the reference to muscle wasting.
	Muscular Dystrophy UK	Mortality is not an appropriate outcome measure as non-dystrophic myotonia is not usually life-limiting in the adult population. The key outcome measure is around the impact of the treatment on symptoms of the condition and how this impacts the individual's quality of life. Serious consideration must be made as to how health-related quality of life is adequately measured in patients	Comment noted. Mortality has been removed as an outcome from the scope.
Economic analysis	Lupin Healthcare (UK) Limited	Aspects of the economic analysis, such as the time horizon, will be detailed in the submission.	Comment noted. No action required.
	The National Hospital for Neurology and Neurosurgery	I don't have any specific comments on this.	Comment noted. No action required.

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	Muscular Dystrophy UK	We are aware that clinicians have met with representatives from NHS England to discuss the possibility of the treatment being commissioned by them directly. Comparative costs to the NHS should be considered.	Comment noted. It has been agreed that mexiletine will progress as in the technology appraisals programme as a single technology appraisal.
Equality and Diversity	Lupin Healthcare (UK) Limited	There are patients with NDM who are currently being treated with unlicensed mexiletine. These patients will not be able to access this now that there is licensed mexiletine (Namuscla) available. Therefore, lack of NICE guidance could make it more difficult in practice for this specific group to access the technology.	Comment noted. Supply and source of the medication is not an issue of equality in access and cannot be addressed by any NICE recommendation.
	The National Hospital for Neurology and Neurosurgery	If a recommendation were to be made for mexiletine to only be prescribed via the HSS for skeletal muscle channelopathies this could limit access to patients who are unable to travel to the clinic in London, either because of disability (patients with non-dystrophic myotonia often do struggle on public transport and are at risk of falls) or because of inability to afford the cost of travel.	Comment noted. Access to specialist centres is an implementation issue; it is not an equality issue to be considered by the committee and cannot be addressed by any NICE recommendation.
	Muscular Dystrophy UK	Consideration must be given as to which centres or clinicians are able to prescribe the treatment to ensure equality of access. Access to prescriptions should not, if possible, be limited to one highly specialised service (e.g can currently be accessed via local neurologists or GP's).	Comment noted. Access to specialist centres is an implementation issue; it is not an equality issue

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			to be considered by the committee and cannot be addressed by any NICE recommendation.
Other considerations	Lupin Healthcare (UK) Limited	The EU Commission Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP") has recognised the importance of establishing a framework for repurposing of established medicines/active substances. A report by Association of Medical Research Charities (2017) on facilitating adoption of off-patent, repurposed medicines into NHS clinical practice has highlighted the important role NICE plays and that NICE has gained a reputation for rigour, independence and objectivity. So, it is appropriate that NICE conducts a Technology Appraisal of Namuscla.	Comment noted. Mexiletine will be progressed as a single technology appraisal.
	The National Hospital for Neurology and Neurosurgery	How do we ensure continuity of care for patients already established on mexiletine whilst processes to determine re-imbursement costs are ongoing.	Comment noted. The funding arrangement for people already established on mexiletine will not be affected by any future recommendation.
	Muscular Dystrophy UK	It is important that continuity of care is guaranteed for patients already established on mexiletine during the appraisal process. Newly diagnosed patients should also be able to access the treatment during the appraisal. Patient wellbeing must come first.	Comment noted. The funding arrangement for people already established on mexiletine will not be affected by any future recommendation.

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Innovation	Lupin Healthcare (UK) Limited	Mexiletine is an established first choice treatment for NDM. For many patients, treatment with mexiletine is transformational and effectively a step-change in their life. A patient survey has highlighted the dramatic impact mexiletine had on symptoms and how their condition greatly worsened as a result of not being treated with mexiletine (Lupin confidential, Orphan Drug Maintenance report, 2018d). Mexiletine received marketing authorisation in 1975 for the treatment of ventricular arrhythmias before it was discontinued in 2008 for commercial reasons. Whilst mexiletine cannot be considered a new medicine per se, the availability of a licensed mexiletine (Namuscla) will offer patient access to a medicine that have been proven to improve outcomes and quality of life for people with NDM.	Comment noted. The extent to which the technology may be innovative will be considered in any appraisal of the technology.
	The National Hospital for Neurology and Neurosurgery	This is not innovative technology, it has been standard of care for at least 10 years as an unlicensed product.	Comment noted. The extent to which the technology may be innovative will be considered in any appraisal of the technology.
	Muscular Dystrophy UK	This is not innovative technology, it has been standard of care for at least 10 years as an unlicensed product.	Comment noted. The extent to which the technology may or may not be innovative will be considered in any appraisal of the technology.

