NaMuscla®
MEXILETINE

FORMULARY PACK

This is a clinical data formulary pack, created by Lupin Healthcare (UK) Ltd, to provide an overview of the Namuscla (Mexiletine) data. Namuscla is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

Prescribing information to be found on page 39

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Executive Summary

- Non-dystrophic myotonic disorders (NDM) are rare, genetic diseases that arise from mutations in skeletal muscle chloride and sodium ion channels resulting in disabling altered membrane excitability causing prolonged muscle contraction and delayed relaxation
- Namuscla (mexiletine) is the only pharmacological approved treatment for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders[1]
- The Myomex trial was the key phase 3 trial which demonstrated a significant improvement in stiffness.[1,15]
- Namuscla is shown to have a good safety profile[1]
- Funding of this product is through NHS England (List price £5000 for Namuscla 167mg, 100 capsules)
- In England as of 1st April 2019, Namuscla for Non dystrophic myotonia is funded by NHS England as part of an interim agreement with confidential price agreed and therefore is a pass-through (non tariff/ ex PBR) drug with no impact on local trust budget.
- For initial orders, please contact Lupin Healthcare (UK) to allow access for purchase of Namuscla (mexiletine) against your account.
  Email: information@lupin.com
  Telephone: +44 (0) 1565 751 378 Option 2 or ext:218
- Product can then be ordered from Lupin's distribution partner **Alloga UK**. Contact details are below:
  Email: allogauk.orders@alloga.co.uk
  Phone Orders: + 44 (0) 1773 441702/ + 44 (0) 1773 441700
- Note; Licensed Namuscla (Mexiletine) 167mg corresponds to unlicensed special Mexiletine hydrochloride salt based weight 200mg[1]

CONTENTS

CHAPTER 1

Background and subclassification 4
Epidemiology 4
Aetiology 5
Clinical overview and diagnosis 7
Therapeutic challenges 9

CHAPTER 2

Namuscla (Mexiletine) mechanism of action 10

CHAPTER 3

Pharmacokinetics 12

CHAPTER 4

Clinical efficacy 14

CHAPTER 5

Safety and tolerability 25
Drug-interactions 28

CHAPTER 6

Dosage and administration 32
Pharmaceutical particulars 32

CHAPTER 7

Supply chain, tariff status and drug price 33

CHAPTER 8

References 34

CHAPTER 9 - APPENDICES

NHS templated circular 35
MHRA guidance 37
Blueteq 37
Patient alert card 38
HCP guidance for minimising risks 38

CHAPTER 1

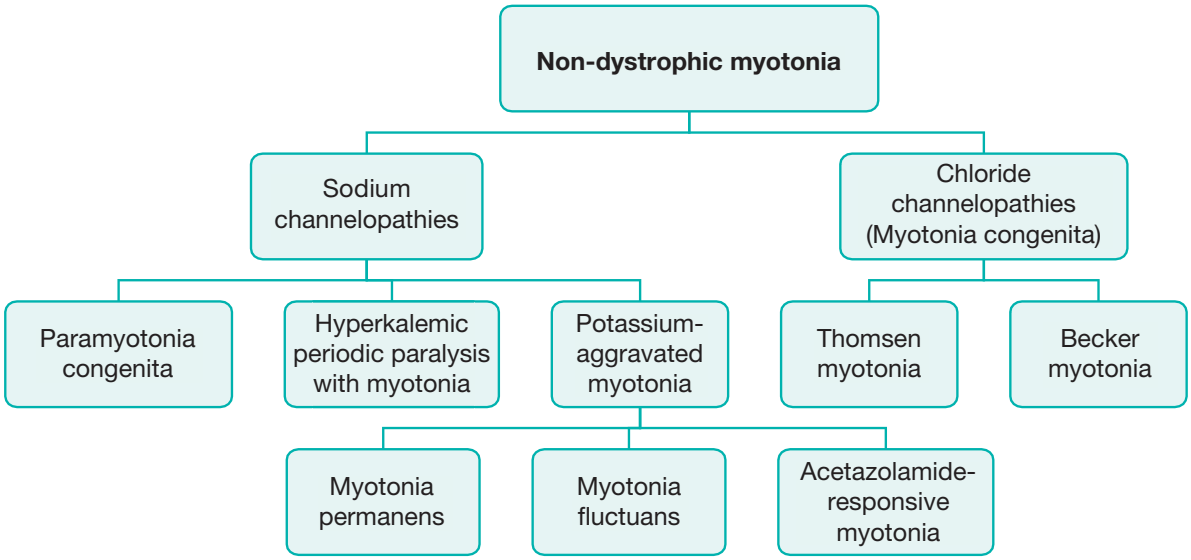
Background

Non-dystrophic myotonic disorders (NDM) are rare, genetic diseases that arise from mutations in skeletal muscle chloride and sodium ion channels resulting in disabling altered membrane excitability causing prolonged muscle contraction and delayed relaxation.[2,3] Emotional surprises, stress, cold, potassium or exercise but also rest are potential triggers for myotonia which makes the onset of symptoms unpredictable.[4]

1.1 Subclassification of NDM

NDM is divided into sodium channelopathies and chloride channelopathies and can further be sub-classified according to the affected pathway (Figure 1).[3,4]

Figure 1. NDM sub-classification



Adapted from Matthews et al,[3] Mankodi et al[4]

1.2 Epidemiology

The prevalence of these rare, heterogeneous diseases is not well documented. However, evidence suggests that there is an overall prevalence of 1:100,000 of population with some forms of the disease being more present than others.[5,6,7]

The results of an epidemiological study of 665 patients in England are summarised in Table 1.[8] The differences in prevalence are not only due to geographic variation in disease prevalence but no doubt also due to the lack of diagnosis or long time to diagnosis because of the rarity of the conditions and the lack of widespread expertise,[9] as well as the confounding effect of the phenotypic overlap between diseases.[10]

Table 1. Demographic characteristics and minimum point prevalence rates

	Patients (pedigrees)	Age, y, mean ± SD[a]	Male/female ratio	Patients from England, n (%)	Prevalence rate ($x10^{-5}$), (95% CI)
NDM	449 (322)	38.0 ± 17.5	1.57	395 (88)	0.75 (0.67–0.82)
MC	321 (252)	39.0 ± 16.3	1.97	277 (86)	0.52 (0.46–0.59)
AD MC	99 (50)	40.8 ± 17.3	1.30	73 (74)	0.14 (0.11–0.17)
AR MC	69 (49)	33.5 ±17.7	2.00	63 (91)	0.12 (0.09–0.15)
Other[b]	153 (153)	40.2 ± 14.5	2.64	141 (92)	0.27 (0.22–0.31)
PMC[c,d]	96 (56)	35.1 ± 19.5	0.88	88 (92)	0.17 (0.13–0.20)
SCM	32 (14)	37.7 ± 21.3	1.00	30 (94)	0.06 (0.04–0.08)
PP	216 (131)	39.1 ±18.3	2.27	198 (92)	0.37 (0.32–0.43)
HypoPP	95 (59)	36.6 ± 18.1	3.52	88 (93)	0.17 (0.13–0.20)
HyperPP	77 (48)	40.2 ±19.3	2.08	70 (91)	0.13 (0.10–0.17)
ATS	44 (24)	42.7 ± 16.2	1.20	40 (91)	0.08 (0.05–0.10)

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; ATS = Andersen-Tawil syndrome; CI = confidence interval; HyperPP = hyperkalemic periodic paralysis; HypoPP = hypokalemic periodic paralysis; MC = myotonia congenita; NDM = nondystrophic myotonias; PMC = paramyotonia congenita; PP = periodic paralyses; SCM = sodium channel myotonias.

Adapted from Holga et al[8]

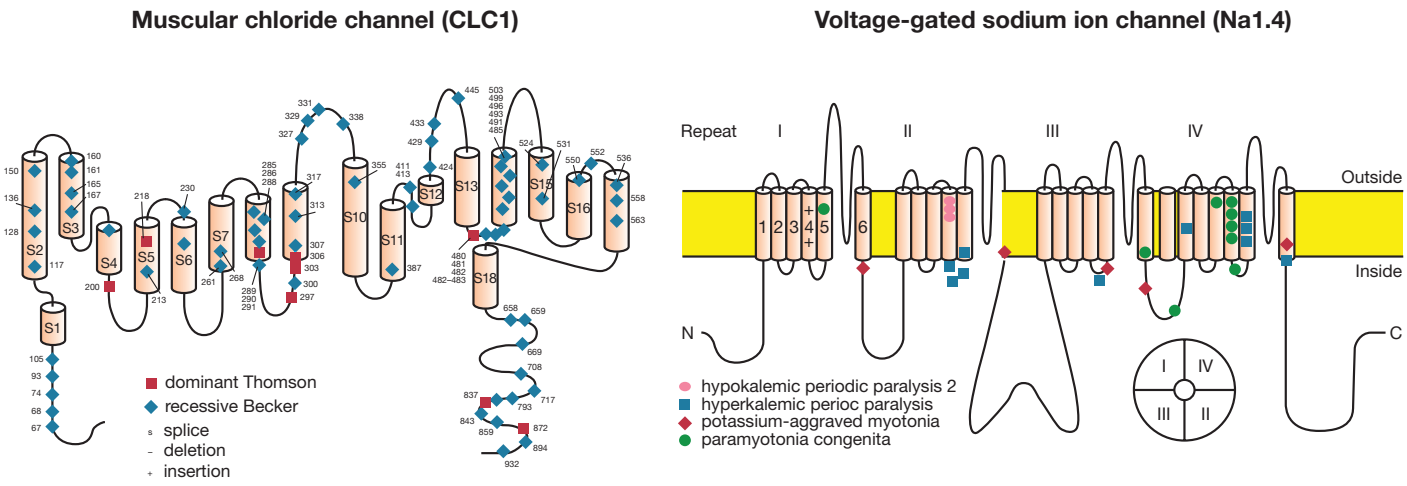
1.3 Aetiology

Sodium channelopathies are a group of autosomal dominantly inherited myotonic disorders that arise from point mutations in the skeletal muscle voltage gated sodium channel gene (SCN4A) on chromosome 17q23 that codes for the sodium channel Nav1.4 of skeletal muscle. The mutations lead to sodium channels in the sarcolemma that show impaired gating and inactivation.[11,12]

This result is an increased inflow of sodium into the muscle fibres and a transient intracellular sodium accumulation. If the sodium inflow is only slightly increased, repetitive action potentials are generated that lead to the symptom of myotonia. If the sodium inflow is considerably increased, the cell membranes tend to depolarise for a longer time and to a degree where intact sodium channels are inactivated. This leads to inexcitability of the sarcolemma. Hyperactivity and hypoactivity may overlap so that muscles are both stiff and weak at the same time (figure 2).[11]

The chloride channelopathies, myotonia congenita, can present as an autosomal dominant form (Thomsen myotonia) or autosomal recessive form (Becker myotonia). Myotonia congenita is the most common inherited skeletal muscle channelopathy.[3,8] All forms of myotonia congenita are caused by mutations or deletions in the CLCN1 gene (the gene which codes for the muscular chloride channel) that result in loss of function of the chloride channel ClC-1, which is expressed exclusively in skeletal muscle membrane.[4,11] The mutations lead to faulty or missing chloride channels in the fibre membrane. The activity of the chloride channels at the resting potential of the muscle fibres is decreased and this increases the excitability of the membrane. Series of involuntary action potentials following voluntary action potentials result in muscle stiffness (figure 3).[11]

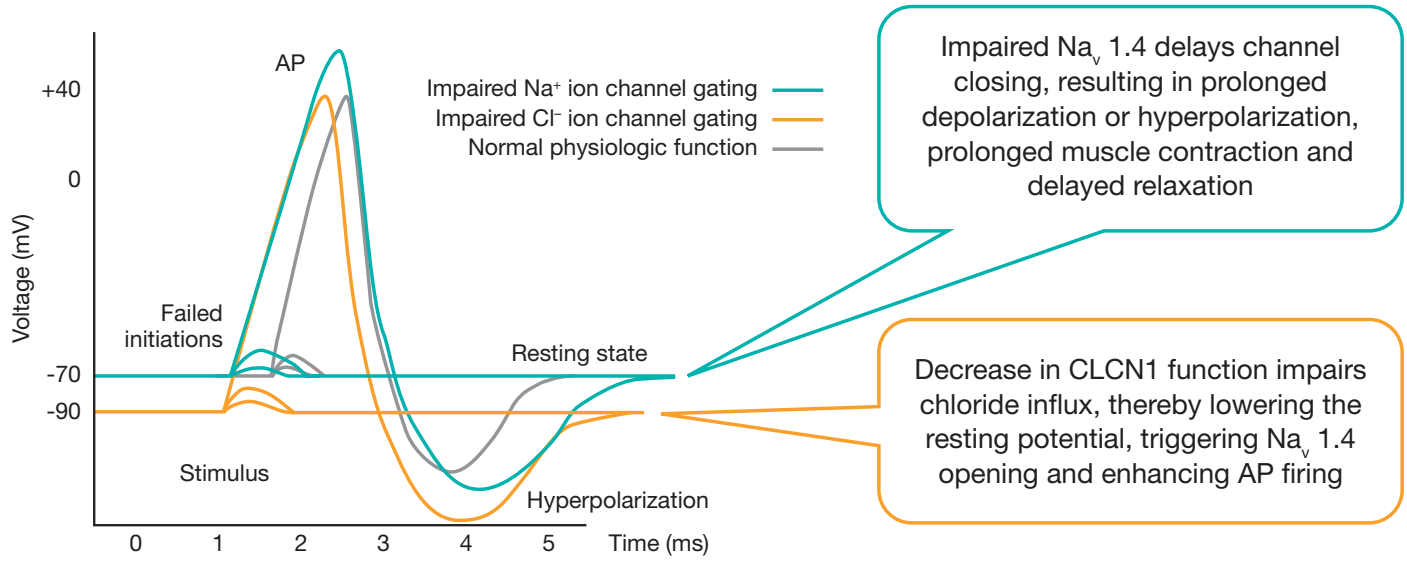
Figure 2. Structure of the chloride and sodium channel



NDM (also called channelopathies) has been associated with ≥100 mutation in the *CLCN1* and ≥20 mutations in *SCN4A*[2]

Adapted from Lehmann-Horn et al[11]

Figure 3. Pathophysiology of impaired Na+ and Cl– ion channels in NDM



Both conditions predispose the muscle to hyperexcitability, with repetitive discharges rendering the muscle unable to relax, causing myotonia

Adapted from Lehmann-Horn et al[11]

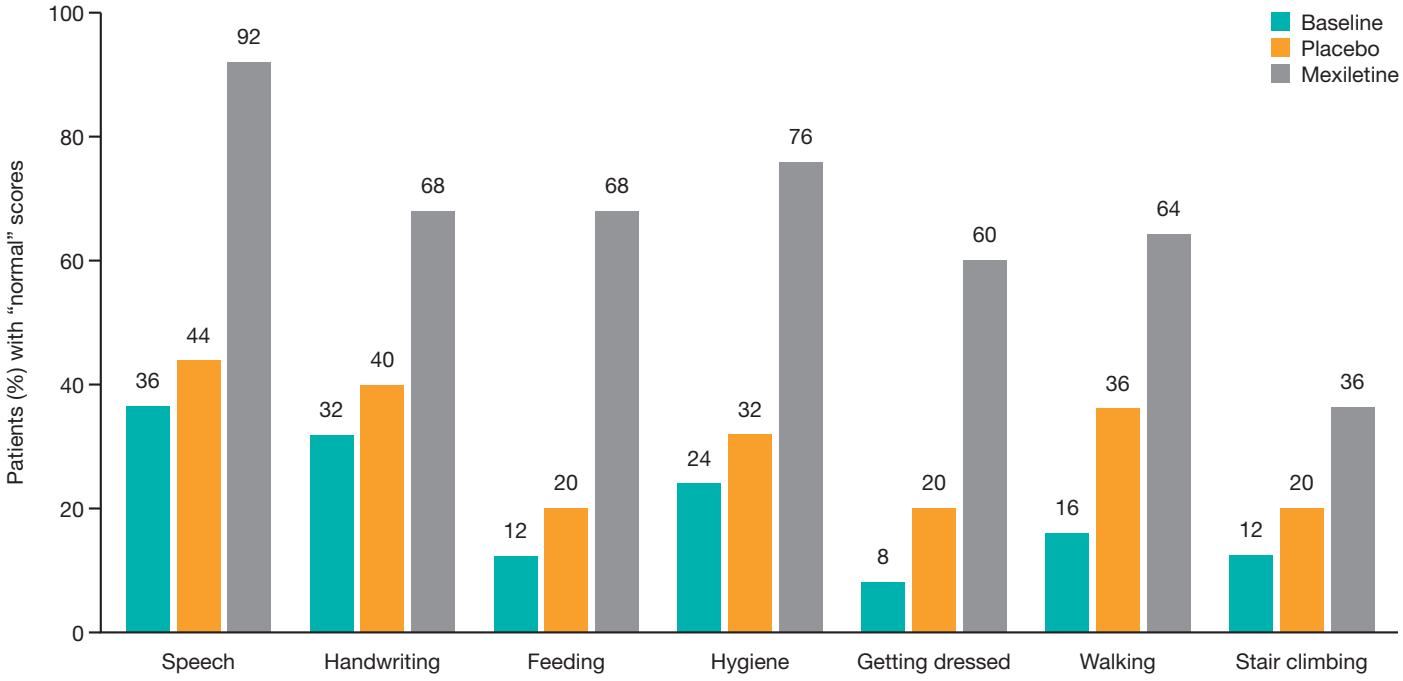
1.4 Clinical overview and diagnosis

The major clinical manifestation of myotonia is muscle stiffness. Patients also experience pain, weakness, impaired mobility, affected speech and may have a higher risk of falling.[13] Myotonia can also affect muscles of mastication and swallowing.[10] Each of the NDM disorders has distinctive clinical findings.[14]

In the clinical study with mexiletine, the baseline scores for each of the disability categories highlight the significantly disabling impact of disease as listed below.[15] Of all the patients included in the study, normal disability scores were only seen in:

- 36% for speaking
- 32% for handwriting
- 8% were able to dress unassisted
- 12% could self-feed and use cutlery
- 24% could perform their daily hygiene normally
- 16% described being able to walk normally
- 12% were able to climb stairs up and down normally.

