EU Risk Management Plan for

Namuscla

(Mexiletine hard capsule 42 mg, 62 mg, 83 mg and 167 mg)

RMP version to be assessed as part of this application:

RMP Version number: 5.3

Data lock point for this RMP: 23 March 2026

Date of final sign off: 24 March 2026

Rationale for submitting an updated RMP:

- To address the comments received from EMA on RMP V5.2 as part of the D203 questions and to align with the updated SmPC.

Summary of significant changes in this RMP:

Part I, II, V and VI	Wording of indication aligned with SmPC

Other RMP versions under evaluation: None

Table of content

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Mexiletine hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	Cardiac therapy, antiarrhythmics, class Ib, ATC code: C01BB02.
Marketing Authorisation Holder	Lupin Europe GmbH
Medicinal products to which this RMP refers	4 (not every product might be available in each country)
Invented name(s) in the European Economic Area (EEA)/United Kingdom (UK)	Namuscla 42 mg, 62 mg, 83 mg and 167 mg, hard capsules
Marketing authorisation procedure	Centralised (EU)
Brief description of the product	Chemical class Cardiac therapy, antiarrhythmics, class Ib
	Summary of mode of action The clinical usefulness of mexiletine resides in the ability to block 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.
	Important information about its composition Mexiletine is a local anaesthetic, antiarrhythmic agent, structurally similar to lidocaine, but orally active.
Hyperlink to the Product Information	Please refer to module M 1.3.1 of the eCTD sequence
Indication(s) in the EEA/UK	Current: **Namuscla 167 mg hard capsules:** Namuscla is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

	Proposed: **EEA:** **Namuscla 167 mg, 83 mg and 62 mg hard capsules:** Namuscla is indicated for the symptomatic treatment of myotonia in children aged 6 to 11 years weighing at least 20 kg, adolescents aged 12 to 17 years and adult patients ≥ 18 years with non-dystrophic myotonic disorders.
Dosage in the EEA/UK	Current: **Namuscla 167 mg hard capsules:** **Adults over 18 years of age:** 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 as required. 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 experience benefit of the treatment. Method of administration Oral use. The whole capsules should be swallowed with water, avoiding the supine position. In case of digestive intolerance, capsules should be taken during a meal.
	Not every strengths of Namuscla might be available in each country. Proposed: **Namuscla 42 mg:** Adults: The recommended starting dose of mexiletine is 167 mg daily. After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333 mg daily. After at least 1 further week

	of treatment, based on clinical response, dose can be further increased to 500 mg daily. Depending on clinical response and tolerability, a slower dose escalation may be considered based on clinical assessment. Maintenance treatment is between 167 mg – 500 mg daily, according to the intensity of symptoms and the clinical response, taken regularly throughout the day. Namuscla 83 mg capsules and/or 167 mg capsules can be substituted at equivalent doses to the 42mg capsules to rationalise the dosing regimen and reduce the capsule burden to the patient. 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 experience 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. **Namuscla 83 mg:** Adults The recommended starting dose of mexiletine is 167 mg daily. After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333 mg daily. After at least 1 further week of treatment, based on clinical response, dose can be further increased to 500 mg daily. Depending on clinical response and tolerability, a slower dose escalation may be considered based on clinical assessment. Namuscla 42 mg capsules and/or 83 mg capsules can be used for this purpose if deemed clinically appropriate. Maintenance treatment is between 167 mg – 500 mg daily, according to the intensity of symptoms and the clinical response, taken regularly throughout the day. Namuscla 167 mg capsules can be substituted at equivalent doses to the 83 mg capsules to rationalise the dosing regimen and reduce the capsules burden to the patient. 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 experience 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. **Namuscla 167 mg hard capsules:** <u>Adults from 18 years and above:</u>

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 as required.

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

Namuscla 167 mg, 83 mg and 62 mg hard capsules:

Children and adolescents (from 6 to 17 years of age):
In paediatric patients, the recommended dose is dependent on body weight:

Body weight (kg)	Mexiletine dose			
	Once daily (morning)	Twice daily (morning and evening)	Three times daily (morning, afternoon and evening)	Maximum total daily dose
20-30 kg	62 mg (1 x 62 mg)	124 mg (2 x 62 mg)	186 mg (3 x 62 mg)	≈187 mg/day
30-40 kg	83 mg (1 x 83 mg)	166 mg (2 x 83 mg)	249 mg (3 x 83 mg) Alternative: 248 mg (4 x 62 mg)	≈250mg/day
40-60 kg	124 mg (2 x 62 mg)	248 mg (4 x 62 mg)	372 mg (6 x 62 mg)	≈375 mg/day
≥ 60 kg	167 mg (1 x 167 mg or 2 x 83 mg)	334 mg (2 x 167 mg or 4 x 83 mg)	501 mg (as 3 x 167 mg or 6 x 83 mg)	≈500 mg/day

Children less than 6 years of age

The safety and efficacy of mexiletine in children aged below 6 years or weighing below 20 kg have not yet been established. No data are available.

Pharmaceutical form(s) and strengths in the EEA

Current:

Form: Hard capsule

	Strength:167 mg
	Proposed: Form: Hard capsule Strengths: 62 mg, 83 mg and 167 mg
Pharmaceutical form(s) and strengths in the GB/UK	Form: Hard capsule Strengths: 167 mg
	Proposed: Form: Hard capsule Strengths: 42 mg, 62 mg, 83 mg and 167 mg
Is/will the product be subject to additional monitoring in the EU/UK?	No

Part II: Safety specification

This RMP was prepared for Namuscla 62 mg, 83 mg and 167 mg, hard capsules authorised under centralised procedure (Article 8.3).Relevant safety information is included in the respective modules below.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Mexiletine is indicated for the symptomatic treatment of myotonia in children aged 6 to 11 years weighing at least 20 kg, adolescents aged 12 to 17 years and adult patients ≥ 18 years, with non-dystrophic myotonic disorders.

Myotonic disorders
Myotonic disorders are a heterogeneous group of inherited, rare neuromuscular disorders caused by a malfunction of skeletal ion channels so called channelopathy. This results in repetitive depolarisation of the muscle membrane which share the main clinical symptom of delayed muscle relaxation after voluntary contraction leading to myotonia.

The two main subgroups of myotonic disorders are non-dystrophic myotonia and dystrophic myotonia.

Myotonic dystrophy type 1 (DM1) affects facial and distal muscles and is the most common type of myotonic disorders. The other form of myotonic dystrophy type 2 (DM2) typical affects proximal myotonic muscles. Less common myotonias including the two forms of myotonia congenita (MC), are non-dystrophic myotonias; Myotonia congenita- autosomal dominant Thomsen MC and Becker MC respectively. Other non-dystrophic myotonic disorders include paramyotonia congenita, adynamia episodica hereditaria, and myotonia fluctuans (Ref. Kurihara. T 2005).

Incidence:
In most populations myotonic dystrophy is the most common muscular dystrophy. With an estimated prevalence of 10 per 100,000 people affected in European populations, it is estimated that upwards of 6500 people to be affected in the UK. (Ref. Wood L. 2017).

Prevalence:
Based on available data the prevalence for non-dystrophic myotonias is roughly estimated between 0.2 and 1 per 10,000 (Ref. Public summary of opinion on orphan designation 2014).

Demographics of the population in the proposed indication and risk factors for the disease:
With exception of Becker MC, which is an autosomal recessive genetic disorder, all myotonic disorders are autosomal dominant inherited neuromuscular diseases. In general, both sexes are affected equally, and myotonic symptoms can occur at any age including early childhood. Age of onset of symptoms of myotonic disorder depend on the severity of the disease (Ref. Public summary of opinion on orphan designation 2014).

The main existing treatment options:
Treatment is directed towards activity modifications, avoidance of triggers for myotonia and weakness. In some patients with disabling myotonia pharmacological therapy including mexiletine, tocainide, procainamide, phenytoin or acetazolamide is found to be beneficial.

Natural history of the indicated condition in untreated population, including mortality and morbidity:

Myotonic disorders are long-term debilitating conditions due to muscle stiffness, and, sometimes muscle pain and are associated impaired mobility and activity. The typical location of stiffness varies depending on the underlying disorder but commonly seen in the eyelids, mouth, hands, and proximal legs. Common triggers include cold and stress, and symptoms can worsen during pregnancy and menstruation. Most forms of myotonia demonstrate a "warm-up" phenomenon, where myotonia improves with repeated action. In contrast, paradoxical myotonia or paramyotonia worsens with repeated use. Some forms of myotonia are also associated with diffuse muscle hypertrophy.