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Questions for consultation	Lupin Healthcare (UK) Limited	*Have all relevant comparators for mexiletine been included in the scope?* See above. *Which treatments are considered to be established clinical practice in the NHS for myotonia in adults with non-dystrophic myotonic disorders?* See above – mexiletine is the only one that has a robust evidence base for its use with two RCTs in very rare disease. *Are any antiarrhythmic or antiepileptic medicines used off-label to treat myotonia in adults with non-dystrophic myotonic disorders? If yes, which treatments are used in clinical practice?* See above. *Are the outcomes listed appropriate? Are there any other outcomes that should be included?* See above. *Are there any subgroups of people in whom mexiletine is expected to be more clinically effective and cost effective or other groups that should be examined separately?* There are no groups in this population in whom mexiletine is expected to be more clinically effective. Whilst individual responses may vary to mexiletine it	Comment noted. Please note that comparators are selected on the basis of their current use in clinical practice, not the availability of evidence.

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		is inappropriate to subgroup NDM patients by genotype for instance as this would lead to inequity of access, especially in the context of a very rare disease. The MYOMEX study (Lupin confidential, Myomex CSR, 2017) demonstrated a consistent treatment effect for mexiletine across all chloride and sodium channelopathies of NDM patients as did the Statland study (2012). Similar findings were reported in a retrospective review of UK patients with genetically confirmed NDM prescribed mexiletine with a minimum of 6 months follow-up (Suetterlin, 2015). *Do you consider mexiletine to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* See above. *Do you consider that the use of mexiletine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *In a recent European patient survey (Lupin confidential, Orphan Drug Maintenance Report, 2018patients describe their harm of not having an efficacious treatment of symptoms of myotonia as* [redacted]. For example, imagine experiencing myotonia and not being able to get off at your bus stop because your muscles are locked.	Comment noted. No action required. Comment noted. Consideration can be given to the wider benefits of the technology.

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		Such daily experiences will not be effectively captured in the QALY calculation. *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Data from two randomised double-blind trials for mexiletine will be available for the Appraisal Committee to consider (Statland 2012; MYOMEX CSR,2017). Another aggregated N-of-1 trials with mexiletine in NDM has also been recently published (Stunnenberg, 2018). This level of evidence is relatively unusual to have in the context of a very rare disease to enable the Committee to determine the clinical and cost effectiveness of mexiletine. *To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.* No, Lupin believes there will be no material barriers to adoption. Unlicensed mexiletine is already being used by a highly specialised service at the National Hospital for Neurology and Neurosurgery in Queen Square, London and the availability of licensed mexiletine (Namuscla) will make patient access easier and avoid the issues with the importation and supply of unlicensed mexiletine. As part of the EMA approval for Namuscla Lupin has a risk-management plan commitment which includes the education of healthcare professionals and the provision of a patient alert card which should help ensure Namuscla is introduced appropriately into clinical practice.	Comment noted. We encourage companies to submit all relevant and available evidence for consideration.

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		NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. Lupin believes mexiletine (Namuscla) would be more appropriately assessed via the NICE Highly Specialised Technology (HST) process and that it meets the seven criteria for HST. In particular Lupin would draw attention that the diagnostic services for muscle channelopathies, and the accompanying patient advice and initiation of treatment are provided by one Highly Specialist Rare Neuromuscular Disorders Centre, namely the National Hospital for Neurology and Neurosurgery in Queen Square, London (NHSE, 2013). Other key criteria that Namuscla meets for HST include a very small population (approximately 400 adult patients in England) and as described above can cause significant lifelong disability. Furthermore, [redacted] (*Lupin confidential, Orphan Drug Maintenance Report, 2018*) Lupin wrote to NICE on 26th October with the rationale and justification for the HST appraisal route and this document should be referred to for further details to those in this document.	Comment noted. It was noted during the consultation and workshop that mexiletine has been used as standard of care for more than 10 years in practice, and its prescribing is not restricted to highly specialised services. No action required.

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	The National Hospital for Neurology and Neurosurgery	Most specific questions are answered above. Regarding the remaining questions: Do you consider that the use of mexiletine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Myotonia affects patients on a daily basis. It is not a life-limiting illness in adults and most do maintain employment. However it can have significant impact on quality of life, can influence choice of career and cause significant difficulty in taking public transport. This in turn can limit work and social activity and general independence. As well as the obvious symptom of myotonia (muscle stiffness) it can frequently cause pain and fatigue. Living with a chronic illness can affect mood. Myotonia affecting the leg muscles can lead to falls, and injury. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. There is some published data on quality of life in non-dystrophic myotonia and the clinical experience of the team at the HSS. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. No, Mexiletine is already used in clinical practice across the NHS.	Comment noted. Consideration can be given to the wider benefits of the technology. Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	National Congenital Anomaly and Rare Disease Register; Public Health England	The intended procedure for identifying a suitable cohort of patients with non-dystrophic myotonia with symptomatic myotonia to support the appraisal should be explained in the scope.	Comment noted. The process by which patient experts are selected for attendance at appraisal committee meetings is not defined in the scope. Please see the public involvement webpage for further details. Scope unchanged.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None.