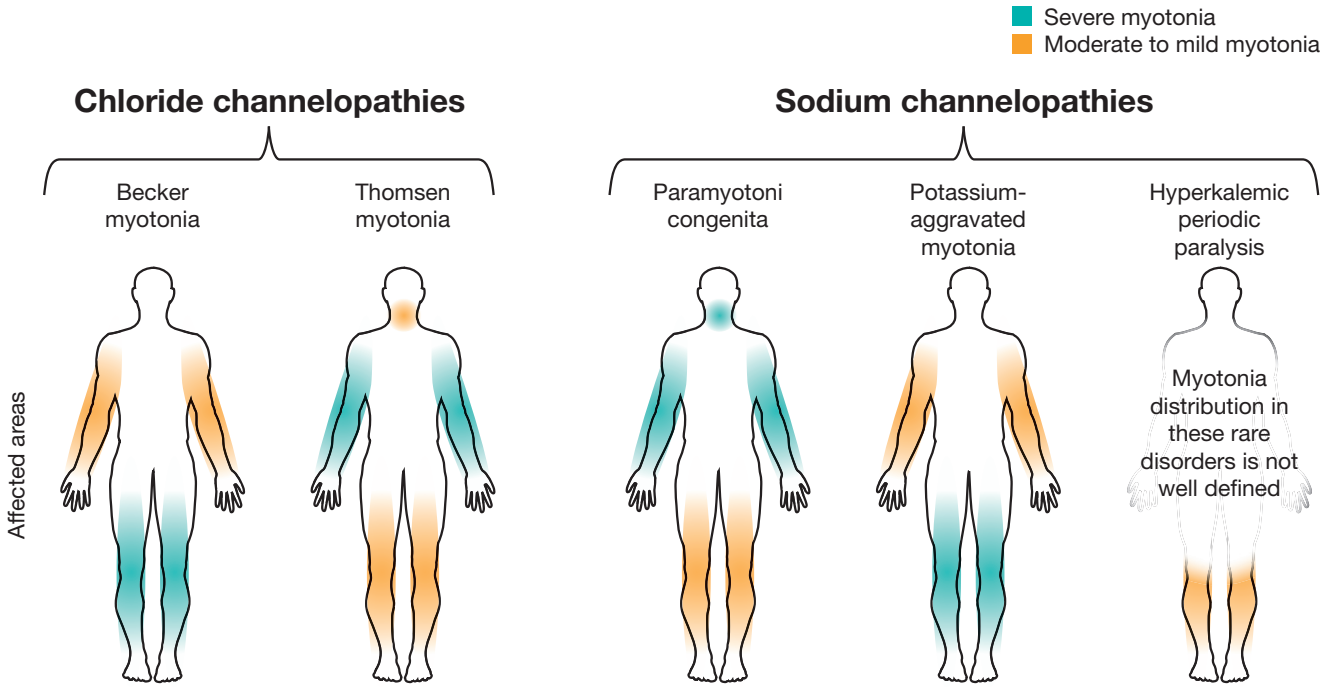
Figure 4. Disability scores from Myomex study



Adapted from Data on File[15]

The location and severity of the myotonia differs between the different clinical phenotypes of the NDM disorders, as shown in Figure 5 which highlights that in some forms of NDM, the most severe sites affected are the legs, (e.g. Becker myotonia) while in others, the legs are less severely affected while other areas (arms, face) are more severely affected by myotonia.

Figure 5. Patterns of myotonia in NDM[3,10,14,16,17]



Clinically, the NDM can usually be differentiated based on their inheritance pattern, involved limbs, response to stimuli (including cold, potassium ingestion, exercise, and drug therapy), electrodiagnostic features, muscle histology, genetic mutations, and myotonia characteristics.

Table 2. Pattern of clinical features observed in NDM[3,10,18]

	Chloride channelopathies		Sodium channelopathies		
Causative gene(s)*	**Becker myotonia**	**Thomsen myotonia**	**Paramyotonia congenita**	**Potassium-aggravated myotonia**	**Potassium-sensitive periodic paralyses**
	CLCN1	*CLCN1*	*SCN4A*	*SCN4A*	1 *SCN4A, CACNA1S*
Area of myotonia	Generalized, legs > face and arms	Generalized, face and arms > legs	Face (eyelids), hands and thighs	Proximal more than distal	Generalized if present
Age of onset	Early childhood	Infancy	Infancy	Childhood to early teens	Infancy to early childhood
Cold trigger	Yes (minimal)	Yes (minimal)	Yes (can be severe)	No	Yes
Warm-up phenomenon	Yes	Yes	No	Yes	Yes
Paradoxical myotonia	No	No	Yes	Sometimes	Sometimes
Episodic weakness	Yes (common)	No	Yes (common)	No	Yes

CLCN1 encodes for chloride channel, SCN4A encodes for voltage gated sodium channel Nav1.4, CACNA1S encodes for voltage gated calcium channel. NDM, non-dystrophic myotonic disorders.

1.5 Therapeutic challenges

NDM episodes of myotonia (attacks) may be experienced as frequently as daily.[19] Treatment for myotonia is focused on reducing the involuntary muscle action potential bursts without blocking the voluntary muscle stimulation. It is important that patients with potassium-aggravated myotonia and paramyotonia congenita modify their lifestyles to avoid the triggers of their diseases such as potassium ingestion or cold temperatures.[20] Similarly, the mainstay for symptomatic management of myotonia congenita focuses on avoiding activities that trigger myotonic responses. Sudden forceful contractions are to be avoided, and instead, a gradual increase of muscular exertion is used to promote warm-up before developing symptomatic muscle stiffness in chloride channelopathies such as Becker and Thomson myotonia.[10] While these episode prevention strategies may seem logical, they are not always pragmatic options and they too impact on the patient's daily activities.

Historically, non-pharmacological strategies such as physiotherapy, lifestyle adaptations, mobility aids and occupational assistance have formed part of the supportive care for NDM patients.[9] Some off-license medications have been tried historically.[21]

There are no over-arching, international treatment guidelines for NDM. National treatment guidelines such as S1 guidelines of the German society of Neurology, recommend the use of mexiletine as a first-line treatment in patients with NDM.[22] In addition to this, diagnostic guidelines in the UK[9] recommend the use of mexiletine as a treatment option in NDM.

Namuscla (mexiletine) is the first treatment for NDM to be granted marketing authorization in Europe and is currently the only licensed pharmacological therapy for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.[1]

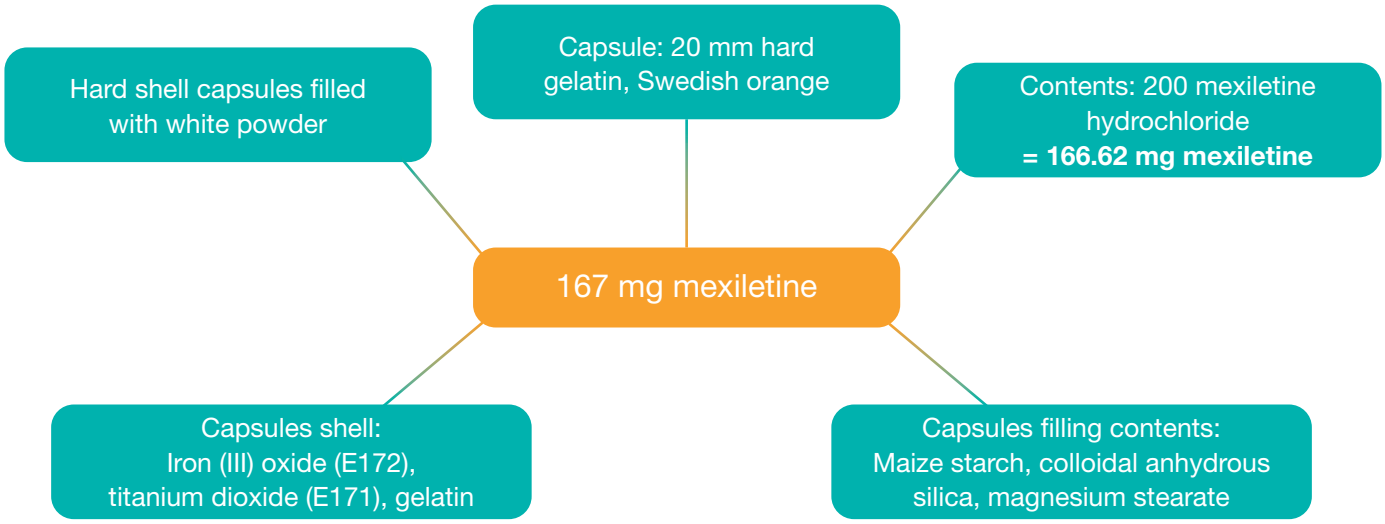
CHAPTER 2

Namuscla (Mexiletine)

Namuscla is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.[15]

Namuscla® (mexiletine hydrochloride) is a non-selective voltage-gated sodium channel blocker which belongs to the Class Ib anti-arrhythmic group of medicines. Namuscla is presented as 167mg hard capsules, each capsule contains 200 mg mexiletine hydrochloride corresponding to 166.62 mg mexiletine[1] - See figure 6

Figure 6. Composition of mexiletine 167mg capsules



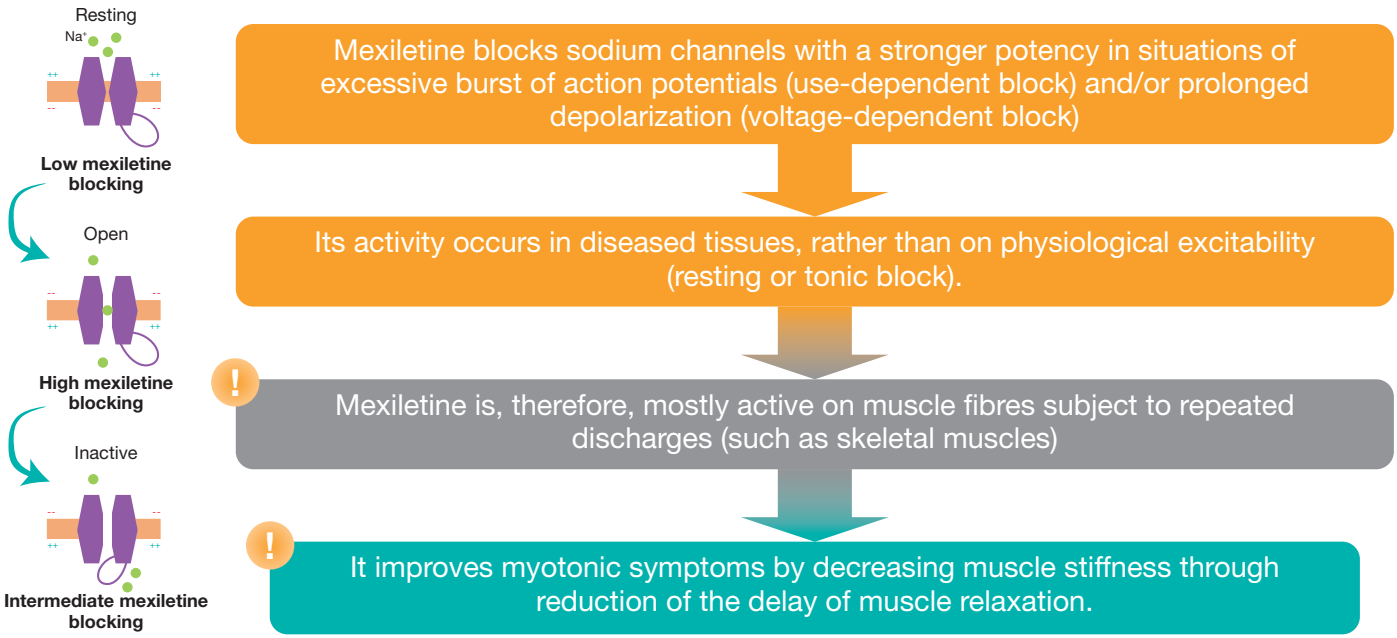
Namuscla blocks sodium channels with a stronger potency in situations of excessive burst of action potentials (use-dependent block) and/or prolonged depolarization (voltage-dependent block), as occurring in diseased tissues, rather than on physiological excitability (resting or tonic block). Mexiletine 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.

- With chloride channelopathies, the resting potential of the muscle cell is decreased, thereby destabilizing the muscle membrane and predisposing it to hyperexcitability.
- With sodium channelopathies, altered channel gating that causes slowed or incomplete inactivation (as well as occasionally enhanced activation) of action potentials is observed.

Mexiletine reduces or abolishes muscle hyperexcitability for both chloride and sodium ion channelopathies by inducing a slower influx of sodium (peak and late currents; sodium channel blocker) and probably a faster membrane repolarisation.

Mexiletine reduces the fast sodium influx into skeletal myocytes depending on the resting potential. As a consequence, the threshold for impulses is increased, and the depolarisation and conduction velocity is decreased. The repolarisation is increased and the effective refractory period shortened. In NDM, where the repolarisation of muscle cell membranes is impaired, the pharmacodynamic property of faster repolarisations and the slower influx of sodium are the mechanistic actions underlying the muscle relaxant effects of mexiletine in patients with muscular sodium or chloride channelopathies.

Figure 7. Mechanism of action of mexiletine



CHAPTER 3

Pharmacokinetics[1]

Pharmacokinetics

The PK data arise from toxicokinetic studies in rats, dogs and monkeys, performed during 26week (PO dosing) and 4 weeks (IV dosing), respectively, which used radioactive material. Results from these studies report the PK fate of both mexiletine and its metabolites and give an indication of the PK of mexiletine. PK data are reported from the scientific literature and consist in Cmax determination.