Myotonic disorder is a cause of death classified under the ICD-10 chapter **diseases of the nervous system** and sub-chapter **diseases of myoneural junction and muscle** and is defined by the ICD-10. Annual Mortality rate of myotonic disorders per 100K people was 0.086.

In 2015 278 people had as the underlying cause of death myotonic disorders in the United States. Additionally, myotonic disorder was reported in 115 other deaths as a contributing cause. The highest death rate was among men (males accounted for 55.0% of deaths). Caucasians, and the age group of 65 to 74 years. In males it has increased by 8.1% between 2010 and 2015 while for females it has decreased by 0.4% between 2010 and 2015.

In 2015 when myotonic disorders were the underlying cause of death, unspecified respiratory failure, unspecified pneumonia and pneumonitis due to food and vomit were the leading causes of death (Health groove).

Important co-morbidities:
There is limited information regarding the impact of NDM on patient's quality of life. However, these patients may be at increased risk of developing pain, fatigue and poor physical functioning. Pain is most common symptom presented by NDM patients.

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

Single dose toxicity

Single doses of mexiletine induced convulsive symptoms, related to the blockade of the sodium channel in all the species tested. The time of occurrence was short for the IV route and delayed from some minutes for the oral dose. The maximal non-lethal doses were in the same range across species via both the oral (64-100 mg/kg) and the IV (10-15 mg/kg) routes, and the LD50's, although decreasing slightly across species, were in a similar range. This suggests that these toxic effects are related to the C_{max} of mexiletine rather than to its AUC, this being consistent with the fast occurrence of the convulsive symptoms.

In the juvenile rat study, the NOAEL dose of 90 mg/kg is approximately 2x of proposed clinical dose in humans 501 mg/day, considering body surface area (BSA) through allometric scaling factor of 6.2 for rats. Although, the steady-state exposure levels at the proposed clinical dose in humans (501 mg/day; administered as 167 mg TID), with mean AUC and Cmax values of 8551.64 ng/mL and 1392.21 ng/mL, respectively. The corresponding exposure margin in rat study at NOAEL: 90mg/kg/day were 0.7x to 1x and 0.1x to 0.8 for Cmax and AUC respectively on day 84. It is to be noted that corresponding exposure margins are approximately 1x for Cmax and 0.5 to 0.8x for AUC on PND7/PND21. In terms of body surface area juvenile rat study is covering two-fold of proposed human dose and approximately similar order of

magnitude exposure (1x) for Cmax, however slightly lower for AUC. The highest dose 90mg/kg in present study was selected based on the results of the preliminary juvenile DRF study (no. AB21945). Dose of 300 mg/kg/day was not tolerated, and animals were euthanised. One animal given 150 mg/kg/day (in Mexiletine HCl) was sacrificed in poor health status with a slight tendency to a reduced body weight gain during the first week of dosing for the other animals at 150 mg/kg/day. In view of these findings and exposure data, a high dose of 90mg/kg is justified and this also posses' limitations to go above 90mg/kg to achieve higher exposure in given species. Therefore, a traditional safety margin based on systemic exposure cannot be established in this model. Despite this limitation, the juvenile rat model remains relevant for paediatric safety assessment.

Maximum non-lethal dose and LD_{50} following acute oral and IV doses of mexiletine across animal species

Species	Oral route			Intravenous route	
	LD_{50} (mg/kg)	Max non-lethal dose[a]		LD_{50} (mg/kg)	Max non-lethal dose[a] (mg/kg)
		(mg/kg)	HED[b] (mg/kg)		
Mice	260 - 400	100	8.1	35 - 50	10
Rats	240 - 630	100	16	27 - 30	15
Rabbits	160 - 450	< 100	< 32	---	---
Dogs	112 - 356	64	36	19-60	12.5

[a]: Lowest value recorded across the studies.
[b]: considering allometric scaling factors of 12.3 for mice, 6.2 for rats, 3.1 for rabbits and 1.8 for dogs.
HED= Human equivalent dose

The clinical findings were consistently related to the blocking effects of mexiletine on the brain and skeletal muscle sodium channels in all the species tested. Findings consisted in ataxia, tremor at the lowest doses. Clonic and tonic convulsions and several associated symptoms (mydriasis, hyperventilation, dyspnoea, opisthotonus and spasms) appear with increasing doses, followed by rapid death at the highest doses. Signs of toxicity, associated to the most toxic doses include vomiting in dogs and necrosis at the sites of administration (gastro-intestinal tract in dogs for the oral route).

Repeat-dose toxicity
The main toxicological effects noted during the repeat-dose toxicity studies were related to exaggerated pharmacological effects. They were not apparent at doses up to 40 mg/kg in rats and 20 mg/kg in dogs. Oral administration of mexiletine led to atactic movements, tremor and signs of convulsive state with dose-dependent incidence, severity and duration. These signs appeared at 80 mg/kg in rats and 30 mg/kg in dogs.

The results of the repeated dose toxicity studies suggest that the NOAEL of mexiletine administered orally is <40 mg/kg/day in rats and 3 mg/kg/day in dogs. Considering allometric scaling factors of 6.2 for rats and 1.8 for dogs, as well as the dosing regimen of 3 x 200 mg/day to 60 kg patients, these NOAELs correspond to <0.65-fold and 0.17-fold the human therapeutic dose in rats and dogs, respectively.

Reproductive/developmental toxicity
Fertility, embryotoxicity (teratogenicity) and peri-/post-natal toxicity studies in rats and rabbits after oral and IV administration did not show any effect of mexiletine on embryos and new-borns, besides expected effects on the mother and the foetus.
Genotoxicity

The Ames test did not show any mutagenic activity. In both studies, mexiletine was soluble and not cytotoxic at concentrations up to 3000 µg/plate and demonstrated no potential to induce reverse mutation in these tests. The incompleteness of the genotoxicity programme is balanced by the lack of carcinogenic potential demonstrated in the 78-week carcinogenicity study in mice and in the 2-year study in rats, as well as by the absence of genotoxic findings during the long term therapeutic use of mexiletine.

Carcinogenicity
The absence of carcinogenic potential of mexiletine has been demonstrated in the studies conducted following oral administration in food for 78 weeks in mice and 105 weeks in rats. No toxicokinetic studies evaluated the systemic exposure to mexiletine. However, no indication of a potential carcinogenic risk of mexiletine has been identified during its therapeutic use and the carcinogenic potential of mexiletine may be considered to be very low

Safety pharmacology

General safety pharmacology
Several studies exploring the effects of mexiletine on the autonomic functions and centrally stimulant agents address partly the absence of receptor studies. The agonistic effect observed on the parasympathetic system at a dose of 30 mg/kg orally or subcutaneously in mice results in mydriasis and slightly increased carbachol-induced salivation. The corresponding Human Equivalent Dose (2.4 mg/kg) is relevant to the therapeutic dose of 3.3 mg/kg, when considering an allometric scaling factor of 12.3 for mice.

Cardiac system
The overall results of the studies evaluating the cardiac safety pharmacology of mexiletine suggest that, upon administration of therapeutic oral doses, very slight cardiac effects (possible increased QRS, decreased QTc, increased PR intervals), tachycardia are likely to occur, which are related to the pharmacological properties of mexiletine.

Central nervous system
The results of the studies evaluating the safety pharmacology of mexiletine on the CNS suggest that administration of a therapeutic dose to humans may lead to motor coordination side effects at doses corresponding to the equivalent therapeutic dose in behavioural studies, while higher doses may lead to ataxia.

Other systems
The increased respiratory rate and decreased tidal volume noted following IV administration of mexiletine is of uncertain relevance to the oral route. Mexiletine had no significant effects on the gastrointestinal and renal systems upon oral administration.

The outcome of the safety pharmacology evaluation of mexiletine suggests that adverse effects related to the mode of action of mexiletine are likely to occur on the cardiovascular and CNS systems upon administration of therapeutic doses. The effects identified include possible changes in the QRS, QTc and PR intervals, tachycardia, motor incoordination, ataxia, as well as mydriasis and salivation.

Part II: Module SIII - Clinical trial exposure

The clinical data already known for Mexitil® is directly applicable to Lupin's Namuscla. In addition, Lupin has completed 02 studies for paediatric use as part of PIP for Mexiletine.

1. MYOMEX:

Study Title: The MYOMEX study was a multicentre, randomised, double-blind, placebo-controlled, cross-over study aimed to compare the effects of mexiletine vs. placebo in patients with myotonia congenita (MC) and paramyotonia congenita (PC) (Vicart S et al, 2021).

Objectives:

- To investigate the efficacy and safety of mexiletine in nondystrophic myotonias.