Absorption

Mexiletine is rapidly and almost completely absorbed following oral administration with a bioavailability of about 90% in healthy subjects. Peak plasma concentrations following oral administration occur within 2 to 3 hours. No notable accumulation of mexiletine was observed after repeated administration.

Food does not affect the rate or extent of absorption of mexiletine. Therefore, mexiletine can be taken with or without food.

Distribution

Mexiletine is rapidly distributed in the body; its volume of distribution is large and varies from 5 to 9 L/kg in healthy individuals.

Mexiletine is weakly bound to plasma proteins (55%).

Mexiletine crosses the placental barrier and diffuses into breast milk.

Biotransformation

Mexiletine is mainly (90%) metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. The metabolic degradation proceeds via various pathways, including aromatic and aliphatic hydroxylation, dealkylation, deamination and N-oxidation. Several of the resulting metabolites are submitted to further conjugation with glucuronic acid (phase II metabolism); among these are the major metabolites p-hydroxymexiletine, hydroxy-methylmexiletine and N-hydroxymexiletine.

The influence of CYP2D6 phenotype on mexiletine metabolism has been extensively investigated. Mexiletine pharmacokinetics are characterised by significantly lower total and renal clearance resulting in prolonged elimination half-life, higher exposure, and lower volume of distribution in poor metabolisers compared to extensive metabolisers.

Approximately 10% is excreted unchanged by the kidney.

Elimination

Mexiletine is eliminated slowly in humans (with a mean elimination half-life of 10 hours, ranging from 5 to 15 hours).

Excretion of mexiletine essentially occurs through the kidney (90% of the dose, including 10% as unchanged mexiletine).

Mexiletine excretion may increase when the urinary pH is acidic, compared to normal or alkaline pH. In a clinical study, 51% of the mexiletine dose was excreted via the kidney at a urinary pH of 5, compared to 10% at normal pH. Changes in urinary pH are not expected to affect efficacy or safety.

Linearity/non-linearity

A linear relationship between mexiletine dose and plasma concentration has been observed in the dose range of 83 to 500 mg.

Special populations

CYP2D6 polymorphism affects mexiletine pharmacokinetics. Individuals who are CYP2D6 poor metabolisers (PM) exhibit higher mexiletine concentrations than CYP2D6 intermediate (IM), extensive (i.e. normal) or ultra-rapid (UM) metabolisers. The proportions of different ethnic populations across these various classes are tabulated below.

Table 3.

Ethnicity	Poor metabolisers (PM)	Intermediate metabolisers (IM)	Ultra-rapid metabolisers (UM)
Caucasians	Up to 10%	1–2%	Up to 10%
Africans	Up to 10%	–	Up to 5%
Asians	Up to 5%	More than 50%	Up to 2%

Adapted from SmPC[1]

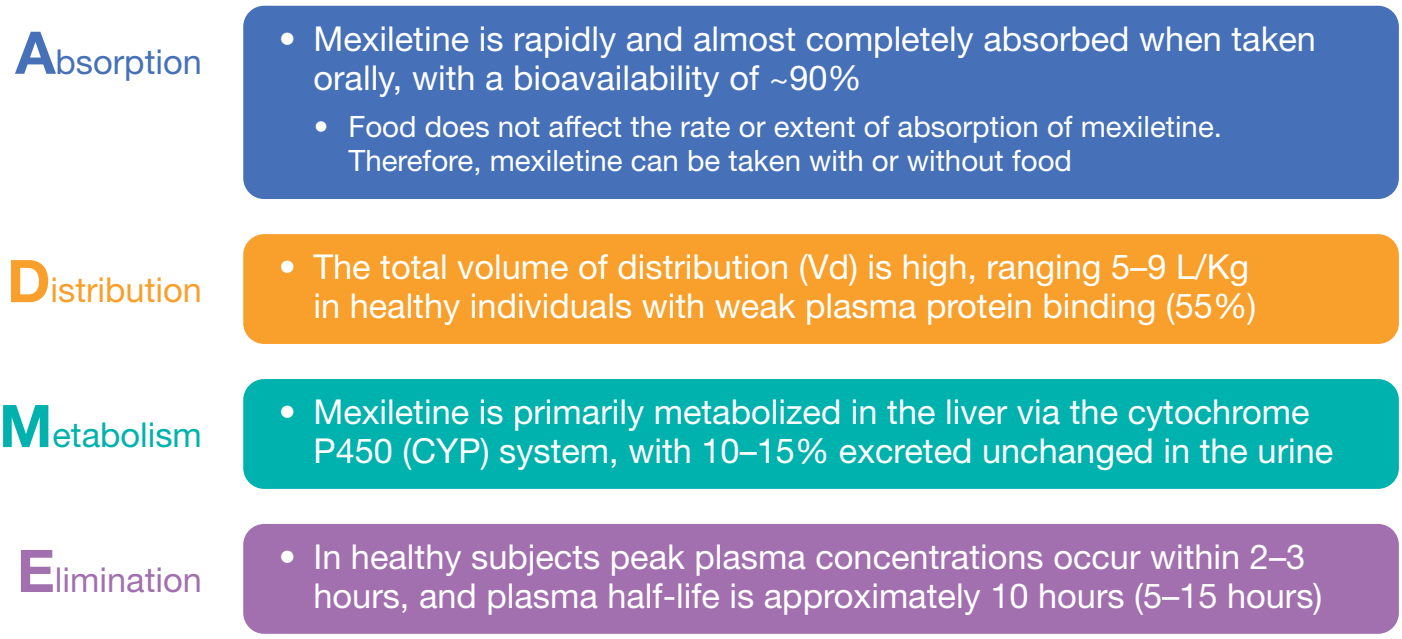
Weight

In population pharmacokinetic analyses, weight was found to influence mexiletine pharmacokinetics.

Age

There is no clinically relevant effect of age on the exposure of mexiletine in adults.

Figure 8. Pharmacokinetics of Mexiletine[1]



CHAPTER 4

Clinical Efficacy

The efficacy and safety of mexiletine's anti-myotonic activity has been studied in 2 independent multi-centre clinical studies,[15,23] a series of aggregated, double-blind, randomised, placebo-controlled N-of-1-trials[24] and a single centre study supported by data from long term, retrospective chart review.[25]

Phase 3 Clinical Trial: Myomex

The efficacy and safety of mexiletine in non-dystrophic myotonia was evaluated in MYOMEX, a multi-centre, double-blind, placebo-controlled, cross-over (2 treatment periods of 18 days) study with a 4-day wash-out period in 13 patients with myotonia congenita (MC) and 12 patients with paramyotonia congenita (PC) (mITT. population)

The objectives of the study were:

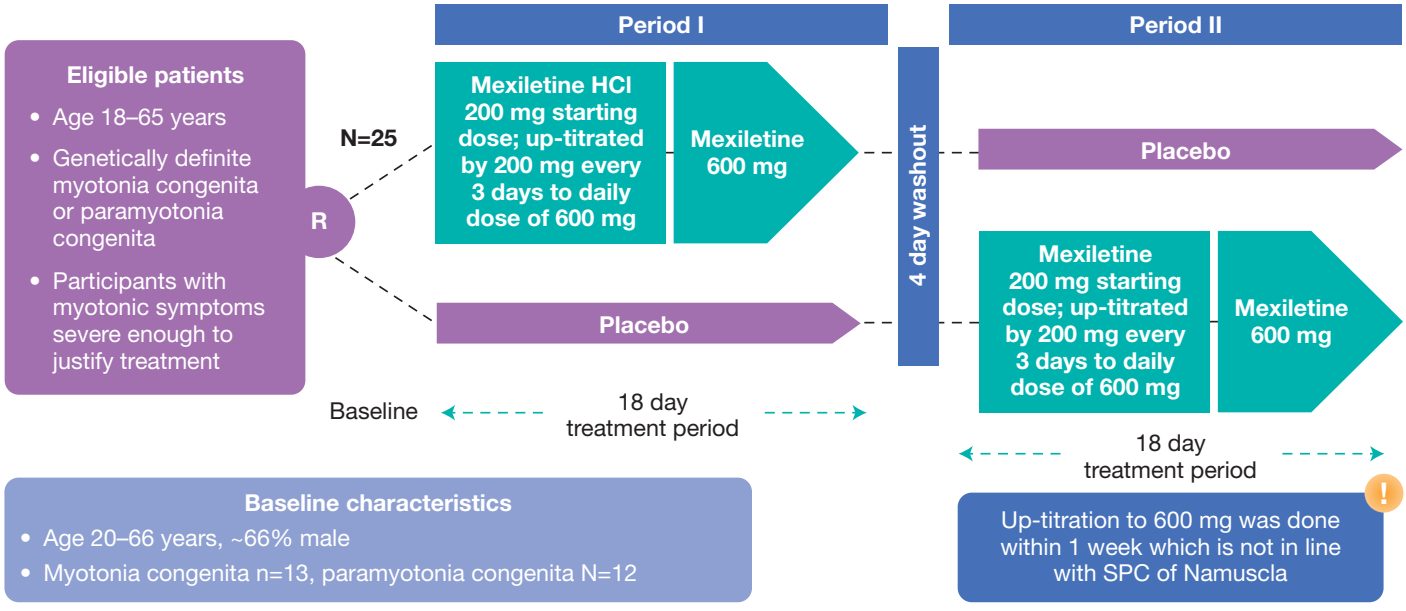
- To study safety and efficacy of mexiletine for the treatment of NDM
- Assess reliability/validity of a new clinical myotonia rating scale (CMS)
- Validate EMG tests as a standardized outcome measure for myotonia

Age of the overall study population ranged from 20 to 66 years old and about 2/3 of the patients were male. Patients who experienced myotonic symptoms that involved at least 2 segments (upper limb, lower limb, face) and that had an impact on at least 3 of 7 daily activities included in the disabling section of the clinical myotonia scale, were included into the study. The patients were randomized according to a cross-over design to a sequence including the 2 following treatments: a) mexiletine, started at **167 mg/day (Corresponds to 200mg Mexiletine hydrochloride salt)** and titrated by increments of 167 mg every 3 days to reach a maximum dose of 500 mg/day in 1 week or b) placebo.

Please note this differed from recommended titration of Mexiletine. As per SmPC, recommended titration:

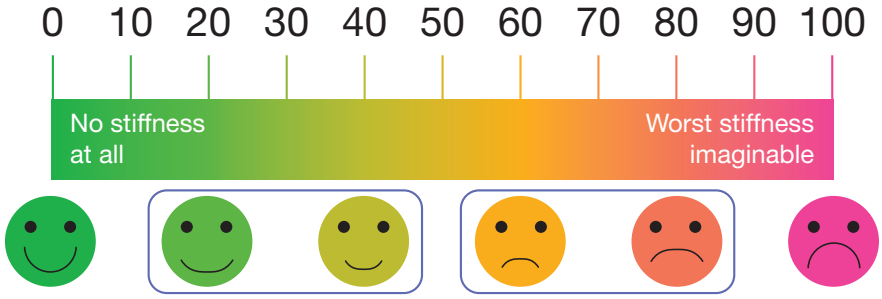
"The recommended starting dose of mexiletine is 167 mg daily (1 capsule per day). After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333 mg daily (2 capsules per day). After at least 1 further week of treatment, based on clinical response, dose can be further increased to 500 mg daily (3 capsules per day)"

Figure 9. Study design of Myomex



The primary efficacy measure for both MC and PC was the score of stiffness severity as self-reported by the patients on a Visual Analogue Scale (VAS). The VAS is constructed as an absolute measure, with a 100 mm straight horizontal line having the endpoints “no stiffness at all” (0) and “worst possible stiffness” (100).

Figure 10. VAS scale



The key secondary endpoints were:

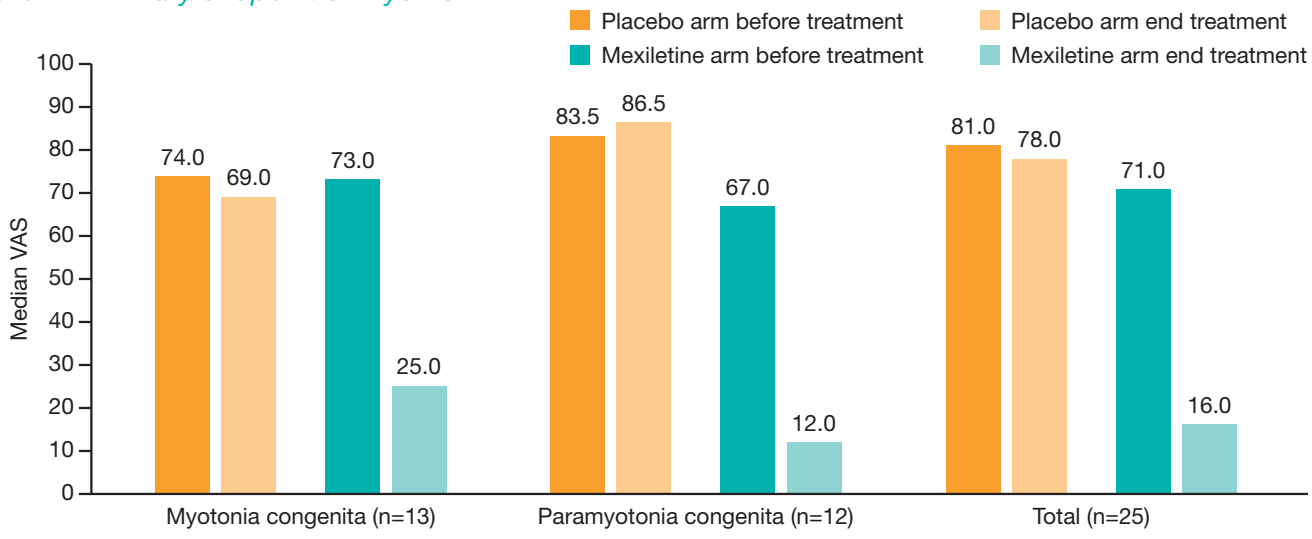
- The time needed to stand up from a chair, walk around the chair and sit down again (Chair Test)
- Changes in health-related quality-of-life as measured with the INQoL scale
- Clinical global impression (CGI) Efficacy index
- Preference between the 2 treatment periods and willingness to continue the treatment
- Number of intolerable increases in myotonia severity necessitating withdrawal
- Measure of the compound muscle action potential (CMAP) amplitude decline recorded from the abductor digiti minimi muscle after repeated short exercise test at room temperature and after cooling
- Score of a CMS.
- Mexiletine plasma concentrations

Results

Primary endpoint

Treatment with mexiletine led to a significant improvement in stiffness. The individual stiffness visual analogue scale (VAS) score for patients receiving placebo generally remained stable. The median stiffness VAS scores for patients receiving mexiletine in the 25 participants in the modified intent-to-treat (mITT) population were of 71 at baseline and decreased to 16 at the end of the treatment period, while those on placebo did not change (81 vs 78 at baseline and end of treatment, respectively). According to the mixed effect linear model, mexiletine treatment allowed a highly significant stiffness improvement regardless of the subjects’ diagnostic ($p<0.001$), i.e. myotonia congenita or paramyotonia congenita. The mixed effect linear model evidenced no carry-over effect (treatment sequence effect, $p=0.845$). These results are shown in Figure 11.[15]

Figure 11. Primary endpoint of Myomex[15]



Note: The study was not powered for subgroup analysis of myotonia congenita and paramyotonia congenita and no formal testing was done

Secondary endpoints

Chair test

Overall, at baseline, the mean time required to stand up from a chair, walk around and sit down again was longer for the patients with MC compared to patients with PC (9.1 ± 3.7 seconds for patients with MC versus 5.3 ± 1.9 seconds for patients with PC) in the mITT population.

The absolute values and the absolute change from baseline values of the chair test before and after treatment in the mITT population are presented in Table 4. Median duration to stand up, turn around the chair and sit down was around 6.0 seconds after placebo and around 5.0 seconds after mexiletine, with longer times observed in patients with MC compared to patients with PC (median after placebo: 9.0 versus 6.0 seconds; median after mexiletine: 6.0 versus 5.0 seconds, respectively).

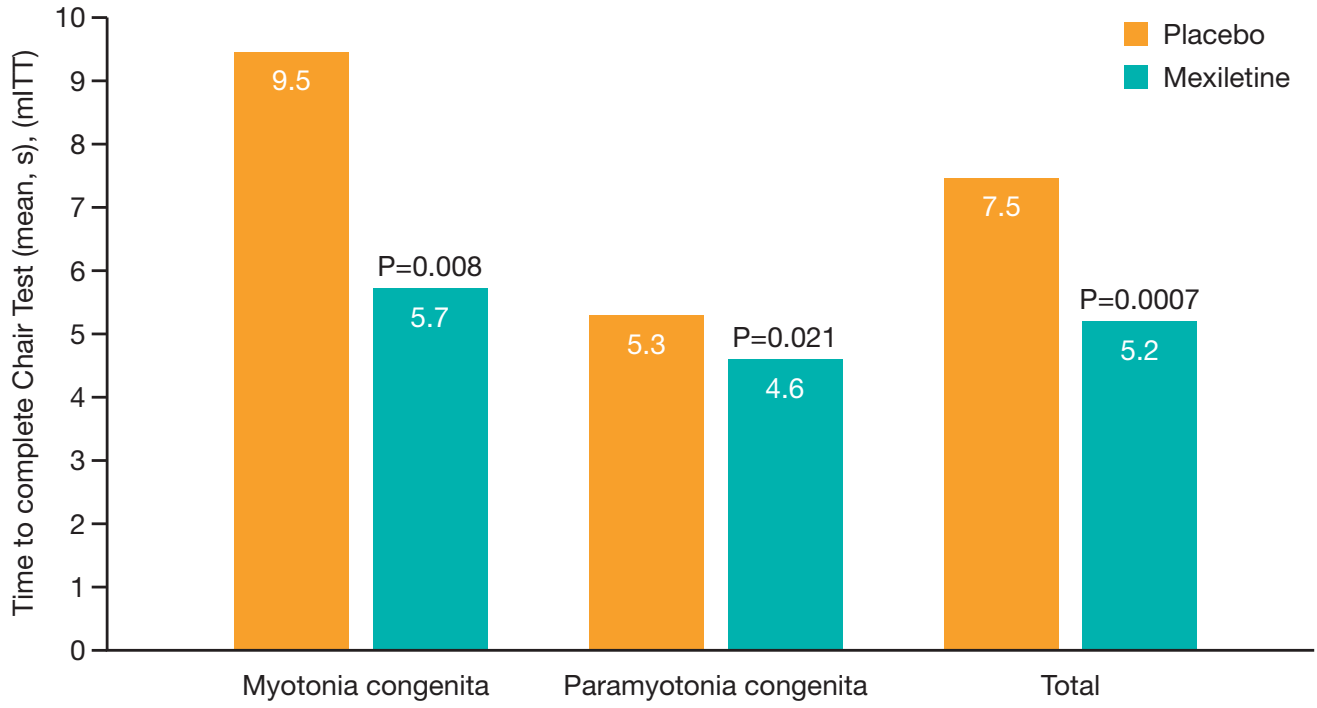
Overall, the change in the time recorded for the chair test at the end of the treatment period was significantly higher after mexiletine treatment (p (Wilcoxon signed-rank test) = 0.0007). Changes from baseline indicated an improvement after mexiletine treatment mainly for patients with MC (median improvement of 3.0 seconds) while no marked changes were observed for patients with PC.

Table 4. Change in time for chair test before and after treatment with mexiletine and placebo

Diagnosis		Chair test (seconds): Absolute values			Chair test (seconds): Absolute changes from V2	
		Before treatment (V2)	Placebo	Mexiletine	Placebo	Mexiletine
MC (N=13)	Mean (SD)	9.1 (3.7)	9.5 (4.8)	5.7 (1.8)	0.5 (1.9)	-3.4 (3.3)
	Med [range]	9.0 [4;16]	9.0 [4;20]	6.0 [3;10]	0.0 [-2;4]	-3.0 [-11.0]
	p*				0.008	
PC (N=12)	Mean (SD)	5.3 (1.9)	5.3 (1.5)	4.6 (1.0)	0.0 (1.3)	-0.8 (1.5)
	Med [range]	5.0 [3;10]	6.0 [3;7]	5.0 [3;6]	0.0 [-3;2]	0.0 [-5;0]
	p*				0.021	
Total (N=25)	**Mean (SD)**	**7.3 (3.5)**	**7.5 (4.1)**	**5.2 (1.6)**	**0.2 (1.6)**	**-2.1 (2.9)**
	Med [range]	**6.0 [3;16]**	**6.0 [3;20]**	**5.0 [3;10]**	**0.0 [3;4]**	**-1.0 [-11;0]**
	p*				**0.0007**	

*Wilcoxon signed-rank test p value
Adapted from Data on File[15]

Figure 12. Time taken by each group of patients to complete the Chair Test[15]



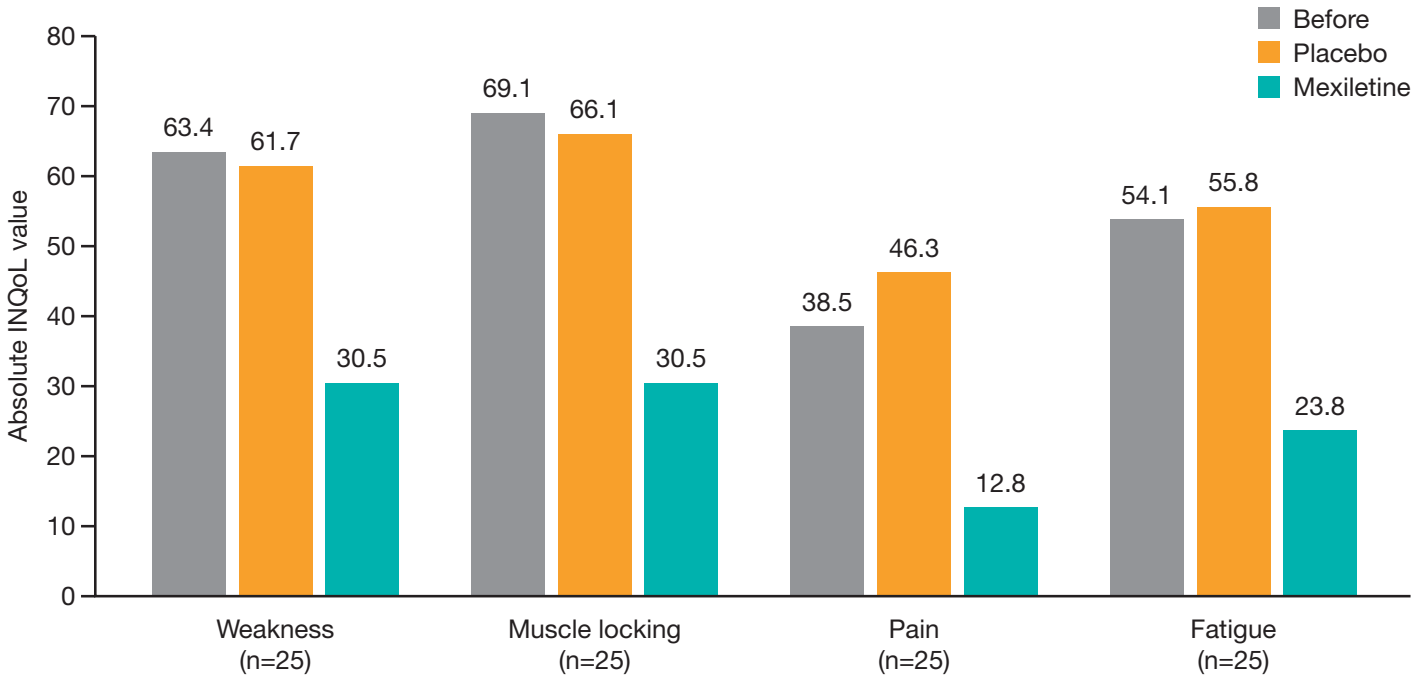
INQOL

The INQoL includes the categories of activities, independence, social relationship, emotions, and body image which are indices of quality of life. Subdomains of myotonia/looking, weakness, pain, and fatigue are indicator of restrictions of daily life. Hence, outcomes of INQoL reflect the impact of key symptoms and their effects on specific areas of life as well as QoL.

After treatment with mexiletine, all the indicators of the QoL domains of INQoL improved, with highest impact on patient's activity. Although the study was not powered for sub-group analysis, in patients with paramyotonia congenita, overall quality of life (aggregation of the five life subdomains) scores improved after mexiletine treatment compared with placebo (-28.1 vs. 2.8, respectively). However, the difference was less pronounced in patients with myotonia congenita. For symptom scores (weakness, locking, pain and fatigue subdomains) which are indices of restrictions of daily life the median change from baseline remained stable after the administration of placebo but decreased after the administration of mexiletine. Similarly, life scores (activities, independence, social relationships, emotions, and body image subdomains) decreased after mexiletine treatment and remained stable following placebo (data on file).

The results for the INQoL scores are shown in two figures. Figure 11 and Figure 12 show the mean individualized quality of life before and after treatment, for the MITT population.

Figure 13. Mean individualized quality of life before and after treatment, for the MITT population

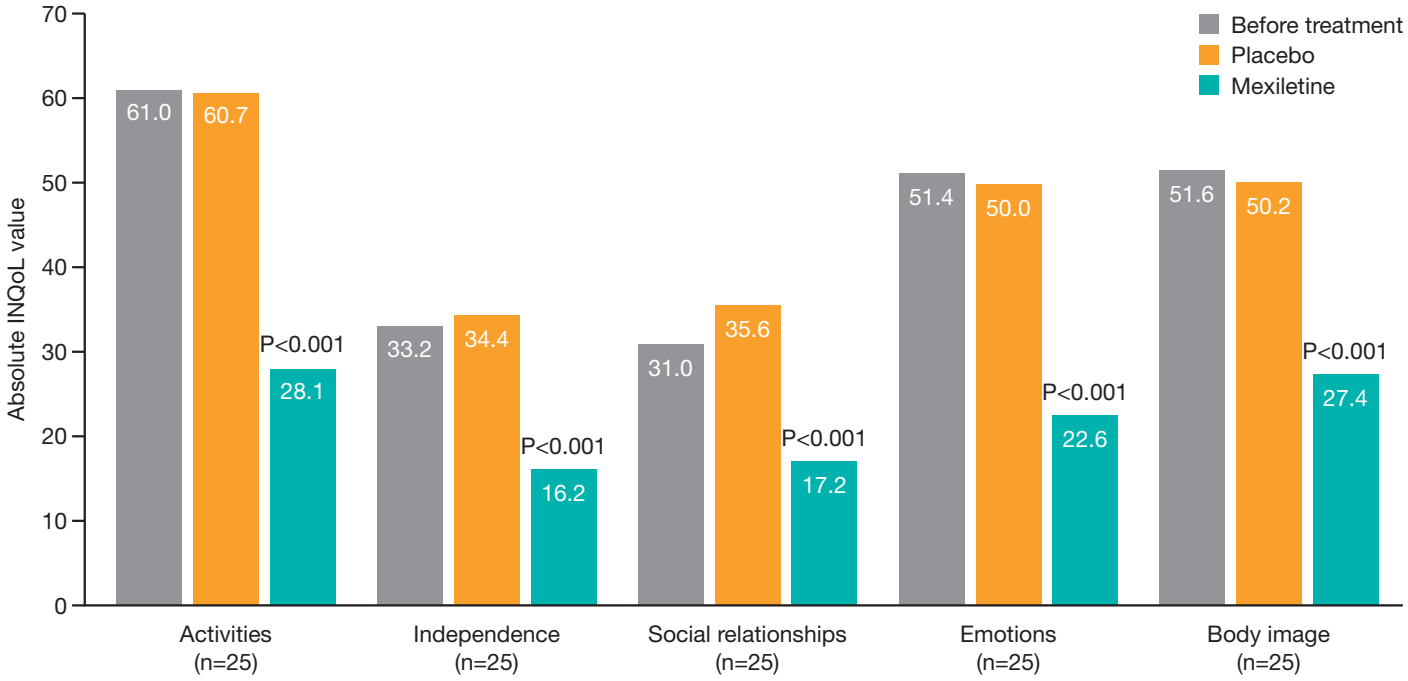


INQoL: Individualized Neuromuscular Quality of Life Questionnaire. A higher score indicates greater impact, with the exception of treatment effects, where a higher score indicates perceived effectiveness.

mITT: Modified intention to treat

Adapted from data on file[15]

Figure 14. Mean individualized quality of life before and after treatment, for the MITT population



INQoL: Individualized Neuromuscular Quality of Life Questionnaire. A higher score indicates greater impact, with the exception of treatment effects, where a higher score indicates perceived effectiveness.

mITT: Modified intention to treat

Adapted from data on file[15]

Patient preference

Overall, the patients significantly preferred the mexiletine treatment period (20 patients [80%]; binomial test p=0.0041). Placebo was considered as the preferred treatment by one patient with paramyotonia congenita (8.3%) and by 4 patients with myotonia congenita (31%) including the one who did not have any preference and the one who prematurely discontinued study treatment due to an adverse event.

CGI index

The CGI-Efficacy index was rated on a 4-point rating scale (good, fair, poor, none) by the patients and the investigator. The investigators reported the mexiletine treatment as efficient for all but 2 patients with myotonia congenita (92% of the total population) while they considered the placebo as poorly efficient for most patients (80% of the total population, 11/13 patients with myotonia congenita and 9/12 patients with paramyotonia congenita; p<0.001). All but 2 patients with myotonia congenita (92% of the total population) reported the mexiletine treatment as efficient (11 patients with myotonia congenita and 12 patients with paramyotonia congenita) while most patients (76% of the total population, 10 patients with myotonia congenita and 9 with paramyotonia congenita) considered the placebo as poorly efficient (p<0.001).

Clinical Myotonia Scale

A new CMS for non-dystrophic myotonias, based on the model developed in primary dystonia, which is also a disease with an episodic and segmental expression[26] has been developed for this study. The validation of this new scale for rating myotonia in NDM is ongoing.

The score of the clinical myotonia rating scale (CMS) is based on two sections:[27]

a. A myotonia severity scale based on examination of the patient which addresses severity and provoking factors of myotonia in 8 regions using a scale of 0 to 4 that measures both intensity and frequency, and
b. A disability scale based on the patient's view of disability in activities of daily living using gives ratings for 7 activities of daily living, using a scale of 0 to 4 (for most scales except feeding).

An improvement in both the severity global score and the disability global score was seen in NDM patients after mexiletine as compared with placebo.