Primary Endpoint: The score of stiffness severity self-reported by the patients on a 100-mm visual analogic scale (VAS) ranging from “no stiffness at all” (0 mm) and “worst possible stiffness” (100 mm) was assessed at the beginning (Visits 2 and 4) and at the end (Visits 3 and 5) of each period.

Secondary Endpoint: The second efficacy outcomes were assessed at baseline (Visit 2) and at the end of each period (Visits 3 and 5)

- Time needed to stand up from a chair, walk around the chair and sit down again (chair test). Impact of the disease on health-related quality of life

- EMG (Electromyography)tests were performed to evaluate the decline of the compound muscle action potential (CMAP) amplitude.

- The Clinical Global Impression (CGI) for efficacy was assessed at the end of each period.

- At the end of the study, patients were asked on their preference for one or the other study period and for their willingness to continue mexiletine.

Results: This study demonstrated a significant effect of mexiletine versus placebo in patients with nondystrophic myotonia. The primary criterion was stiffness self-reported by patients and it was significantly improved in both periods of the cross-over study. The other efficacy tests confirmed the positive impact of mexiletine on symptoms of nondystrophic mytonias. Clinical improvement with mexiletine was reflected in quality of life with a significant treatment effect on all domain of the Individualized Neuromuscular Quality of Life (INQoL) questionnaire. No serious adverse event was reported. Adverse events were more frequently reported in the Gastrointestinal Disorders System Organ Class (SOC) (8 events in 7 patients overall, 24% of subjects in the mexiletine period and 8% of subjects in the placebo period). The adverse events reported in at least two patients during mexiletine treatment which were considered as related to mexiletine were upper abdominal pain (*n* = 2), nausea (*n* = 2) and insomnia (*n* = 3), all reported in patients with PC. An adverse event (palpitations) led to mexiletine discontinuation in one MC patient. It occurred in a stressful context and resolved spontaneously in few hours. No significant variations were observed in 12-lead ECG or in the portable ECG device parameters (HR, PR, QRS, QTc) between baseline and the end of the treatment period, either with placebo or mexiletine.

Conclusion: Mexiletine significantly improved stiffness and quality of life in patients with nondystrophic myotonia and was well tolerated over the 18-day treatment period.

The following sections therefore describe data on mexiletine from the MYOMEX trial. Patient exposure to mexiletine throughout the study is provided in Table SIII.1 and SIII.2. Patients

received mexiletine and placebo for 2 periods of about 18 days each. Actual mean treatment durations were 18.7 days (Standard deviation: 1.8) for placebo and 19.0 days (Standard deviation: 2.4) for mexiletine.

Table SIII.1: Duration of exposure

Cumulative for myotonic disorders (person time)		
Duration of exposure	Patients	Person time
200 mg/day for 2 days, 400 mg/day for 2 days, 600 mg/day for 14-18 days	25	Mean ± SD treatment duration: 20.2 ± 2.2 days Median (range): 20 (12-22) days **Overall exposure: 1.4 patient-years**

Table SIII.2: Age group and gender

Parameter	**Diagnosis**		**mITT population**			**PP population**		
			Treatment sequence			**Treatment sequence**		
			Placebo-mexiletine	**Mexiletine-placebo**	**Total**	**Placebo-mexiletine**	**Mexiletine-placebo**	**Total**
Age (years)	MC	N	6	7	**13**	4	6	**10**
		Mean (SD)	34.9 (8.3)	44.8 (13.6)	**40.3 (12.2)**	35.4 (10.3)	45.1 (14.9)	**41.2 (13.6)**
		Med [range]	34.8 [23.7;48.4]	44.9 [20.2;66.0]	**40.9 [20.2;66.0]**	34.8 [23.7;48.4]	46.0 [20.2;66.0]	**42.9 [20.2;66.0]**
	PC	N	7	5	**12**	7	5	**12**
		Mean (SD)	45.6 (12.9)	46.46 (6.2)	**46.0 (10.2)**	45.6 (12.9)	46.5 (6.2)	**46.0 (10.2)**
		Med [range]	49.2 [21.8;59.6]	45.5 [39.0;52.9]	**48.9 [21.8;59.6]**	49.2 [21.8;59.6]	45.5 [39.0;52.9]	**48.9 [21.8;59.6]**
	Total	**N**	**13**	**12**	**25**	**11**	**11**	**N=22**
		Mean (SD)	40.7 (12.0)	45.5 (10.8)	**43.0 (11.4)**	41.9 (12.6)	45.7 (11.3)	**43.8 (11.8)**
		Med [range]	37.3 [21.8;59.6]	45.2 [20.2;66.0]	**44.9 [20.2;66.0]**	48.4 [21.8;59.6]	45.5 [20.2;66.0]	**46.3 [20.2;66.0]**
Gender	MC	N	6	7	**13**	4	6	**10**
		Male, n (%)	5 (83.3%)	6 (85.7%)	**11 (84.6%)**	4 (100.0%)	5 (83.3%)	**9 (90.0%)**
		Female, n (%)	1 (16.7%)	1 (14.3%)	**2 (15.4%)**	0	1 (16.7%)	**1 (10.0%)**
	PC	N	7	5	**12**	7	5	**12**
		Male, n (%)	4 (57.1%)	2 (40.0%)	**6 (50.0%)**	4 (57.1%)	2 (40.0%)	**6 (50.0%)**
		Female, n (%)	3 (42.9%)	3 (60.0%)	**6 (50.0%)**	3 (42.9%)	3 (60.0%)	**6 (50.0%)**
	Total	**N**	**13**	**12**	**25**	**11**	**11**	**22**
		Male, n (%)	9 (69.2%)	8 (66.7%)	**17 (68.0%)**	8 (72.7%)	7 (63.6%)	**15 (68.2%)**
		Female, n (%)	4 (30.8%)	4 (33.3%)	**8 (32.0%)**	3 (27.3%)	4 (36.4%)	**7 (31.2%)**

MC: Myotonia congenita; Med: median; mITT: modified intention-to-treat population; PP: Per Protocol PC: Paramyotonia congenita; SD: Standard deviation

Table SIII.3: Dose

Dose of exposure	Patients	Patient exposure
Mexiletine 200 mg for 2 days	25	Mean ± SD treatment duration: 20.2 ± 2.2 days Median (range): 20 (12-22) days
Mexiletine 400 mg for 2 days		
Mexiletine 600 mg for 14-18 days		
Total		**1.4 patient-years**

Table SIII.4: Ethnic origin

Not applicable for MYOMEX study.

2. Paediatric Investigation Plan (PIP)

A) PIP 4 (MEX-NM-301)

Study Title:
An Open-Label, Non-Comparative Study to Evaluate the Steady-State Pharmacokinetics, Safety, and Efficacy of Mexiletine in Adolescents and Children with Myotonic Disorders.

Objectives:

Primary

The co-primary objectives of this study are

- To evaluate the safety of mexiletine in adolescents (aged 12 to <18 years) and children (aged 6 to <12 years) for the treatment of myotonia
- To evaluate the efficacy of mexiletine for the treatment of myotonia

Secondary

The secondary objectives are:

- To evaluate the efficacy of mexiletine for the treatment of myotonia as assessed by patient-reported outcomes
- To evaluate efficacy and tolerability of mexiletine as measured by Clinical Global Impression (CGI) scale indices
- To determine changes in health-related quality-of-life as measured by the PedsQL Quality of Life and Neuromuscular module.
- To determine the steady-state pharmacokinetics (PK) of mexiletine in children (6 to <12 years) and adolescents (aged 12 to <18 years)
- To assess the acceptability of the capsule formulation.
- Palatability of alternative administration (capsule content with milk/juice or sprinkled on food) by 5-point facial hedonic scale correlated with 100-point VAS.

Results: In this study, 7 of 12 subjects (58.3%) reported Treatment Emergent Adverse Events (TEAEs). The most frequently reported System Organ Class category was Gastrointestinal disorders including the most frequently reported TEAE (preferred term) of abdominal pain (3 subjects (25%) with 3 events) and nausea (3 subjects (25%) with 4 events). All TEAEs were considered mild and most were unrelated. Two subjects including headache, nausea, vertigo, cardiac palpitations, diarrhea, abdominal pain, nausea (2 events), asthenia, pallor, reported related TEAEs; drug was temporarily withdrawn/delayed in both cases. No deaths, serious

TEAEs, or TEAEs leading to study discontinuation were reported. These TEAEs are consistent with the Namuscla SMPC which list the most commonly reported adverse reactions in patients treated with mexiletine. One subject reported study drug interruption (due to abdominal pain, nausea and asthenia)

Conclusion: Overall, the study has demonstrated that Mexiletine was generally well-tolerated and its effectiveness has been maintained allowing patients to continue in open label extension phase.