Table 5. Severity global score and disability global score in Myomex study

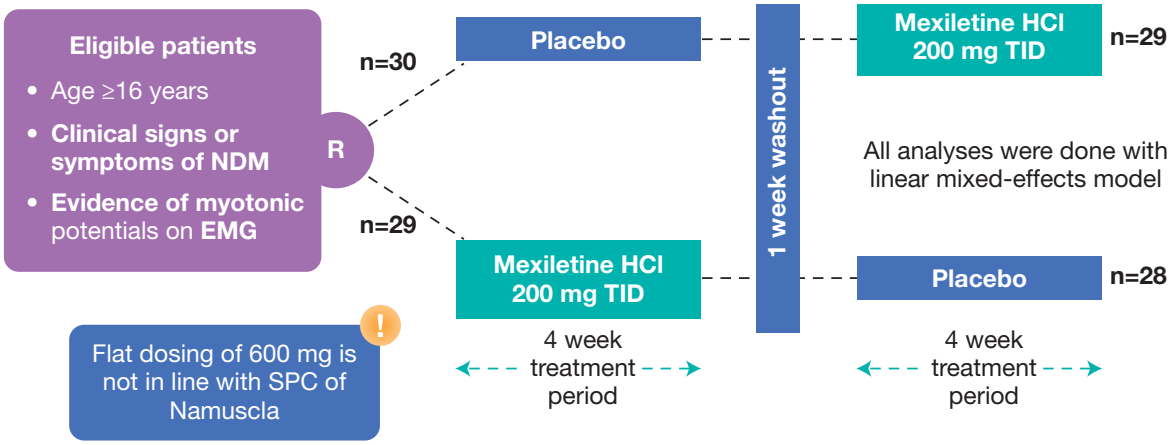
Clinical Myotonia Scale – Severity Global Score	Mexiletine	Placebo
Number of subjects	25	25
Mean (SD) value at Baseline	53.8 (10.0)	
Mean (SD) value at Day 18	24.0 (17.1)	47.6 (23.3)
Mean (SD) absolute change from baseline	-29.8 (16.0)	-6.2 (19.0)
Effect of treatment (linear mixed model)	$p < 0.001$	
Clinical Myotonia Scale – Disability Global Score		
Number of subjects	25	25
Mean (SD) value at Baseline	7.8 (2.8)	
Mean (SD) value at Day 18	2.7 (2.6)	7.0 (3.8)
Mean (SD) absolute change from baseline	-5.1 (3.1)	-0.8 (3.4)
Effect of treatment (linear mixed model)	$p < 0.001$	

Adapted from data on file[15]

Phase 2 clinical study: Statland et al (2012)

A randomised, double-blind, placebo-controlled, two-period cross-over trial was conducted at 7 centres in 4 countries and included participants with genetically confirmed NDM or having the clinical features of NDM but negative myotonic dystrophy DNA testing. Patients already taking anti-myotonic treatments were first required to complete a washout period. Participants were randomised to mexiletine hydrochloride 200 mg capsules (**corresponding to 167 mg mexiletine**) three times a day (TID or placebo capsules TID for 4 weeks. After a one week washout period, they were placed on the opposite intervention for 4 weeks. Patients were randomly assigned the order of the two treatments in a 1:1 ratio, stratified by institution.[23]

Figure 15. Study design in Statland et al[23]



Please note this differed from recommended titration of Mexiletine. As per SmPC, recommended titration: "The recommended starting dose of mexiletine is 167 mg daily (1 capsule per day). After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333 mg daily (2 capsules per day). After at least 1 further week of treatment, based on clinical response, dose can be further increased to 500 mg daily (3 capsules per day)"

The study included eligible patients at least 16 years of age who had clinical symptoms or signs of NDM and myotonic potentials on electromyography.

The primary endpoint was defined as the severity score of stiffness reported by the participants during the 3rd and 4th week of each treatment period, using the Interactive Voice Response Diary (IVR). Symptoms were recorded on a severity scale of 1 to 9, with 1 being minimal severity and 9 being the worst ever experienced, and if there was no symptom, a score of 0.

The secondary endpoints included:

- Pain, weakness, tiredness, measured daily over the 3rd and 4th weeks of treatment period using the IVR
- Clinical myotonia bedside assessment of eyelid and fist function measured five times in sequence at each clinic visit using a stopwatch to measure response time
- Handgrip myotonia, using a commercially available grip dynamometer and computerised capture system
- The maximal post-exercise decrement in compound muscle action potential (CMAP) after short and long exercise
- Myotonia on needle electromyography was graded on a 1+ to 3+ scale in the right abductor digiti minimi (hand muscle) and right tibialis anterior (lower leg muscle)
- Health-related quality of life using the SF-36 and the INQoL

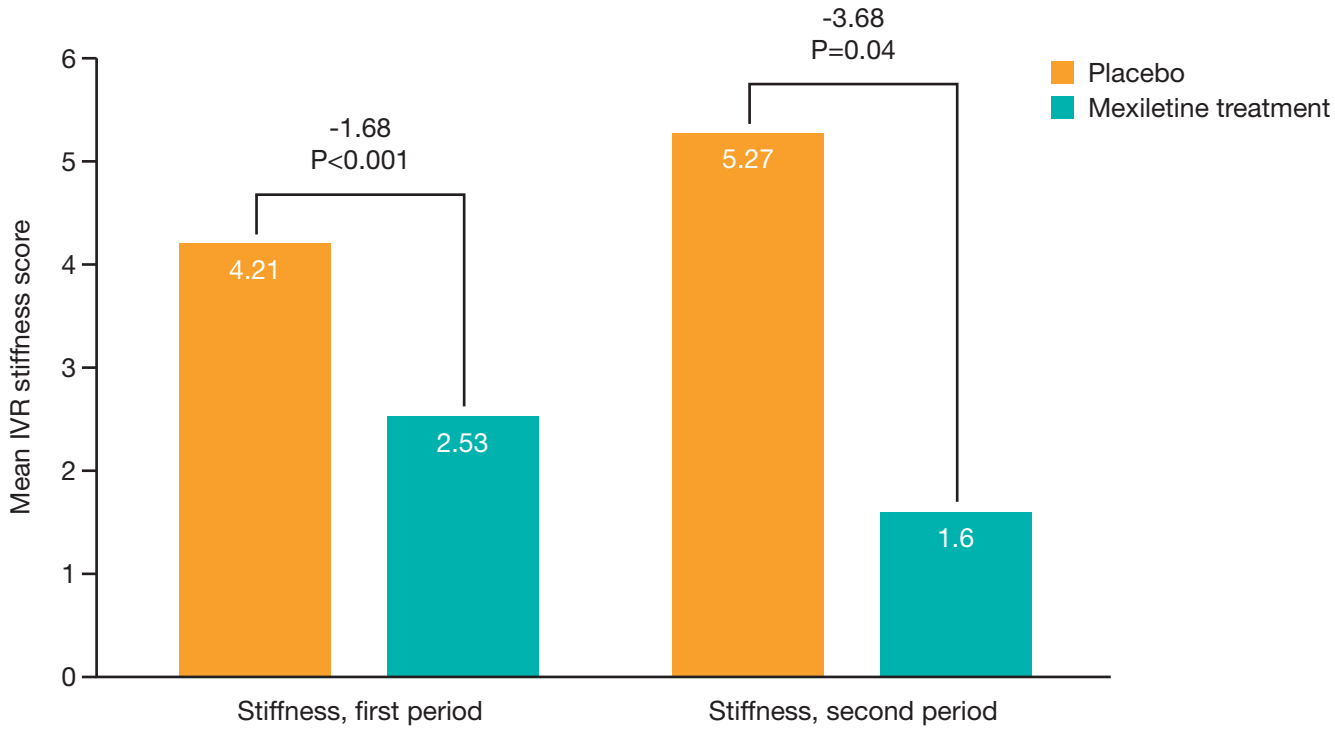
Of the 59 participants included in the study, 34 had chloride channel mutations and 21 had sodium channelopathies and 4 participants had no identified mutation. Seventeen participants were taking medications for myotonia prior to the start of the study, including 13 (22%) taking mexiletine. Randomisation between groups was balanced with the exception of more men in the placebo followed by mexiletine group.[23]

Results:

Primary endpoint

Mexiletine significantly reduced patient-reported stiffness on the IVR in both treatment periods.

Figure 16. Stiffness score n=57; mexiletine and placebo arms

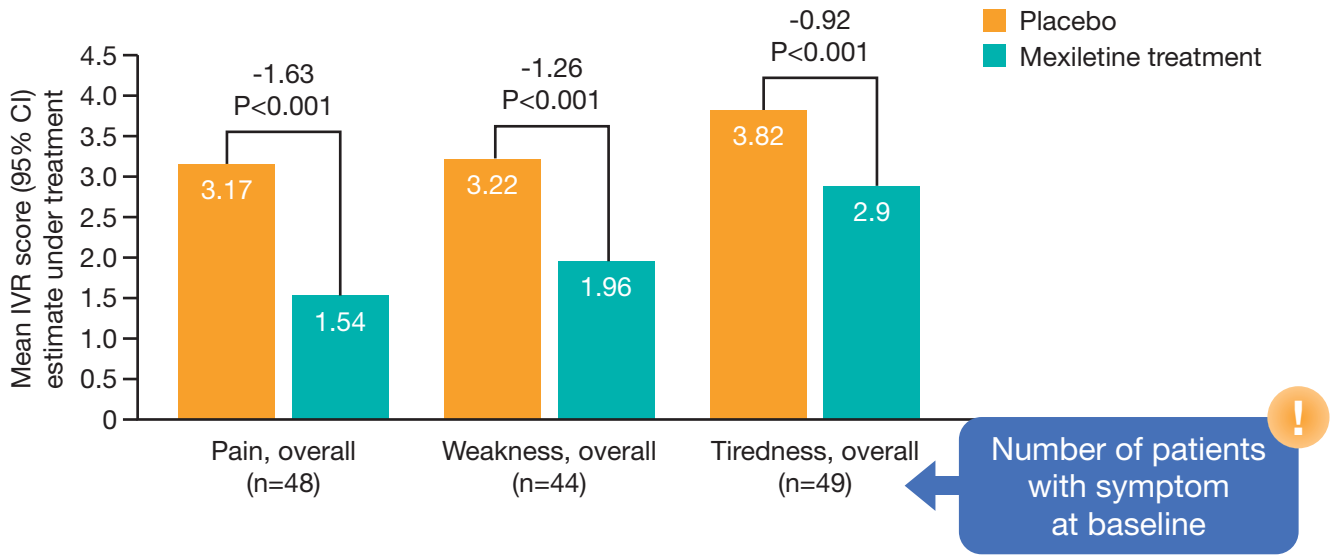


Adapted from Statland et al[23]

Secondary endpoints

Mexiletine improved mean IVR score in overall pain, weakness and tiredness as compared to placebo

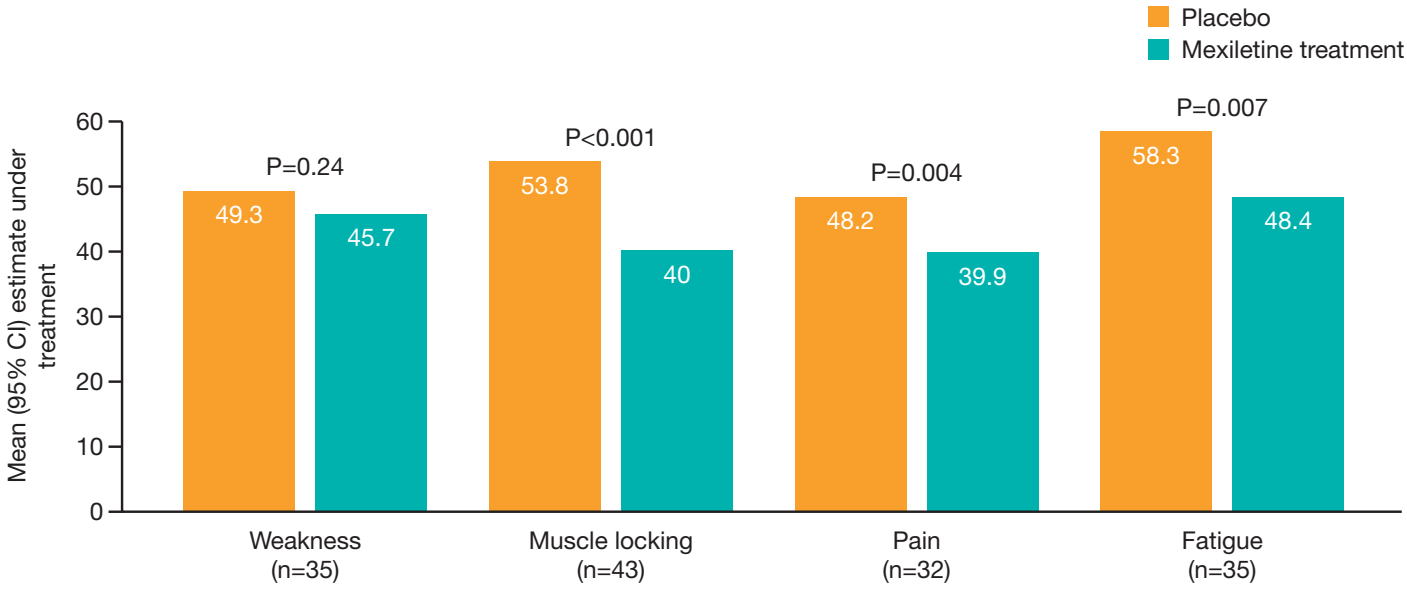
Figure 17. Mixed model results for mexiletine and placebo treatments



Adapted from Statland et al[23]

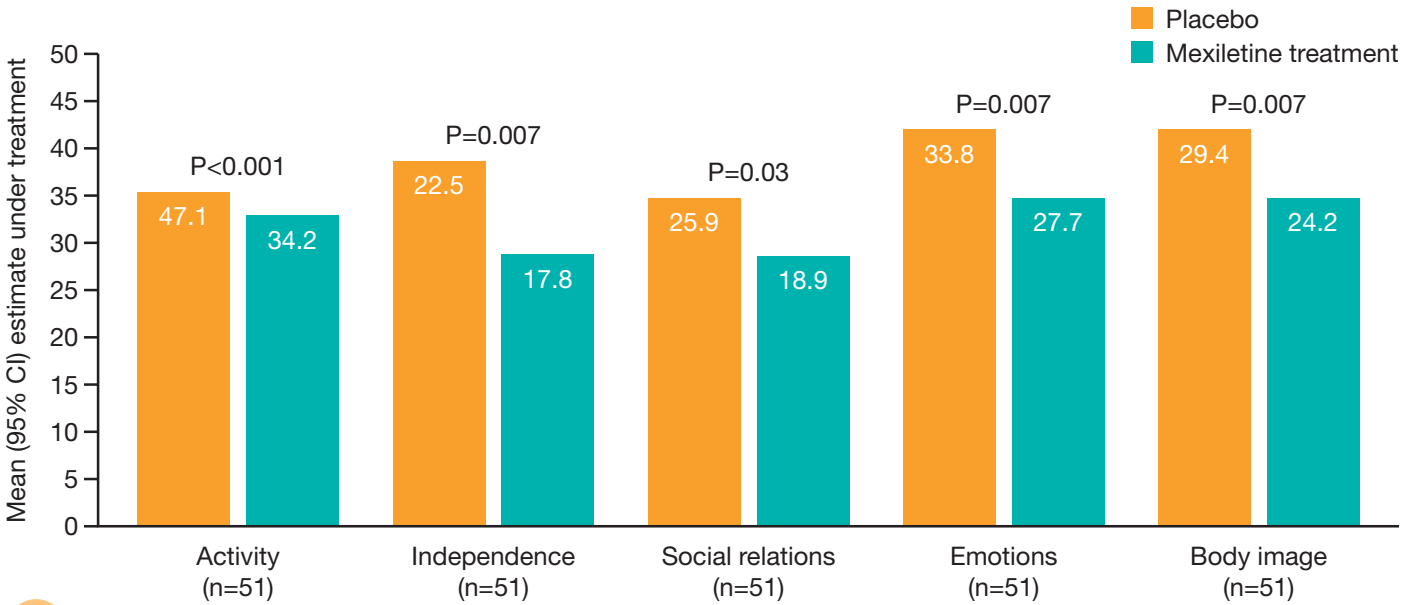
Furthermore, mexiletine improved the INQoL score and improved the SF-36 physical composite score (mexiletine 44.8, placebo 39.2, difference 5.58, 95% CI 3.44, 7.72, P<0.001) and INQoL summary QOL score (mexiletine 14.0, placebo 16.7, difference –2.69, 95% CI –4.07, –1.30, P<0.001). The detailed results are below.[23]

Figure 18. Mixed model results for mexiletine and placebo treatments, overall



Adapted from Statland et al[23]