B) PIP 7 (MEX-NM-303)

Study Title:

An Open-label Extension Study to Evaluate the Long-term Safety and Efficacy of Mexiletine in Paediatric Patients with Myotonic Disorders Who Have Completed MEX-NM-301 Study.

Objectives

The aim of this study is to obtain additional information regarding the long-term safety and efficacy of mexiletine for the symptomatic treatment of myotonia in paediatric subjects who have completed the initial paediatric study MEX-NM-301.

Co-Primary

- To assess the long-term safety and tolerability of mexiletine in paediatric patients (aged 6 to < 18 years) with myotonic disorders.
- To evaluate long-term effectiveness of oral dosing with mexiletine

Secondary

Children and adolescents aged 6 to < 18 years:

- To evaluate the efficacy of mexiletine for the treatment of myotonia as assessed by patient-reported outcomes
- To evaluate efficacy and tolerability of mexiletine as measured by Clinical Global Impression (CGI) scale indices
- To determine changes in health-related quality-of-life as measured by the PedsQL Quality of Life and Neuromuscular module.

Result and Conclusion: This study is ongoing and overall results will be updated once the study is completed.

Patient exposure to mexiletine in PIP studies is provided in Table SIII.5.

Table SIII 5: Cumulative Subjects Exposure to Study Drug in PIP studies

	Number of subjects dosed			
Clinical Trial	**Total daily dose (mg) unit dose (mg) and frequency**	**Cohort 1, 12-<18 years old**	**Cohort 2, 6-<12 years old**	**Total**
PIP4	**186** (62 mg 1 capsule 3xday)	1	3	4
	248 (2 capsules 62mg twice/day)	2	0	2
	249 (83mg 1 capsule 3xday)	0	2	2
	334 (167mg 1 capsule twice/day)	1	0	1
	372 (2 capsules 62mg 3xday)	1	0	1
	501 (167mg 1 capsule 3xday)	2	0	2
Total PIP4	**Number of subjects**	7	5	**12**
PIP7	**186** (62 mg 1 capsule 3xday)	1	3	4
	248 (2 capsules 62mg twice/day)	2	0	2
	249 (83mg 1 capsule 3xday)	0	2	2
	334 (167mg 1 capsule twice/day)	2	0	2
	372 (2 capsules 62mg 3xday)	1	0	1
	501 (167mg 1 capsule 3xday)	1	0	1
Total PIP7	**Number of subjects (total)**	**7**	**5**	**12**

[Note: Once a subject completes PIP4, they roll over to PIP 7.]

SIII 6: Gender

Clinical study	**Number of patients exposed**		**Total**
Mexiletine (Namuscla)	**Male**	**Female**	
PIP 4	5	7	12
PIP 7	5	7	12

[Note: Once a subject completes PIP4, they roll over to PIP 7.]

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria for MYOMEX trial:

- Intercurrent event which could interfere with the muscle function (infection, trauma, fracture, etc.).
- Coincidental renal, hepatic, respiratory, thyroid, other neuromuscular disease or heart disease that contraindicated mexiletine or interfered with clinical evaluation.
- Use of any of the following medications that can interfere with muscle function: diuretics, anti-epileptics (sodium channel blockers), anti-arrhythmics, corticosteroids, and beta-blockers.
- Allergy to mexiletine.
- Women of childbearing potential not using a medically-accepted contraceptive regimen.

Exclusion criteria for PIP study:

- Any clinically significant illness, laboratory findings, ECG, or other clinical symptoms, which in the opinion of the investigator could affect the patient's optimal participation in the study
- Strong inducer or inhibitor of CYP2D6 or CYP1A2 within 7 days prior to study drug administration
- Any concurrent illness, or medications which could affect the muscle function
- Seizure disorder, diabetes mellitus requiring treatment by insulin
  Concurrent participation in any other clinical trial.

Reason for exclusion: Use in patient with these conditions would either interfere with clinical evaluation and/or use of mexiletine in these conditions is contraindicated.

Is it considered to be included as missing information? Yes, use in patients with severe renal impairment is included as missing information.

Rationale: For other exclusion criteria, adequate information is available, and these have been included under important identified risks (severe cutaneous adverse reactions (SCARs), risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment and risk of toxicity of CYP1A2 substrate with narrow therapeutic window such as theophylline, caffeine or tizanidine) or important potential risks (Increased frequency of seizure episodes in patients with epilepsy).

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	

Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

Part II: Module SV - Post-authorisation experience

The approximate patient exposure is calculated based on the average daily dosage of 334 mg for Namuscla® 167mg hard capsules. The patient exposure since the launch date (28 Jan 2019) until the data lock point of this RMP (18 Sep 2025) is estimated to be 8,910 patient treatment years.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Mexiletine does not belong to a pharmacological class associated with drug abuse. Although, the abuse potential of mexiletine was not specifically studied, there is no available data which would suggest that mexiletine may lead to drug abuse.

Part II: Module SVII - Identified and potential risks

The safety of mexiletine has been investigated in 13 patients with myotonia congenita (MC) and 12 patients with paramyotonia congenita (PC) during 18 days for the symptomatic treatment of myotonic disorders (MYOMEX study). The list of safety concerns discussed below has been established based on adverse reactions identified in the MYOMEX study and on post-marketing data of the use of mexiletine in patients with myotonic disorders and in patients with ventricular tachycardia.

Important identified risks	1. Severe cutaneous adverse reactions (SCARs) 2. Cardiac arrhythmia 3. Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine 4. Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment
Important potential risks	5. Increased frequency of seizure episodes in patients with epilepsy 6. Off-label use in DM1 and DM2 patients
Missing information	7. Long term use in adult patients with myotonic disorders 8. Effect on fertility and use in pregnancy 9. Safety in elderly 10. Use in patients with severe renal impairment 11. Long-term safety in paediatric population

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

• insomnia • somnolence • hallucinations • confusional state • headache • paraesthesia • vision blurred • diplopia • dysgeusia • vertigo • flushing • hypotension • hot flush	• abdominal pain • nausea • diarrhoea • vomiting • hepatic function abnormal • acne • pain in the extremities • fatigue • asthenia • chest discomfort • malaise

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

• leukopenia • thrombocytopenia • lupus-like syndrome • seizure • speech disorders • circulatory collapse	• pulmonary fibrosis • oesophageal ulcers and perforation • drug-induced liver injury • liver disorder • hepatitis

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

None.

Known risks that do not impact the risk-benefit profile:

None.

Other reasons for considering the risks not important:

In accordance with the guidance provided in GVP module V, this population has been excluded from the clinical investigation, also no specific safety concern is associated with this potential off-lable use. Therefore removed from the list of important potential risk.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks

1. **Severe cutaneous adverse reactions (SCARs)**

Risk-benefit impact: Cases of severe cutaneous adverse reactions (SCARs) present usually with severe cutaneous eruption and one or several of these symptoms: fever, lymphadenopathy, hyper-eosinophilia, lymphocytosis and organ damage (notably liver and kidney). SCARs include acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis). This risk is considered as an important identified risk.

2. **Cardiac arrhythmia**

Risk-benefit impact: Mexiletine is a class Ib antiarrhythmic drug according to the Vaughan Williams classification, and as such, it may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed. Mexiletine should be administered with caution in patients with pre-existing cardiac conduction anomalies.

Mexiletine is contraindicated in patients with ventricular tachyarrhythmia, complete heart block, any heart 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), and co-administration with medicinal products inducing torsades de pointes. For other cardiac disorders not listed above, the benefit of the anti-myotonic 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 above are detected. Considering the severity of this risk and the requirement to closely monitor the patients for this

potentially preventable risk while on mexiletine, cardiac arrhythmia is considered as an important identified risk. Co-administration of mexiletine with a hepatic enzyme (CYP1A2 or CYP2D6) inhibitor (such as ciprofloxacin, fluvoxamine, propafenone or quinidine) significantly increases mexiletine exposure and thus the associated risk of side effects of mexiletine especially cardiac arrhythmia.

3. Risk of toxicity of CYP1A2 substrate with narrow therapeutic window such as theophylline, caffeine or tizanidine

Risk-benefit impact: Mexiletine is a potent inhibitor of CYP1A2; therefore, co-administration of mexiletine with a medicinal product metabolised by CYP1A2 such as theophylline, caffeine or tizanidine, may be associated with elevations in plasma concentrations of the concomitant medicine that could increase or prolong the therapeutic efficacy and/or adverse events, especially if the CYP1A2 substrate has a narrow therapeutic window such as theophylline, caffeine and tizanidine.

4. Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment

Risk-benefit impact: Mexiletine undergoes extensive hepatic metabolism; only 10-15% of the drug is eliminated as the parent molecule. Hepatic function has a significant influence on mexiletine pharmacokinetics given that mexiletine is primarily eliminated via hepatic metabolism. In two studies (Studies U88-0397 and U84-0946), the elimination of mexiletine was markedly retarded in patients with hepatic impairment as reflected by a prolonged elimination t1/2 (2 to 3-fold) and decreased clearance (30-60%) compared to healthy subjects. Mexiletine should be used with caution in patients with mild or moderate hepatic impairment and is not recommended in patients with severe hepatic impairment.

Important potential risk

5. Increased frequency of seizure episodes in patients with epilepsy

Risk-benefit impact: Epileptic patients need to be monitored because mexiletine can increase the frequency of seizure episodes.

6. Off-label use in DM1 and DM2 patients

Risk-benefit impact: Physcians of patients with DM type 1 and 2 may prescribe due to studies which indicate positive effects of mexiletine on myotonia in DM1 and DM2 patients. Therefore, the possibility of off-label use in DM1 and DM2 patients cannot be excluded.

Missing information

7. Long term use in adult patients with myotonic disorders

Risk-benefit impact: The information on the long-term safety of mexiletine in patients with non-dystrophic myotonic disorders has not been systematically collected so far. This needs to be monitored after marketing.

8. Effect on fertility and use in pregnancy

Risk-benefit impact: There are no or limited amount of data from the use of mexiletine in pregnant women. Myotonic disorders are usually congenital, and they begin to affect people in early childhood. The symptoms of one of these disorders can first be noticed as late as the teenage years or adulthood. Therefore, individuals in fertile age group may be exposed to mexiletine or women of childbearing age may be exposed to mexiletine during pregnancy. Limited clinical data of the use of mexiletine in pregnant women shows that mexiletine crosses the placenta and reaches the foetus. 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 or reproductive toxicity.

9. Safety in elderly

Risk-benefit impact: Experience with mexiletine in patient with myotonic disorders aged > 65 years is still limited. This population is not studied in clinical trial for mexiletine. Based on the pharmacokinetic properties of mexiletine, no dosage adjustment are required in patients aged 65 years and over.

10. Use in patients with severe renal impairment

Risk-benefit impact: The experience with mexiletine in patients with renal impairment is limited. However, the bioavailability of mexiletine does not seem to be modified in subjects with mild or moderate renal insufficiency. The elimination half-life seems to be slightly longer in patients with severe renal insufficiency or end-stage renal disease.

11. Long-term safety in paediatric population

Risk-benefit impact: Non-dystrophic and dystrophic myotonic disorders are congenital, and their onset may occur at all ages, including infancy, childhood and adolescence. The safety and efficacy of Mexiletine in children and adolescents aged 0 to < 18 years have not been established. Long-term safety and efficacy study of Mexiletine in paediatric population i.e. PIP 7 (MEX-NM-303) is ongoing. The information on the long-term safety of mexiletine in paediatric population with non-dystrophic myotonic disorders is currently under investigation.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

With the application of use in paediatric population > 6 years of age and in alignment with comments received from EMA and MHRA “Long-term safety in paediatric population” is added as missing information and “Off-label use in children (under 6 years of age) is removed.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

1. Severe cutaneous adverse reactions (SCARs)

Potential mechanisms:

Severe cutaneous adverse reactions (SCARs) to drugs cover a broad spectrum of entities mainly consisting of Stevens-Johnson syndrome and toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Despite their low annual incidence, SCARs, especially Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS syndrome, can be life threatening and responsible for severe, potentially chronic sequelae. The incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis is estimated to be two per 1 million people, whereas the incidence of DRESS syndrome in new users of antiepileptic drugs (e.g. carbamazepine or phenytoin) is estimated to be one per 1,000 to one per 10,000.

The clinical heterogeneity of SCARs might be explained by the activation of different effector or regulatory cells secreting specific cytokines. SCARs are considered to be non-immediate hypersensitivity reactions with four proposed subgroups: IVa, mediated by type 1 T helper (Th1) T cells; IVb, mediated by Th2 T cells and interleukins 5, 4, and 13, and eotaxin cytokines (as occurs in DRESS syndrome); IVc, mediated by cytotoxic T cells (as occurs in Stevens-Johnson syndrome and toxic epidermal necrolysis); and IVd, mediated by T cells and neutrophils via chemokine (C-X-C motif) ligand 8 (CXCL-8) and granulocyte-macrophage colony-stimulating factor cytokines (Ref. Duong. TA et al 2017). Several mechanistic models

have been proposed to explain the recognition by T cells of small compounds (i.e., drugs) and the ability of T cells to promote an immune response. After drug stimulation via HLA-encoded MHC proteins, immune mechanisms of SCARs include the activation of drug-specific cytotoxic T cells, inflammatory cells, or regulatory T cells (T-regs) and the differential secretion of inflammatory cytokines.

Evidence source(s) and strength of evidence:
Mexiletine is contraindicated in patients with known hypersensitivity to mexiletine, to any of the other ingredients of this product, or to any local anaesthetic as there is possibility of occurrence of severe cutaneous adverse reactions, usually severe cutaneous eruption along with fever, lymphadenopathy, hypereosinophilia, lymphocytosis or organ damage (notably liver and kidney).

Characterisation of the risk:
The frequency of this adverse event is not known and cannot be estimated from the available data.

Risk factors and risk groups:
Patients with known hypersensitivity to mexiletine or any other ingredients of this product or to any local anaesthetic are at high risk of developing SCARs.

Preventability:
Mexiletine should not be used in patients with known hypersensitivity to mexiletine, to any of the other ingredients of this product, or to any local anaesthetic.

Impact on the risk-benefit balance of the product:
Although there are bibliographic reports of SCARs due to mexiletine no such adverse events were reported during MYOMEX study.

Public health impact:
The expected post marketing frequency of occurrence and incidence of this adverse event cannot be estimated precisely from available data. This safety concern is preventable if avoided in patient already at risk and with known hypersensitivity to this product or other local anaesthetics.

2. Cardiac arrhythmia

Potential mechanisms:
Mexiletine is a class I b antiarrhythmic drug according to the Vaughan Williams classification, and as such, it may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed.

Evidence source(s) and strength of evidence:
Mexiletine should be administered with caution in patients with pre-existing cardiac conduction anomalies. The advent (under mexiletine therapy) of an atrioventricular block, a permanent complete heart block, or a sinoatrial block necessitates the interruption of the mexiletine treatment.

Characterisation of the risk:
The frequency of this adverse event is not known and cannot be estimated from the available data. Like all drugs having anti- or pro-arrhythmic effects, mexiletine can aggravate pre-existing arrhythmia or trigger new arrhythmia episodes.

Risk factors and risk groups:

Patients with Dystrophic Myotonia and patients with existing cardiac conduction abnormalities will be at a risk of developing cardiac arrhythmias. Mexiletine should be administered with caution in patients with pre-existing cardiac conduction anomalies. The benefit-risk ratio needs to be assessed on case by case basis for the benefit on the myotonia versus the risk of rhythm complication. The concomitant use of mexiletine and antiarrhythmic drug inducing torsades de pointes is contraindicated. Co-administration of mexiletine with a hepatic enzyme (CYP1A2 or CYP2D6) inhibitor (such as ciprofloxacin, fluvoxamine, propafenone or quinidine) may significantly increase mexiletine exposure and thus the associated risk of side effects of mexiletine including arrhythmias.

Preventability:
Mexiletine should not be used in patients with complete heart block, fascicular block, second- and third-degree atrioventricular block, sinus node dysfunction without any pacemaker, along with drugs inducing torsade de pointes, other anti-arrhythmic drugs or with hepatic enzyme (CYP1A2 or CYP2D6) inhibitors. Patients may inform their HCPs about ongoing treatment with mexiletine before starting any other medication. A cardiac evaluation and an ECG should be performed before and during treatment with mexiletine. Periodic ECG monitoring will be adapted individually is recommended, as required, depending on cardiac condition of patient.

Impact on the risk-benefit balance of the product:
The occurrence of any cardiac arrhythmia requires the immediate reconsideration of the benefits of pursuing the treatment with mexiletine. Mexiletine should be administered with caution in patients with pre-existing conduction anomalies. If patient (under mexiletine therapy) develops an atrioventricular block, a permanent complete heart block, or a sinoatrial block, it necessitates the interruption of the mexiletine treatment.

Public health impact:
The expected post marketing frequency of occurrence and incidence of this adverse event cannot be estimated precisely from available data. This safety concern is preventable if a cardiac evaluation and an ECG is performed before and during treatment with mexiletine. Periodic ECG monitoring, to be adapted individually, is recommended, as required, depending on cardiac condition of patient.

3. Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine

Potential mechanisms:
Mexiletine is a potent inhibitor of CYP1A2; therefore, co-administration of mexiletine with a medicinal product metabolised by CYP1A2 such as theophylline, caffeine or tizanidine, may be associated with elevations in plasma concentrations of these drugs and could significantly increase or prolong their therapeutic efficacy and/or adverse events, especially of mexiletine is co-administered with CYP1A2 substrate with narrow therapeutic window.

Evidence source(s) and strength of evidence:
A study in eight normal subjects showed a 65% mean increase in plasma theophylline levels when mexiletine was used concomitantly. In a clinical study in 12 subjects (5 healthy subjects and 7 patients with cardiac arrhythmias), the clearance of caffeine was decreased by 50% following the administration of mexiletine.

Characterisation of the risk:
If mexiletine and a CYP1A2 substrate with a narrow therapeutic window (such as theophylline, caffeine or tizanidine) are to be used concurrently, the CYP1A2 substrate blood levels should be monitored, particularly when the mexiletine dose is changed.

Increased concentrations of caffeine occurring with the co-administration of mexiletine may be of concern in patients with cardiac arrhythmia.

Risk factors and risk groups:
Patients with myotonic disorder and respiratory disorders and/ or requiring co-administration of CYP1A2 substrate might be at risk of increased exposure to these drugs more so for the drugs with narrow therapeutic window.

Preventability:
Patient may inform their HCPs about ongoing treatment with mexiletine before starting any medication especially for preventing and treating symptoms and blockage of airway due to asthma or other lung diseases.

Impact on the risk-benefit balance of the product:
If mexiletine and a CYP1A2 substrate with a narrow therapeutic window (such as theophylline, caffeine or tizanidine) are to be used concurrently, blood levels of such drugs should be monitored, particularly when the mexiletine dose is changed. An appropriate adjustment in dose of such drugs should be considered.

Public health impact:
Co-administration of mexiletine with drugs having narrow therapeutic window (such as theophylline, caffeine or tizanidine) could increase or prolong the therapeutic effect and/or adverse events of these drugs. Increased plasma concentration of theophylline or caffeine after co-administration with mexiletine may be of concern in patients with cardiac arrhythmia.

4. Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment

Potential mechanisms:
Mexiletine is mainly (90%) metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. In patients with hepatic impairment such as liver cirrhosis total clearance will diminish which can lead to considerable increase in plasma levels of mexiletine and associated risk of side effects of mexiletine.
Evidence source(s) and strength of evidence:
Cirrhosis of the liver markedly alters the pharmacokinetics of mexiletine. The steady state serum concentration of mexiletine is significantly higher in patients with cirrhosis of the liver compared with patients without liver disease. Following administration of a single intravenous dose of mexiletine hydrochloride 200mg to patients with cirrhosis or healthy controls, the clearance and elimination rate constant were significantly lower in patients with cirrhosis compared with the control group. Indeed, the mean half-life of mexiletine in patients with cirrhosis was 2.9 times that found in the control group (Labbe. L et al 1999).

Characterisation of the risk:
The metabolism of mexiletine is delayed in patients with hepatic impairment and use of mexiletine this population may lead to considerable increase in plasma levels of mexiletine and associated risk of side effects of mexiletine.

Risk factors and risk groups:
Mexiletine may be used with caution in patients with mild or moderate hepatic impairment however it should not be used in patients with severe hepatic impairment.

Preventability:
Mexiletine should be used with caution in patients with mild or moderate hepatic impairment and should not be used in patients with severe hepatic impairment. The proposed dose escalation period of 7 days may not be sufficient for this patient group therefore patients with

hepatic impairment might require further caution and a dose escalation of at least 14 days shall be considered by physicians.

Impact on the risk-benefit balance of the product:
Mexiletine may be used with caution in patients with mild or moderate hepatic impairment however if used in patients with severe hepatic impairment it may lead to considerable increase in plasma levels of mexiletine and associated risk of side effects of mexiletine.

Public health impact:
The expected post marketing frequency of occurrence of adverse events due to use of mexiletine in severe hepatic impairment is minimal. The instructions for not using mexiletine in severe hepatic impairment is sufficient to avoid its use in this group of population. Mexiletine should be used with caution in patients with mild or moderate hepatic impairment. If mexiletine is used in patients with severe hepatic impairment, it may lead to considerable increase in plasma levels of mexiletine and associated risk of side effects of mexiletine.

5. Increased frequency of seizure episodes in patients with epilepsy

Potential mechanisms:
Common elements of pathogenesis create a basis for the assumption that antiarrhythmic drugs (AADs) may affect seizure phenomena and interact with antiepileptic drugs (AEDs).

Evidence source(s) and strength of evidence:
There are no studies to demonstrate this however considering the pharmacological properties of mexiletine and pathophysiology of epilepsy potential for increase in frequency of seizure episodes in epileptic patients cannot be excluded.

Characterisation of the risk:
This risk needs to be characterised further.

Risk factors and risk groups:
Patients with known history of epilepsy and on AEDs.
Preventability:
Mexiletine should be used with caution in patients with known history of epilepsy and/or patients on AEDs.

Impact on the risk-benefit balance of the product:
Epileptic patients need to be monitored because mexiletine can increase the frequency of seizure episodes.

Public health impact:
Although there are no reports of increase in frequency of seizure episodes in epileptic patients, this may be due to limited exposure of this population group. Considering the pharmacological properties of mexiletine and pathophysiology of epilepsy there is a potential risk for increase in frequency of seizure episodes in epileptic patients after exposure to mexiletine.

6. Off-label use in DM1 and DM2 patients

Potential mechanisms:
There are studies published which indicate positive effects of mexiletine on myotonia in DM1 and DM2 patients.

Evidence source(s) and strength of evidence:

Given that mexiletine is already approved for symptomatic management of myotonia in DM1 and DM2 in France and the pharmacological properties of mexiletine, the possibility of off-label use in DM1 and DM2 patients cannot be excluded.

Characterisation of the risk:
This risk needs to be characterised further based on data available from pharmacovigilance activities.

Risk factors and risk groups:
1) There is currently no symptomatic treatment for myotonia in DM1 and DM2 patients in Europe hence clinicians may consider Namuscla as a treatment option.
2) DM1 and DM2 patients primarily presenting with myotonias.

Preventability:
Namuscla product information (SmPC and PL) clearly mentions that Namuscla should only be used in the adult population with NDM.

Impact on the risk-benefit balance of the product:
The use of mexiletine in DM1 and DM2 patients has been the subject of studies and case reports. It is possible that clinicians may want to use Namuscla in the DM1 and DM2 patients, hence off-label use of Namuscla in DM1 and DM2 patients is a potential risk.

Public health impact:
Although there are reports of safety and efficacy of mexiletine use in DM1 and DM2 patients, there is not sufficient clinical trial data available regarding the safety and efficacy of Namuscla in DM1 and DM2 patients.

SVII.3.2. Presentation of the missing information

7. Long term use in adult patients with myotonic disorders

Evidence source:
Information on the chronic and long-term use of mexiletine for the symptomatic management of myotonia is available from the literature and post-marketing use of mexiletine in the indication of myotonic disorders. Long-term treatment should not be continued in patients not responding to or experiencing benefit of the treatment.

Population in need of further characterisation:
Risk in this population cannot be determined based on available evidence.

8. Effect on fertility and use in pregnancy:

Evidence source:
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.

There are no or limited amount of data from the use of mexiletine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Population in need of further characterisation:
Risk in this population cannot be determined based on available evidence

9. Safety in elderly:

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

Population in need of further characterisation:
Risk in this population needs to be further characterised.

10. Use in patients with severe renal impairment:

Evidence source: According to the current available data 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.

Population in need of further characterisation:
Risk in population with severe renal impairment needs to be further characterised.

11. Long-term safety in paediatric population

Evidence source: Non-dystrophic and dystrophic myotonic disorders are congenital, and their onset may occur at all ages, including infancy, childhood and adolescence. The safety and efficacy of Mexiletine in children and adolescents aged 0 to < 18 years have not been established. Long-term safety and efficacy study of Mexiletine in paediatric population i.e.PIP 7 (MEX-NM-303) is ongoing. The information on the long-term safety of mexiletine in paediatric population with non-dystrophic myotonic disorders is currently not adequate.