Figure 19. Mixed model results for mexiletine and placebo treatments, overall

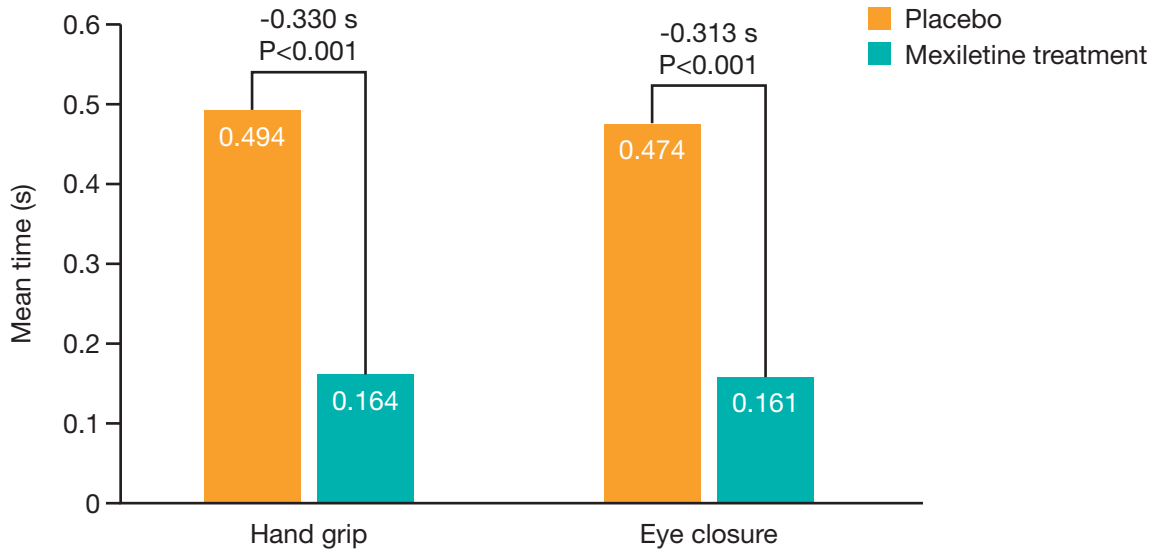


These 5 domains (activity, independence, social relation, emotions and body image) refer to QoL score

Adapted from Statland et al[23]

Mexiletine decreased the mean handgrip myotonia on clinical examinations as compared to placebo as per figure 15

Figure 20. Time taken to squeeze eyes or hands closed and open them

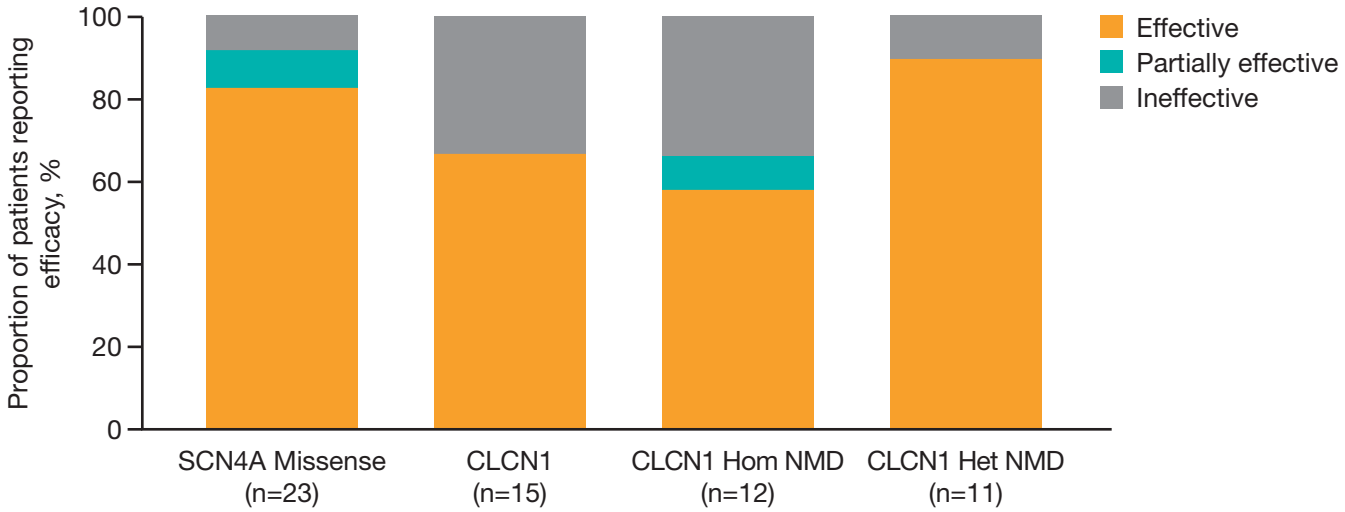


Adapted from Statland et al[23]

Retrospective chart review: Suetterlin et al (2015)[25]

A retrospective analysis of a database of 63 patients with genetically confirmed NDM or hyperkalemic periodic paralysis that had been prescribed mexiletine for a minimum of 6 months was performed. Patients had been titrated in increments of 50mg to 100mg of mexiletine hydrochloride per week until symptoms resolved or a total daily dose of 600mg was reached. Efficacy was determined by subjective patient report as documented by the clinician. Forty patients had mutations in CLCN1, 21 in SCN4A, and 2 in both CLCN1 and SCN4A (subsequently analysed with the SCN4A group). The mean length of follow-up was 4.8 years (range, 6 months to 17.8 years). Figure 21 describes the efficacy of mexiletine in the sub-groups, ranging from 58% efficacy to 93% efficacy. Twelve patients were refractory to mexiletine treatment.[25]

Figure 21. Proportion of patients reporting efficacy per channel mutation



CLCN1 missense indicates all patients with CLCN1 missense mutations only (dominant or recessive myotonia congenita); heterozygous (Het) NMD, patients with recessive myotonia congenita with 1 CLCN1 missense mutation and 1 CLCN1 mutation associated with nonsense mediated decay; homozygous (Hom) NMD, patients with recessive myotonia congenita with 2 mutations associated with nonsense mediated decay; and SCN4A missense, all patients with SCN4A mutations.

Adapted from Suetterlin et al[25]

Please note this differed from recommended titration of Mexiletine. As per SmPC, recommended titration: "The recommended starting dose of mexiletine is 167 mg daily (1 capsule per day). After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333 mg daily (2 capsules per day). After at least 1 further week of treatment, based on clinical response, dose can be further increased to 500 mg daily (3 capsules per day)"

Aggregated N-of-1 Trials (Stunnenberg, Raaphorst et al. 2018)[24]

A series of double-blind, randomised, placebo-controlled N-of-1 trials in adult patients with a clinical phenotype and genetically confirmed diagnosis of NDM, without cardiac or psychiatric comorbidity or comedication was performed in 30 patients (27 included in the analysis) in The Netherlands.

Inclusion and exclusion criteria are summarised in Table 6. Each N-of-1 trial consisted of 1 to 4 treatment sets, comprising 11 weeks each: a 4-week period of mexiletine and a 4-week period of placebo treatment, block-randomised, with a 1-week washout in between and 2 weeks for statistical interim analysis at the end. Patients were randomly assigned to receive **mexiletine hydrochloride (200mg) capsules (equivalent to mexiletine 167 mg)**, or placebo capsules, 3 times daily. Patients receiving antimyotonic treatment underwent a 2-week washout period before baseline.[24]

Table 6. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
At least 18 years of age	Inability or willingness to approve to provide informed consent
Genetically confirmed diagnosis of NDM	Other neurological conditions that might affect the assessment of the study measurement
	Genetically confirmed myotonic dystrophy
	Existing cardiac conduction defects, evidenced on ECG including but not limited to the following conditions: malignant arrythmia or cardiac conduction disturbance (such as second-degree AV block, third degree AV block, or prolonged QT interval >500ms or QRS duration >150msec)
	Current use of the following antiarrhythmic medication for a cardiac disorder: flecainide acetate, encainide, disopyramide, procainamide, quinidine, propafenone or mexiletine
	Women who are pregnant or lactating
	Currently on medication for myotonia such as phenytoin and flecainide acetate within 5 days of enrolment, carbamazepine and mexiletine within 3 days of enrolment, or propafenone, procainamide, disopyramide, quinidine and encainide within 2 days of enrolment
	Renal or hepatic disease, heart failure, history of myocardial infarction, or seizure disorders

Adapted from Stunnenberg et al[24]

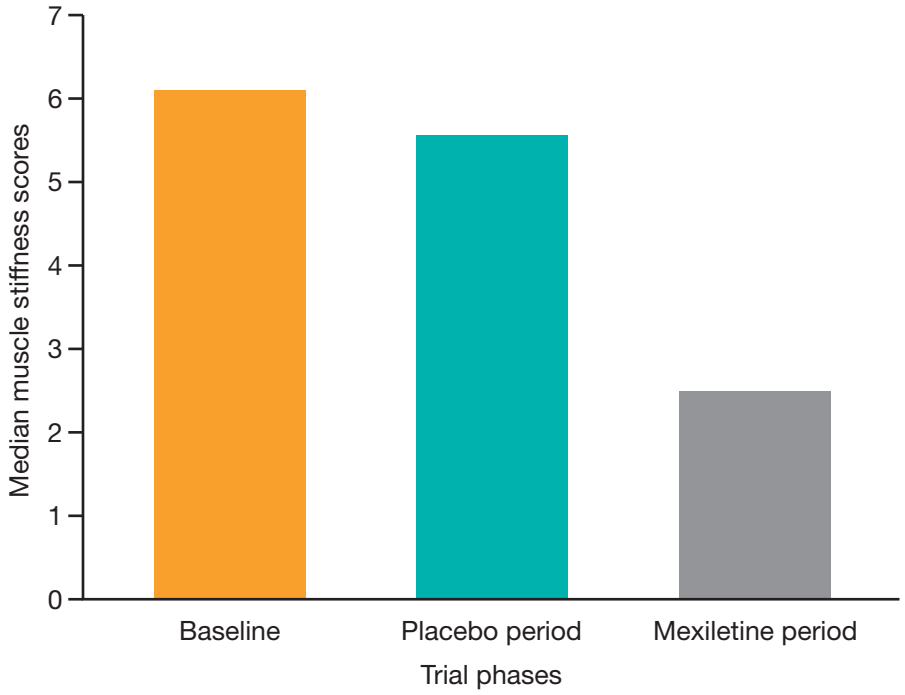
The primary outcome measure was the self-reported stiffness severity score reported using an interactive voice response diary similar to methodology of used by Statland et al.[23] Patients noted if they experienced symptoms during the previous 24 hours and rated the severity of the symptoms on an ordinal scale (1-9, with 9 being the worst ever experienced). Based on clinical experience (consensus meeting with 3 clinical experts), a 0.75-point difference was considered a clinically meaningful difference for all 4 interactive voice response (IVR) scores.

Results

In 89% of the patients, mexiletine was seen to have met the predefined clinically meaningful measure of effectiveness. In these patients, the individual N-of-1 trial was stopped and mexiletine treatment was continued in a normal clinical care setting. In 3 patients (11%), Bayesian analysis showed the predefined clinical ineffectiveness of mexiletine. Their individual N-of-1 trials were stopped and mexiletine treatment was discontinued. There were three subjects with no reduction of IVR score receiving mexiletine ("nonresponders"). They all had a SCN4A genotype.

The median muscle stiffness scores are shown in Figure 22.

Figure 22. Median muscle scores



Adapted from Stunnenberg et al[24]

CHAPTER 5

Safety and Tolerability

Safety data initially submitted for licence, to support the proposed indication included:

- Safety data from the MYOMEX clinical study in 25 patients with non-dystrophic myotonias
- Published studies
- Post-marketing safety data
- PSURs

Non clinical

Non-clinical data revealed no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development. The main observed effects in rats and/or dogs were vomiting, diarrhoea, tremor, ataxia, convulsions and tachycardia. However, these studies were not performed in accordance with contemporary standards and are, hence, of unclear clinical relevance.

The studies in rats on carcinogenic potential were negative, but not performed in accordance with current standards and therefore of unclear clinical relevance. The negative genotoxicity potential does not indicate an increased carcinogenic risk of treatment with mexiletine.[1]

Clinical

From myomex,[28] the number of Adverse events are shown below.

Table 7.

Diagnosis	Type of Adverse Event	Placebo		Mexiletine	
		Number of AEs	Patient* n (%)	Number of AEs	Patient* n (%)
MC N=13	Any AE Related AE** Severe AE Serious AE Death AE leading to treatment withdrawal AE requiring concomitant medication	9 8 0 0 0 0 1	4 (30.8%) 3 (23.1%) 0 0 0 0 1 (7.7%)	16 13 1 0 0 1 3	6 (46.2%) 4 (30.8%) 1 (7.7%) 0 0 1 (7.7%) 2 (15.4%)
PC N=12	Any AE Related AE** Severe AE Serious AE Death AE leading to treatment withdrawal AE requiring concomitant medication	5 0 0 0 0 3	5 (41.7%) 0 (0%) 0 0 0 3 (25.0%)	24 12 0 0 0 5	9 (75.0%) 7 (58.3%) 0 0 0 4 (33.3%)
Total N=25	**Any AE Related AE** Severe AE Serious AE Death AE leading to treatment withdrawal AE requiring concomitant medication**	**14 8 0 0 0 0 4**	**9 (36.0%) 3 (12.0%) 0 0 0 0 4 (16.0%)**	**40 25 1 0 0 1 8**	**15 (60.0%) 11 (44.0%) 1 (4.0%) 0 0 1 (4.0%) 6 (24.0%)**

*Patient with at least one AE
**Probable, possible or unknown relationship to study drug
AE: adverse event; MC: myotonia congenita; PC: paramyotonia congenita
Adapted from data on file[28]

Table 8.

Diagnosis	SOC	Placebo		Mexiletine	
		Number of AEs	Patient[1] n (%)	Number of AEs	Patient[1] n (%)
MC N=13	**Overall**	**9**	**4 (30.8%)**	**16**	**6 (46.2%)**
	Cardiac Disorders	0	0 (0%)	1	1 (7.7%)
	Ear and Labyrinth Disorders	0	0 (0%)	1	1 (7.7%)
	Gastrointestinal Disorders	2	2 (15.4%)	1	1 (7.7%)
	General Disorders and Administration Site Conditions	3	2 (15.4%)	4	2 (15.4%)
	Injury, Poisoning and Procedural Complications	0	0 (0%)	2	2 (15.4%)
	Musculoskeletal and Connective Tissue Disorders	0	0 (0%)	2	2 (15.4%)
	Nervous System Disorders	2	2 (15.4%)	3	2 (15.4%)
	Respiratory, Thoracic and Mediastinal Disorders	1	1 (7.7%)	0	0 (0%)
	Skin and Subcutaneous Tissue Disorders	1	1 (7.7%)	0	0 (0%)
	Vascular Disorders	0	0 (0%)	2	2 (15.4%)
PC N=12	**Overall**	**5**	**5 (41.7%)**	**24**	**9 (75.0%)**
	Blood and Lymphatic System Disorders	1	1 (8.3%)	0	0 (0%)
	Ear and Labyrinth Disorders	0	0 (0%)	1	1 (8.3%)
	Eye Disorders	0	0 (0%)	1	1 (8.3%)
	Gastrointestinal Disorders	0	0 (0%)	6	5 (41.7%)
	Infections and Infestations	3	3 (25.0%)	6	5 (41.7%)
	Musculoskeletal and Connective Tissue Disorders	0	0 (0%)	1	1 (8.3%)
	Nervous System Disorders	1	1 (8.3%)	2	1 (8.3%)
	Psychiatric Disorders	0	0 (0%)	4	4 (33.3%)
	Reproductive System and Brest Disorders	0	0 (0%)	1	1 (8.3%)
	Respiratory, Thoracic and Mediastinal Disorders	0	0 (0%)	1	1 (8.3%)
	Skin and Subcutaneous Tissue Disorders	0	0 (0%)	1	1 (8.3%)
All patients[2] N=25	**Overall**	**14**	**9 (36.0%)**	**40**	**15 (60.0%)**
	Blood and Lymphatic System Disorders	1	1 (4.0%)	0	0 (0%)
	Cardiac Disorders	0	0 (0%)	1	1 (4.0%)
	Ear and Labyrinth Disorders	0	0 (0%)	2	2 (8.0%)
	Eye Disorders	0	0 (0%)	1	1 (4.0%)
	Gastrointestinal Disorders	2	2 (8.0%)	7	6 (24.0%)
	General Disorders and Administration Site Conditions	3	2 (8.0%)	4	2 (8.0%)
	Infections and Infestations	3	3 (12.0%)	6	5 (20.0%)
	Injury, Poisoning and Procedural Complications	0	0 (0%)	2	2 (8.0%)
	Musculoskeletal and Connective Tissue Disorders	0	0 (0%)	3	3 (12.0%)
	Nervous System Disorders	3	3 (12.0%)	5	3 (12.0%)
	Psychiatric Disorders	0	0 (0%)	4	4 (16.0%)
	Reproductive System and Brest Disorders	0	0 (0%)	1	1 (4.0%)
	Respiratory, Thoracic and Mediastinal Disorders	1	1 (4.0%)	1	1 (4.0%)
	Skin and Subcutaneous Tissue Disorders	1	1 (4.0%)	1	1 (4.0%)
	Vascular Disorders	0	0 (0%)	2	2 (8.0%)

[1]Patient with at least one AE; [2]Total = MC + PC
AE: adverse event; MC: myotonia congenita; PC: paramyotonia congenita; SAF: Safety population.
Source: MYOMEX CSR, Table 12-3

Adapted from data on file[28]

Contraindications[1]

- Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1 of the SmPC
- Hypersensitivity to any local anaesthetic
- Ventricular tachyarrhythmia
- Complete heart block (i.e. third-degree atrioventricular block) or any heart block susceptible to evolve to complete heart block (first-degree atrioventricular block with markedly prolonged PR interval (≥ 240 ms) and/or wide QRS complex (≥ 120 ms), second-degree atrioventricular block, bundle branch block, bifascicular and trifascicular block),
- Myocardial infarction (acute or past), or abnormal Q-waves
- Symptomatic coronary artery disease
- Heart failure with mid-range (40-49%) and reduced (<40%) ejection fraction
- Atrial tachyarrhythmia, fibrillation or flutter
- Sinus node dysfunction (including sinus rate < 50 bpm)
- Co-administration with medicinal products inducing torsades de pointes (see section 4.5)
- Co-administration with medicinal products with narrow therapeutic index (see section 4.5).

Special warnings and precautions for use[1]

Cardiac arrhythmogenic effects

Mexiletine may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed. See also sections 4.3 and 4.5 of the SmPC regarding association with other products with arrhythmogenic effects.

Before starting mexiletine treatment, detailed and careful cardiac evaluation (ECG, 24-48-hour Holter-monitoring and echocardiography) should be carried out in all patients in order to determine the cardiac tolerability of mexiletine. A cardiac evaluation is recommended shortly after treatment start (e.g. within 48 hours).

Throughout treatment with mexiletine, and in relation with dose changes, cardiac monitoring of patients needs to be adapted as a function of the heart condition of the patient:

- In patients without cardiac abnormalities, periodic ECG monitoring is recommended (every 2 years or more frequently if considered necessary).
- In patients with cardiac abnormalities, and in patients prone to such abnormalities, detailed cardiac evaluation, including ECG, should be carried out before and after any dose increase. During maintenance treatment, detailed cardiac evaluation, including ECG, 24-48 hour Holter-monitoring and echocardiography, is recommended at least annually, or more frequently if considered necessary as part of routine cardiac assessment.

Patients should be informed about the presenting symptoms of arrhythmias (fainting, palpitation, chest pain, shortness of breath, light-headedness, lipothymia, and syncope) and should be advised to immediately contact an emergency centre if there are any symptoms of arrhythmias.

For cardiac disorders not listed in section 4.3 of the SmPC, the benefit of the antimyotonic effects of mexiletine needs to be balanced against the risk of cardiac complications on a case by case basis.

Mexiletine should be stopped immediately in case any cardiac conduction abnormalities or any of the contraindications listed in the section 4.3 of the SmPC are detected.

Electrolytic imbalance such as hypokalaemia, hyperkalaemia or hypomagnesaemia may increase the proarrhythmic effects of mexiletine. Therefore, electrolytic evaluation should be done prior to initiating therapy with mexiletine in every patient. Electrolyte imbalance needs to be corrected before administering mexiletine and to be monitored throughout treatment (with a periodicity to be adapted patient by patient).

Drug reaction with eosinophilia and systemic symptoms (DRESS)

DRESS refers to a syndrome which includes in its complete form severe cutaneous eruptions, fever, lymphadenopathy, hepatitis, haematological abnormalities with eosinophilia and atypical lymphocytes, and can involve other organs. Symptoms typically occur 1-8 weeks after exposure to the medicinal product. Severe systemic manifestations are responsible for a 10% mortality rate. Incidence of DRESS has been reported between 1:100 and 1:10.000 patients treated.

Several medicinal products including anticonvulsants, antibiotics and also mexiletine have been identified as possible causes. Patients with known hypersensitivity to mexiletine or any other ingredients of this product or to any local anaesthetic are at high risk of developing DRESS and should not receive mexiletine.

Hepatic impairment

The experience with mexiletine in patients with severe hepatic impairment is limited. Therefore, mexiletine should not be used in this patient population (see section 4.2 of the SmPC).

Renal impairment

The experience with mexiletine in patients with severe renal impairment is limited. Therefore, the use of mexiletine is not recommended in this patient population (see section 4.2 of the SmPC).

Epilepsy

Epileptic patients need to be monitored because mexiletine can increase the frequency of seizure episodes.

CYP2D6 polymorphism

CYP2D6 polymorphism may affect mexiletine pharmacokinetics (see section 5.2 of the SmPC). Higher systemic exposure is expected in patients who are CYP2D6 poor metabolisers or who take medicinal products that inhibit CYP2D6 (see section 4.5 of the SmPC). A period of at least 7 days before dose increase must be respected to ensure that steady-state levels are reached and that mexiletine is well tolerated in all patients, irrespective of CYP450 polymorphism.

Smoking

Smoking affects mexiletine pharmacokinetics (see section 4.5 of the SmPC). Mexiletine dose may need to be increased if a patient starts to smoke and decreased if a patient stops to smoke.

Interaction with other medicinal products and other forms of interaction[1]

Pharmacodynamic interactions

Antiarrhythmics inducing torsades de pointes (class Ia, Ic, III antiarrhythmics):

Co-administration of mexiletine and antiarrhythmics inducing torsades de pointes (*class Ia*: quinidine, procainamide, disopyramide, ajmaline; *class Ic*: encainide, flecainide, propafenone, moricizine; *class III*: amiodarone, sotalol, ibutilide, dofetilide, dronedarone, vernakalant) increases the risk of potentially lethal torsades de pointes. The concomitant use of mexiletine and antiarrhythmic medicines inducing torsades de pointes is contraindicated (see section 4.3 of the SmPC).

Other antiarrhythmics (class Ib, II, IV antiarrhythmics):

Co-administration of mexiletine and other classes of antiarrhythmics (*class Ib*: lidocaine, phenytoin, tocainide; *class II*: propranolol, esmolol, timolol, metoprolol, atenolol, carvedilol, bisoprolol, nebivolol; *class IV*: verapamil, diltiazem) is not recommended, unless exceptionally, because of the increased risk of adverse cardiac reactions (see section 4.4 of the SmPC).

Pharmacokinetic interactions

Effect of other medicinal products on mexiletine

Mexiletine is a substrate for the metabolic pathways involving hepatic enzymes; inhibition or induction of these enzymes is expected to alter mexiletine plasma concentrations.

CYP1A2 & CYP2D6 inhibitors

Co-administration of mexiletine with a hepatic enzyme inhibitor (CYP1A2 inhibitor: ciprofloxacin, fluvoxamine, propafenone; CYP2D6 inhibitor: propafenone, quinidine) significantly increases mexiletine exposure and thus the associated risk of adverse reactions to mexiletine.

In a single-dose interaction study, the clearance of mexiletine was decreased by 38% following the co-administration of fluvoxamine, an inhibitor of CYP1A2.

Therefore, clinical and ECG monitoring, as well as adaptation of mexiletine dosage may be indicated throughout and after treatment with a CYP1A2 or CYP2D6 inhibitor.

CYP1A2 & CYP2D6 inducers

Co-administration of mexiletine with a hepatic enzyme inducer (CYP1A2 inducer: omeprazole; CYP2D6 inducer: phenytoin, rifampicin) may increase the clearance and elimination rate of mexiletine due to an increased hepatic metabolism, resulting in decreased plasmatic concentrations and half-life of mexiletine.

In a clinical study, co-administration of mexiletine with phenytoin resulted in a significant decrease in exposure to mexiletine ($p < 0.003$) due to enhanced clearance as reflected in significantly decreased elimination half-life (17.2 to 8.4 hours, $p < 0.02$).

Therefore, based on the clinical response, the mexiletine dosage should be adapted during and after treatment with the enzyme inducer.

After the oral administration of single (167 mg) and multiple (83 mg twice a day during 8 days) doses of mexiletine, total clearance of mexiletine is significantly increased in smokers (1.3 to 1.7-fold) due to induction of CYP1A2, resulting in a correspondingly decreased elimination half-life and drug exposure. Mexiletine dose may need to be increased if a patient starts to smoke during mexiletine treatment and decreased if a patient stops smoking.

Effect of mexiletine on other medicinal products

The potential of mexiletine as a drug-drug-interaction perpetrator is unknown. Patients should be carefully monitored if co-treated with other medicinal products with especially emphasis to medicinal products with narrow therapeutic windows.

Table 9. Effect of mexiletine on other medicinal products

Product	Interaction description	Recommendations
Caffeine	Mexiletine can increase the concentration of caffeine	Reduce caffeine intake during treatment with mexiletine
Cigarette smoking	Increases clearance of mexiletine and may reduce effective serum concentrations	
CYP1A2 substrates	Mexiletine is a potent inhibitor of CYP1A2; therefore, co-administration of mexiletine with medicinal products metabolised by CYP1A2 (such as theophylline, caffeine, lidocaine or tizanidine) may be associated with elevations in plasma concentrations of the concomitant medicine that could increase or prolong the therapeutic efficacy and/or the adverse reactions, especially if mexiletine is co-administered with CYP1A2 substrates with narrow therapeutic window, e.g. theophylline and tizanidine.	The CYP1A2 substrate blood levels should be monitored, particularly when the mexiletine dose is changed. An appropriate adjustment in the dose of the CYP1A2 substrate should be considered.
Substrates of other enzymes and transporters	The potential interactions between mexiletine and substrates of other common enzymes and transporters have not yet been assessed	It is currently contra-indicated to use mexiletine with any substrate having a narrow therapeutic window such as digoxin, lithium, phenytoin, theophylline or warfarin
Organic cation transporter 2 (OCT2) substrates	The organic cation transporter 2 (OCT2) provides an important pathway for the uptake of cationic compounds in the kidney. Mexiletine may interact with drugs transported by OCT2 (such as metformin and dofetilide).	If mexiletine and other OCT2 substrates are to be used concurrently, the OCT2 substrate blood levels should be monitored, particularly when the mexiletine dose is changed. An appropriate adjustment in the dose of the OCT2 substrate should be considered.

Adapted from SmPC[1]

4.6 Fertility, pregnancy and lactation[1]

Pregnancy

There are no or limited amount of data from the use of mexiletine in pregnant women. Limited clinical data of the use of mexiletine in pregnant women shows that mexiletine crosses the placenta and reaches the foetus. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of mexiletine during pregnancy.

Breast-feeding

Mexiletine is excreted in human milk. There is insufficient information on the effects of mexiletine in newborns/infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from mexiletine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

The effects of mexiletine on fertility in humans have not been studied. Animal studies with mexiletine do not indicate harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines[1]

Mexiletine may have minor influence on the ability to drive and use machines. Fatigue, confusion, blurred vision may occur following administration of mexiletine (see section 4.8).

4.8 Undesirable effects[1]

Table 10. Summary of the safety profile

	Treatment-related AE	
	Very common (≥1/10)	Common (≥1/100 to <1/10)
Abdominal pain	✔	
Insomnia	✔	
Vertigo		✔
Nausea		✔
Fatigue, asthenia, chest discomfort, malaise		✔
Somnolence		✔
Tachycardia		✔
Flushing, hypotension		✔
Acne		✔
Headach, paresthesia, vision blurred		✔

Adapted from SmPC[1]

The most commonly reported adverse reactions in patients treated with mexiletine are abdominal pain (12%), vertigo (8%) and insomnia (12%).

The most serious reported adverse reactions in patients treated with mexiletine are drug reaction with eosinophilia and systemic symptoms and arrhythmia (atrioventricular block, arrhythmia, ventricular fibrillation).

Table 11. Tabulated list of adverse reactions

Frequency categories are derived according to the following conventions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Very common and common adverse reactions are derived from data from the MYOMEX study; less common adverse effects are derived from post-marketing data.

Blood and lymphatic system disorders Not known: leukopenia, thrombocytopenia
Immune system disorders Very rare: drug reaction with eosinophilia and systemic symptoms Not known: lupus-like syndrome, dermatitis exfoliative, Stevens-Johnson syndrome
Psychiatric disorders Very common: insomnia Common: somnolence Not known: hallucinations, confusional state
Nervous system disorders Common: headache, paraesthesia, vision blurred Uncommon: seizure, speech disorders Not known: diplopia, dysgeusia
Ear and labyrinth disorders Common: vertigo
Cardiac disorders Common: tachycardia Uncommon: bradycardia Not known: atrioventricular block
Vascular disorders Common: flushing, hypotension Not known: circulatory collapse, hot flush
Respiratory, thoracic and mediastinal disorders Not known: pulmonary fibrosis
Gastrointestinal disorders Very common: abdominal pain Common: nausea Not known: diarrhoea, vomiting, oesophageal ulcers and perforation
Hepatobiliary disorders Rare: hepatic function abnormal Very rare: drug-induced liver injury, liver disorder, hepatitis
Skin and subcutaneous tissue disorders Common: acne
Musculoskeletal and connective tissue disorders Common: pain in the extremities
General disorders and administration site conditions Common: fatigue, asthenia, chest discomfort, malaise

Adapted from SmPC[1]

CHAPTER 6

Dosage and Administration, Pharmaceutical particulars[1]

Posology

The recommended starting dose of mexiletine is 167 mg daily (1 capsule per day). After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333 mg daily (2 capsules per day). After at least 1 further week of treatment, based on clinical response, dose can be further increased to 500 mg daily (3 capsules per day).

Maintenance treatment is between 167 mg – 500 mg daily (1 to 3 capsules per day), according to the intensity of symptoms and the clinical response, taken regularly throughout the day.

The dose should not exceed 500 mg/day. Regular reassessment should be implemented, not to continue long-term treatment in a patient not responding or not experiencing benefit of the treatment.

Before starting mexiletine treatment, detailed and careful cardiac evaluation should be carried out; throughout treatment with mexiletine, cardiac monitoring needs to be continued and adapted as a function of the heart condition of the patient (see contraindications in section 4.3 and warning in section 4.4 of the SmPC).

Patients with cardiac disorders

In case of modification of the mexiletine dose, or if medicinal products susceptible to affect cardiac conduction are co-administered with mexiletine, patients should be closely monitored by ECG (especially patients with conduction anomalies) (see sections 4.3 and 4.4 of the SmPC).

Elderly

Experience with mexiletine in patients with myotonic disorders aged > 65 years is limited. Based on the pharmacokinetic properties of mexiletine, no dosage adjustment is required in patients aged 65 years and over.

Hepatic impairment

Mexiletine should be used with caution in patients with mild or moderate hepatic impairment. In these patients, it is recommended that the dose should only be increased after at least 2 weeks of treatment.

Mexiletine should not be used in patients with severe hepatic impairment (see section 4.4 of the SmPC).

Renal impairment

No dosage adjustment is considered necessary in patients with mild or moderate renal impairment. The experience with mexiletine in patients with severe renal impairment is limited. Therefore, the use of mexiletine is not recommended in this patient population (see section 4.4 of the SmPC).

Paediatric population

The safety and efficacy of mexiletine in children and adolescents aged 0 to 18 years have not been established. No data are available.

Poor and extensive CYP2D6 metabolisers

Patients who are CYP2D6 poor metabolisers may exhibit higher mexiletine blood levels (see section 5.2 of the SmPC). A period of at least 7 days before dose increase must be respected to ensure that steady-state levels are reached, irrespective of the patient's CYP450 polymorphism.