Population in need of further characterisation:
Risk in this population is currently under investigation.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	1. Severe cutaneous adverse drug reactions (SCARs) 2. Cardiac arrhythmia 3. Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine 4. Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment
Important potential risks	5. Increased frequency of seizure episodes in patients with epilepsy 6. Off-label use in DM1 and DM2 patients
Missing information	7. Long term use in adult patients with myotonic disorders 8. Effect on fertility and use in pregnancy 9. Safety in elderly 10. Use in patients with severe renal impairment 11. Long-term safety in paediatric population

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for cardiac arrhythmia:

To obtain structured information and further characterisation of risk of Cardiac Arrhythmia. For all spontaneous reports of cardiac arrhythmia while on mexiletine, use of targeted follow-up questionnaire is planned to further characterise the risk and for assessing the effectiveness of risk minimisation measures. Refer to Annex 4.

Other forms of routine pharmacovigilance activities:
Not applicable

III.2 Additional pharmacovigilance activities

LUP/MEX/2018/001: An Observational Study to Describe the Long-term Safety and Effectiveness of Namuscla in the Symptomatic Management of Myotonia in Adult Patients with Non-Dystrophic Myotonic Disorders ongoing in UK, France and Germany.

- **Non-interventional, Prospective Post Authorisation Safety Study (PASS)**

Rationale and study objectives:
To date, randomised studies conducted for mexiletine have assessed only short-term efficacy and safety with little supporting data for long-term use from observational research. This non-interventional study collect data on the long-term (12 months to 3 years) safety of Namuscla in a real-world setting.

Primary Objective:
To describe the long-term safety and tolerability of Namuscla for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

Secondary Objectives:

1. To evaluate the safety of Namuscla in NDM patients
2. To evaluate the safety of Namuscla in special populations:
    - patients with hepatic impairment
    - patients with severe renal impairment
    - elderly patients (aged 65 years and above),
    - patients with seizure disorders,
3. To assess the occurrence of severe cutaneous adverse reactions (SCARS), cardiac arrhythmia, and seizures on treatment with Namuscla.
4. To evaluate the clinical effectiveness of Namuscla in NDM patients in terms of clinical evaluation and based on patient-reported outcomes (PRO).

Study Design

This is a non-interventional, prospective, observational, multicenter Post Authorisation Safety Study.

Study Population:

This study involves adult male and female patients with:

- Patients newly initiated on Namuscla for the treatment of NDM (newly exposed)
- Patients already on Namuscla/ mexiletine at enrolment - For patients receiving mexiletine other than Namuscla, only those who switch to Namuscla will be included in the study.

Patients meeting all the inclusion criteria and none of the exclusion criteria will be eligible for enrolment in the study.

Milestones:

Milestone	**Planned Due Date**
Protocol approval	27 Feb 2020
Start of data collection	December 2020
End of data collection	December 2025
Study progress report	To be included in Periodic Benefit-Risk Evaluation Report (PBRER) no. 06 for the period 18 Dec 2021 to 17 Dec 2022
Interim Analysis 1	April 2022
Interim Analysis 2	April 2024
Final Study Report	July 2026

For details regarding the PASS, please refer to Annex 3.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: Ongoing additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
PASS LUP/MEX/ 2018/001 (Ongoing)	To describe the long-term safety and tolerability of Namuscla for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders Secondary Objectives: 1. To evaluate the safety of Namuscla in NDM patients	1. Severe cutaneous adverse reactions 2. Cardiac arrhythmia 3. Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment 4. Increased frequency of seizure episodes in patients with epilepsy	Study protocol approval	27 February 2020
			Start of data collection: Patients will be enrolled for a period of 2 years.	December 2020

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	2. To evaluate the safety of Namuscla in special populations: - patients with hepatic impairment - patients with severe renal impairment - elderly patients (aged 65 years and above), - patients with seizure disorders, 3. To assess the occurrence of severe cutaneous adverse reactions (SCARS), cardiac arrhythmia, and seizures on treatment with Namuscla 4. To evaluate the clinical effectiveness of Namuscla in NDM patients in terms of clinical evaluation and based on patient-reported outcomes (PRO).	5. Long term use in adult patients with myotonic disorders 6. Safety in elderly 7. Use in patients with severe renal impairment	Interim Analysis 1:	April 2022
			Interim Analysis 2:	April 2024
			Periodic update on data collection	Included in PSUR no. 06. for the period 18 Dec 2021 to 17 Dec 2022
			End of data collection	December 2025
			Final Study Report	July 2026

Part IV: Plans for post-authorisation efficacy studies

None proposed.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
1. Severe cutaneous adverse reactions (SCARs)	Routine risk communication: SmPC section 4.3 and 4.8. PL section 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: *SmPC*: Contraindication for use in patients with known hypersensitivity to mexiletine or to any of the excipients and hypersensitivity to any local anaesthetic is included in SmPC section 4.3. *PL*: Warning for not taking mexiletine if patient is having history of allergy/ hypersensitivity to mexiletine or to any local anaesthetic, is included in PL section 2. Other routine risk minimisation measures beyond the Product Information: None.
2. Cardiac arrhythmia	Routine risk communication: SmPC section 4.3, 4.4 and 4.8. PL section 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Contraindication for use in patients with 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 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) and co-

Safety concern	Routine risk minimisation activities
	administration with medicinal products inducing torsade de pointes is included in SmPC section 4.3. The notion that Mexiletine may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed is included in section 4.4. Warning that mexiletine may induce an arrhythmia or accentuate a pre-existing arrhythmia, hence cardiac evaluation and monitoring should be performed before and during treatment with mexiletine and warning that co-administration of mexiletine with antiarrhythmic agents inducing torsade de pointes (such as class III [amiodarone, ibutilide, sotalol], class Ia [disopyramide, procainamide, quinidine] and Class Ic antiarrhythmics [flecainide, propafenone, moricizine]) increases the risk of potentially lethal torsade de pointes is mentioned in section 4.5. Furthermore, increased risk of cardiac arrhythmia associated with concomitant use with other anti-arrhythmic drugs and CYP1A2 & CYP2D6 inhibitors are included in section 4.5. PL: Warning for not taking mexiletine if patient is having cardiac disorders especially cardiac rhythm disorders, Instruction for informing the doctor or pharmacist if patient is taking, have recently taken or might take any other medicines and if used must be used under cardiac monitoring, is included in PL section 2. Warning to go to the doctor or to nearest emergency center immediately if experiencing - arrhythmia (atrioventricular block, rapid heart rate, ventricular fibrillation) is included in PL section 4. <u>Other routine risk minimisation measures beyond the Product Information</u>: None.
3. Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine	<u>Routine risk communication</u>: SmPC section 4.5. PL section 2. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk</u>: SmPC: Instructions that patients should be carefully monitored if co-treated with other medicinal products with special emphasis to medicinal products with narrow therapeutic windows (section 4.5). PL: Instruction for informing the doctor or pharmacist if patient is taking, have recently taken or might take any other medicines, is included in PL section 2.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: None.
4. Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment	Routine risk communication: SmPC section 4.2 and 4.8. PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Warning that mexiletine should be used with caution in patients with mild (5-6 Child-Pugh score) or moderate (7-9 Child-Pugh score) 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 is included in SmPC sections 4.2. PL: Before taking mexiletine patient is advised to talk to the doctor or pharmacist or nurse if patient has liver problems is included in PL section 2. Other routine risk minimisation measures beyond the Product Information: None.
5. Increased frequency of seizure episodes in patients with epilepsy	Routine risk communication: SmPC section 4.4 and 4.8. PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Caution that mexiletine may increase frequency of seizure episodes in epileptic patients is included in section 4.4. PL: Caution for monitoring the epileptic patients while on mexiletine, is included in PL section 2. Other routine risk minimisation measures beyond the Product Information: None.
6. Off-label use in DM1 and DM2 patients	Routine risk communication: SmPC Section 4.1 PL Section 1 Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
	SmPC: Information on indication of Mexiletine for the symptomatic treatment of myotonia in patients with non-dystrophic myotonic disorders is included in section 4.1 and in PL Section 1. Other routine risk minimisation measures beyond the Product Information: None.
7. Long term use in adult patients with myotonic disorders	Routine risk communication: SmPC section 4.2. PL: Not applicable. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC and PL will be updated as and when information regarding long term use in patients with myotonic disorders becomes available. Other routine risk minimisation measures beyond the Product Information: None.
8. Effect on fertility and use in pregnancy	Routine risk communication: SmPC section 4.6. PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Information that as a precautionary measure, it is preferable to avoid the use of Namuscla during pregnancy as there are no or limited amount of data from the use of mexiletine in pregnant women, is included in section 4.6. Also, information that the effects of mexiletine on fertility in humans have not been studied, is included in section 4.6. PL: Instruction for informing the doctor or pharmacist if patient thinks she may be pregnant or is planning to have a baby while on mexiletine, is included in PL section 2. Other routine risk minimisation measures beyond the Product Information: None.
9. Safety in elderly	Routine risk communication: SmPC section 4.2. PL: Not applicable. Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
	SmPC: Information that experience with mexiletine in patients with myotonic disorders >65 years is limited, is included in section 4.2. Other routine risk minimisation measures beyond the Product Information: None.
10. Use in patients with severe renal impairment	Routine risk communication: SmPC section 4.2 PL: Not applicable. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Information that experience with mexiletine in patients with severe renal impairment is limited and recommendation for not using mexiletine in this patient population, is included in section 4.2. Other routine risk minimisation measures beyond the Product Information: None.
11. Long-term safety in paediatric population	Routine risk communication: SmPC section 4.2. and 4.8 PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Dose recommendations for Paediatric population (from 6 to < 18 years of age) are mentioned in section 4.2 based on the body weight. Information that the safety and efficacy of mexiletine in children less than 6 years of age have not been established is included in section 4.2. Section 4.8 contains data regarding Clinical efficacy and safety (Children and adolescents from 6 to < 18 years of age) PL: Warning that Namuscla should not be used in children under 6 years of age or weighing below 20 kg is included in PL section 2. Other routine risk minimisation measures beyond the Product Information: None.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described above are sufficient to manage the safety concerns of the medicinal product except for the risk of “Cardiac arrhythmia” and “Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment”.