Method of administration

Oral use.

The capsules should be swallowed with water, avoiding the supine position. In case of digestive intolerance, capsules should be taken during a meal.

Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

CHAPTER 7

Supply chain, Tariff status and Drug Price

Product and Ordering Details

(Namuscla 167mg corresponds to Mexiletine Hydrochloride 200mg as per SmPC)[1]

Supply

For initial orders, please contact Lupin Healthcare (UK) to allow access for purchase of Namuscla (mexiletine) against your account.

Email: information@lupin.com

Telephone: +44 (0) 1565 751 378 Option 2 or ext:218

Product can then be ordered from Lupin's distribution partner **Alloga UK**. Contact details are below:

Email: allogauk.orders@alloga.co.uk

Phone Orders: + 44 (0) 1773 441702/ + 44 (0) 1773 441700

General lead time from order placement to delivery is 24-48 hours.

Product information for Purchase Orders:

Product Description	EAN Code	PiP Code	Alloga SKU	List Price
Namuscla (Mexiletine) 167mg x 100 Capsules	5060346430393	409-7655	509874	£5,000*

(* Confidential special agreement pricing available from Lupin for NHS Trusts. Price agreement needs to be set up with Lupin in advance of ordering)

NHS funding arrangement

In England as of 1st April 2019, Namuscla for Non dystrophic myotonia is funded by NHS England as part of an interim agreement and therefore is a pass-through (non tariff/ ex PBR) drug with no impact on local trust budget.

Figure 23. Photos of the inner and outer packaging

Note: not to size

Lupin's Namuscla (Mexiletine) Capsules are Swedish orange hard shell gelatin capsules (20 mm) filled with white powder

Pack size: 60mm x 80mm x 147mm

CHAPTER 8

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CHAPTER 9

Appendices

1. NHS England templated circular

NHS England

Recipients Name
Address 1
Address 2
Address 3
Address 4
Postcode

Team/ Directorate
NHS England
Address 1
Address 2
Address 3
Postcode

Telephone

Email Address

Date

Dear <Medical Director>

NaMuscla® (Mexiletine) for the treatment of myotonia in patients with non-dystrophic myotonic disorders

I am writing to advise you regarding NHS England's position on a recently licensed presentation of mexiletine (NaMuscla®) for the treatment of myotonia in patients with non-dystrophic myotonic disorders. This letter advises on where the technology will be commissioned by NHS England and under what circumstances. If your Trust does not meet the definition of a specialised centre and/or cannot meet the conditions within this letter and patients may benefit from the intervention then you should consider onward referral to a specialised neurosciences centre.

Non-dystrophic myotonic disorders are rare neuromuscular conditions. Typically, patients experience adolescent-onset stiffness in their arms, legs and face. It varies in severity but is often disabling; it restricts movement and limits engagement in work or tasks that require motor activity. Many patients cannot do a full-time job and require walking aids.

There are thought to be about 330 affected patients in England. Most patients are diagnosed at the Centre for Neuromuscular Diseases at the National Hospital for Neurology and Neurosurgery, Queen Square. They are given treatment management advice and prescribed treatment by the centre. Recommended drugs may also be prescribed more locally by regional neurosciences centres. One of the drugs recommended by the national centre is mexiletine. This medicine historically has been available in 200mg, 100mg and 50mg mexiletine HCl capsules, imported from Canada via special license.

On 28 January 2019 Lupin Healthcare (UK) Limited launched NaMuscla® 167mg capsules, which is equivalent to a 200mg mexiletine HCl per capsule, for the treatment of myotonia in adults with non-dystrophic myotonic disorders. The maximum recommended dose is 500mg Namuscla (equivalent of 600mg mexiletine HCl daily).

Mexiletine is currently in tariff but will be excluded from tariff from 1 April 2019 for treatment of patients with non-dystrophic myotonia. Therefore, from April 1st 2019 NHS England will commission mexiletine including NaMuscla® as a "pass through" drug for patients with non-dystrophic myotonia within specialised neurosciences centres.

Trusts should prescribe only NaMuscla® for any individual patient doses that are a multiple of 167mg (or the equivalent of 200mg mexiletine HCl.

It should be noted that mexiletine including NaMuscla® will only be funded for patients for this indication when registered via the Blueteq system and where an appropriately constructed MDT has approved its use within specialised neurosciences centres.

This letter gives the required one month's notice as per Schedule 2 Part G (Other Local Agreements, Policies and Procedures) of your Specialised Services contract for prior approval for this treatment/indication. From one month of the date specified above, NHS England will only reimburse this treatment for patients that have been confirmed as meeting the eligibility criteria via the formal Prior Approval Scheme (i.e. Blueteq). You may wish to use the prior approval mechanism earlier than this to expedite access to NaMuscla®.

In addition, approved centres will be required to:

- Be commissioned by NHS England for the provision of specialised neurosciences services to ensure appropriate contractual arrangements are in place
- Comply with treatment indications as defined in the Blueteq form
- Register and comply with data collection required for the prescribing of high cost drugs (Blueteq)
- Purchase NaMuscla® (mexiletine) at the approved discounted price

For Clarity:

1. NHSE will fund NaMuscla® (mexiletine) as a pass-through drug for non-dystrophic myotonic disorders.
2. MHRA have confirmed that the unlicensed 50mg and 100mg mexiletine capsules can continue to be imported from Canada for other doses where a licensed product is not available.
3. Namuscla® (mexiletine) and the imported, unlicensed 50mg and 100mg mexiletine capsules will be funded within tariff for other indications (note that these indications predominantly fall under CCG commissioning responsibility) NICE is considering whether or not to evaluate NaMuscla® (mexiletine) under its Technology Appraisal programme.

Any enquiries from NHS organisations about the interim price offer or commercial arrangements should be directed to: information@lupin.com or telephone 01565 751378

Providers of neurosciences services should engage with their local specialised commissioning team to consider the implications of implementing this guidance.

I would be grateful if you could cascade this information to relevant clinical teams within your organisation to support the consistent adoption of the policy nationally.

With best wishes

<insert name and title>

Cc Provider Chief Executive

2. MHRA guidance

1. MHRA guidance: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf
   a. “An unlicensed medicinal product should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient” – section 2.2
   b. “The requirement for a “special need” relates to the special clinical needs of the individual patient. It does not include reasons of cost, convenience or operational needs” – section 2.3
   c. “if a UK licensed product can meet the clinical need, even off-label, it should be used instead of an unlicensed product” – section 2.4

3. Blueteq form

Click here to access the guidelines/NICE algorithm

NHS England - Initial Funding Application - Mexiletine (NaMuscla®) for the treatment of myotonia in adults with non-dystrophic myotonic disorders.			
Patient NHS No:		**Trust:**	
Patient Hospital No:		**Practice Code:**	
Patient's Initials and DoB:		**GP Postcode:**	
Choose Consultant:			
Consultant Name:		**Other Contact Details:**	
Notification Email Address:	(@NHS.net account ONLY)		
Treatment Start Date:			
BY TICKING THESE BOXES AND SUBMITTING THE APPLICATION THE CLINICIAN IS CONFIRMING THE PATIENT MEETS ALL THE CRITERIA BELOW.			

Please indicate whether patient meets the following criteria:	**Please tick**
1. I confirm the patient has been diagnosed with myotonia associated with a non-dystrophic myotonic disorder.	☐ Yes ☐ No
2. I confirm that the licensed product NaMuscla®* has been prescribed for doses of 167mg daily and multiples thereof. Namuscla 167mg is equivalent to mexiletine HCL 200mg capsules. *This product is not licensed for use in children (ie <18 years of age). Imported mexiletine in strengths of 50mg and 100mg may therefore be prescribed	☐ Yes ☐ No
3. I confirm the use of mexiletine has been discussed at a multi-disciplinary team (MDT) meeting which must include at least two consultants in the subspecialty with active and credible expertise in the relevant field of whom (in the case of prescribing for a child) at least one must be a paediatric neurologist.	☐ Yes ☐ No

4. Alert cards

Namuscla (mexiletine hydrochloride) Patient alert card

This alert card provides additional information on the risk of cardiac arrhythmia (irregular heartbeat) with Namuscla.
Please show it to any doctor, nurse, dentist or pharmacist if they want to treat you with other medicines (this includes medicines sold in pharmacies and herbal treatments).

Why did I get this card?

Namuscla contains mexiletine and some patients taking mexiletine may develop cardiac arrhythmia (irregular heartbeats) which can be life-threatening.

What should I do with this card?

- This card should be kept with you all the time - place it for instance in your wallet or purse
- Inform your doctor/ dentist/ nurse/ pharmacist about your ongoing medications and show them this card before starting any new medication while on treatment with Namuscla

What are the symptoms of cardiac arrhythmia?

Typical symptoms of cardiac arrhythmia include:
- feel like your heart is beating too hard or too fast (palpitations)
- chest pain
- shortness of breath
- light-headedness, dizziness or fainting

Seek urgent medical attention if you experience any of these symptoms!

See reverse of card

Write your treatment and doctor's details below:

Start date of taking Namuscla: _____

Patient Name: _____

Patient contact details: _____

Doctor's Name: _____

Doctor's contact number: _____

What else do I need to know?

Your doctor should perform tests to check on your heart and electrolyte levels before and after starting mexiletine. The heart tests should include a heart wave tracing (electrocardiogram or ECG). If you have any heart problems or are at risk of developing them then you may need closer monitoring particularly after increases in the dose of mexiletine. Please follow your doctor's instructions.

Do not take more than 3 capsules of Namuscla a day, do not take a double dose to make up for a forgotten dose.

Where can I get more information?

See the Namuscla package leaflet for more information or contact
EU-PV@lupin.com
or visit: www.medicines.org.uk/emc/company/3291

LUPIN NEUROSCIENCES

Version 1.1, approved by MHRA Dec. 2018

5. HCP prescribing leaflet for minimising risk

Patient counselling

Before starting treatment with Namuscla, healthcare professionals should:

- Discuss the risk of cardiac arrhythmias with patients and tell them to seek urgent medical attention if they experience any symptoms of an arrhythmia including palpitations, chest pain, light headedness, shortness of breath and syncope;
- Tell patients to inform their physician if they develop any new medical problems including hepatic dysfunction and cardiac disease or if they start any new medication;
- Complete their name and contact details on the patient alert card and give it to the patient.

Reporting adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of Namuscla.

HCPs are asked to report any suspected adverse reactions via the Yellow Cards website https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

Alternatively, prepaid Yellow Cards for reporting are available by writing to FREEPOST YELLOW CARD (no other address details necessary), by emailing yellowcard@mhra.gov.uk, at the back of the British National Formulary (BNF), by telephoning the Commission on Human Medicines (CHM) free phone line: 0800 731 6789, or by downloading and printing a form from the Yellow Card section of the MHRA website

Adverse reactions should also be reported to Lupin via email to:
EU-PV@lupin.com or by phone 01748828380

Namuscla (mexiletine) – Important information on minimising the risks of cardiac arrhythmia and severity of adverse reactions in those with hepatic impairment

Brief introduction

This educational guide is essential to ensure the safe and effective use of Namuscla and manage the risk of cardiac arrhythmia and the risk of adverse reactions in people with reduced mexiletine clearance due to hepatic dysfunction. It aims to educate healthcare professionals (HCPs) to perform cardiac screening procedures in all patients before Namuscla initiation and to exclude those at greater risk of developing cardiac arrhythmias.
The guide aims to support HCPs to be cautious with dosing of patients with hepatic dysfunction and exclude patients with hepatic impairment to reduce the risk of, adverse reactions due to reduced mexiletine clearance in those patients. This educational guide is not promotional but contains important risk minimisation information for HCPs.

General information about Namuscla

The information in this educational material should always be read in conjunction with the Summary of Product Characteristics (SmPC) of Namuscla, please refer to the SmPC before prescribing Namuscla which is available on https://www.medicines.org.uk/emc/company/3291.

Namuscla is indicated for symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

Namuscla is not licensed for use in patients with myotonic dystrophy types 1 and 2 (off-label use).

Namuscla is a sodium channel blocking drug that can cause or exacerbate cardiac arrhythmias in some people due to its cardiac effects. All patients should be screened for cardiac and electrolyte disorders before starting Namuscla and cardiac and electrolyte monitoring is also required during treatment, particularly during dose increments.

Prescribing Information: NaMuscla® *(Mexiletine hydrochloride)*
See Summary of Product Characteristics for full prescribing information.

Active Ingredients Each capsule contains mexiletine hydrochloride corresponding to 166.62 mg mexiletine. **Indication** NaMuscla is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders. **Dosage and Administration** NaMuscla is administered orally. The recommended starting dose is 167 mg daily (1 capsule per day). After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333 mg daily (2 capsules per day). After at least 1 further week of treatment, based on clinical response, dose can be further increased to 500 mg daily (3 capsules per day). Maintenance treatment is between 167 mg – 500 mg daily (1 to 3 capsules per day), according to the intensity of symptoms and the clinical response, taken regularly throughout the day. The dose should not exceed 500 mg/day. Regular reassessment should be implemented, not to continue long-term treatment in a patient not responding or not experiencing benefit of the treatment. **Contraindications** Hypersensitivity to the active substance, or to any of the excipients. Hypersensitivity to any local anesthetic. Ventricular tachyarrhythmia. Complete heart block (i.e. third-degree atrioventricular block) or any heart block susceptible to evolve to complete heart block (first-degree atrioventricular block with markedly prolonged PR interval (≥ 240 ms) and/or wide QRS complex (≥ 120 ms), second-degree atrioventricular block, bundle branch block, bifascicular and trifascicular block). Myocardial infarction (acute or past), or abnormal Q-waves. Symptomatic coronary artery disease. Heart failure with mid-range (40-49%) and reduced (<40%) ejection fraction. Atrial tachyarrhythmia, fibrillation or flutter. Sinus node dysfunction (including sinus rate < 50 bpm). Co-administration with medicinal products inducing torsades de pointes. Co-administration with medicinal products with narrow therapeutic index. Prescribers should consult the summary of product characteristics in relation to other adverse events. **Warnings & Precautions** Mexiletine may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed. **Pregnancy, Lactation & Fertility** There are no or limited amount of data from the use of mexiletine in pregnant women. Limited clinical data of the use of mexiletine in pregnant women shows that mexiletine crosses the placenta and reaches the foetus. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of mexiletine during pregnancy. Mexiletine is excreted in human milk. There is insufficient information on the effects of mexiletine in newborns/infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from mexiletine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. The effects of mexiletine on fertility in humans have not been studied. Animal studies with mexiletine do not indicate harmful effects with respect to fertility. **Effects on the ability to drive or use machines** Mexiletine may have minor influence on the ability to drive and use machines. Fatigue, confusion, blurred vision may occur following administration of mexiletine. **Undesirable Effects** Insomnia, somnolence, headache, paraesthesia, vision blurred, vertigo, tachycardia, flushing, hypotension, abdominal pain, nausea, acne, pain in extremities, fatigue, asthenia, chest discomfort, malaise **Overdose** Fatal outcomes have been reported for acute overdoses at 4.4 g of mexiletine hydrochloride ingestion but survival has also been reported following acute overdose of approximately 4 g of oral mexiletine hydrochloride. The symptoms of mexiletine overdose include neurological disorders (paresthesia, confusion, hallucination, seizure) and cardiac disorders (sinusal bradycardia, hypotension, collapse, and in extreme cases, cardiac arrest). Overdose treatment is mainly symptomatic. The seriousness of the symptoms may require hospital supervision. In case of bradycardia with hypotension, intravenous atropine should be used. In case of seizure, benzodiazepines should be used. **Price of NaMuscla®:** £ 5000 per pack of 100 capsules **Marketing Authorization Holder** Lupin Europe GmbH, Hanauer Landstrasse 139-143, 60314 Frankfurt am Main, Germany **Marketing Authorization Number** EU/1/18/1325/003. **Legal Category** POM **Date of Preparation or Last Review** 17 June 2019

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Lupin Europe GmbH by email at EU-PV@lupin.com

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