For the Important Identified Risk of “Cardiac arrhythmia” and “Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment”, Lupin proposes the following additional risk minimisation measure:

Educational material for risk of cardiac arrhythmia and risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment:

- To general inform about mexiletine and educate HCPs and patients regarding risk of cardiac arrhythmias in patients treated with mexiletine and importance of cardiac monitoring.
- Guidance for identification (and exclusion) of patients who are at a greater risk of developing arrhythmias due to mexiletine;
- Listing contraindications with mexiletine which may increase the susceptibility to arrhythmias
- Explaining the need for cardiac evaluation in patients taking mexiletine
- Information that mexiletine should be stopped immediately if patient develops any cardiac abnormalities and if patient is not responding or experiencing benefit of the Namuscla long-term treatment
- Explaining the risk of decreased mexiletine clearance in patients with hepatic impairment and guidance how to treat those patients

Educational materials for Healthcare professionals and for patients will be made available on the website www.lupin-neurosciences.com or other platforms, as agreed with relevant competent authority.

Educational materials proposed are:

1. Educational guide for Healthcare Professional (Annex 6a)
2. Patient card (Annex 6b)

Rationale for the additional risk minimisation activity:
Mexiletine may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed. Considering the nature of risk and novelty of this product use in myotonic disorders providing essential information to HCPs through educational material as well as website (HCPs and patients) is planned. The content of educational materials, website target audience and communication plan to be agreed with competent authorities.
In addition, the risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment is explained and can by cautious titration be prevented.

Target audience and planned distribution path:
The target audience and communication plan to be agreed with competent authorities in line with local requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:
Routine pharmacovigilance activities, monitoring reports of cardiac arrhythmia and targeted follow-up form for reports of cardiac arrhythmia (Refer to Annex 4). Criteria for success would be no spontaneous cases of cardiac arrhythmia due to use of Namuscla in patients already known to be at risk of cardiac arrhythmia.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Severe cutaneous adverse reactions	Routine risk minimisation measures: SmPC section 4.3.and 4.8. PL section 2 and 4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS - LUP/MEX/2018/001; final study report due date: July 2026
Cardiac arrhythmia	Routine risk minimisation measures: SmPC section 4.3, section 4.4, section 4.5 and section 4.8. PL section 2 and 4. Additional risk minimisation measures: 1. Educational guide for HCPs 2. Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire, to monitor and further characterise the risk of cardiac arrhythmia. Additional pharmacovigilance activities: PASS - LUP/MEX/2018/001; final study report due date: July 2026
Risk of toxicity of CYP1A2 substrate with narrow therapeutic window such as theophylline, caffeine or tizanidine	Routine risk minimisation measures: SmPC section 4.5. PL section 2 Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment	Routine risk minimisation measures: SmPC section 4.2, 4.8. PL section 2. Additional risk minimisation measures: 1. Educational guide for HCPs	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS - LUP/MEX/2018/001; final study report due date: July 2026
Increased frequency of seizure episodes in patients with epilepsy	Routine risk minimisation measures: SmPC section 4.4., 4.8. PL section 2.	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None.	reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS - LUP/MEX/2018/001; final study report due date: July 2026
Off-label use in DM1 and DM2 patients	Routine risk minimisation measure: SmPC section 4.1. PL section 1. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long term use in adult patients with myotonic disorders	Routine risk minimisation measure: None Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS- LUP/MEX/2018/001; final study report due date: July 2026
Effect on fertility and use in pregnancy	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in elderly	Routine risk minimisation measures: SmPC section 4.2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS - LUP/MEX/2018/001; final study report due date: July 2026
Use in patients with severe renal impairment	Routine risk minimisation measures: SmPC Section 4.2.	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS - LUP/MEX/2018/001; final study report due date: July 2026
Long-term safety in paediatric population	Routine risk minimisation measure: SmPC section 4.2 and 4.8 PL section 2 Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Namuscla 42 mg, 62 mg, 83 mg and 167 mg hard capsules (Mexiletine hydrochloride)

This is a summary of the risk management plan (RMP) for Namuscla 42 mg, 62 mg, 83 mg and 167 mg hard capsules (Mexiletine hydrochloride). The RMP details important risks of Namuscla 42mg, 62 mg, 83 mg and 167 mg hard capsules, how these risks can be minimised, and how more information will be obtained about Namuscla 42 mg, 62 mg, 83 mg and 167 mg hard capsule's risks and uncertainties (missing information).

Namuscla 42 mg, 62 mg, 83 mg and 167 mg hard capsule's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Namuscla 42 mg, 62 mg, 83 mg and 167 mg hard capsules should be used.

I. The medicine and what it is used for

EEA
Namuscla 167 mg hard capsules are authorised for the symptomatic treatment of myotonia in children aged 6 to 11 years weighing at least 20 kg, adolescnets aged 12 to 17 years and adult patients ≥18 years and Namuscla 62 mg and 83 mg hard capsules are authorised only for children and adolescents (from 6 to 17 years of age) with non-dystrophic myotonic disorders in the EEA.

It contains mexiletine hydrochloride as the active substance and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Namuscla 42 mg, 62 mg, 83 mg and 167 mg hard capsules, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products include:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Namuscla 42 mg, 62 mg, 83 mg and 167 mg hard capsules, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Reports (PSURs) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities. Periodic update on data collection will be provided in PSURs.

If important information that may affect the safe use of Namuscla is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Namuscla 42 mg, 62 mg, 83 mg and 167 mg hard capsules are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Namuscla 42 mg, 62 mg, 83 mg and 167 mg hard capsules. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risk and missing information	
Important identified risks	1. Severe cutaneous adverse reactions (SCARs) 2. Cardiac arrhythmia 3. Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine 4. Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment
Important potential risks	5. Increased frequency of seizure episodes in patients with epilepsy 6. Off-label use in DM1 and DM2 patients
Missing information	7. Long term use in adult patients with myotonic disorders 8. Effect on fertility and use in pregnancy 9. Safety in elderly 10. Use in patients with severe renal impairment 11. Long-term safety in paediatric population

II.B Summary of important risks

Severe cutaneous adverse reactions (SCARs)	
Evidence for linking the risk to the medicine	Mexiletine is contraindicated in patients with known hypersensitivity to mexiletine, or to any of the excipients or to any local anaesthetic as there is possibility of occurrence of potentially lethal severe cutaneous adverse reactions, usually severe cutaneous eruption along with fever, lymphadenopathy, hypereosinophilia, lymphocytosis or organ damage (notably liver and kidney).
Risk factors and risk groups	Patients with known hypersensitivity to mexiletine or of the excipients or to any local anaesthetic are at high risk of developing SCARs.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.3 and 4.8. PL section 2 and 4. Additional risk minimisation measures None.
Additional pharmacovigilance activities	PASS - LUP/MEX/2018/001 See section II.C of this summary for an overview of the post-authorisation development plan.

Cardiac arrhythmia	
Evidence for linking the risk to the medicine	Mexiletine is a class I b antiarrhythmic drug according to the Vaughan Williams classification, and as such, it may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed. Mexiletine should be administered with caution in patients with pre-existing cardiac conduction anomalies. The advent (under mexiletine therapy) of an atrioventricular block, a permanent complete heart block, or a sinoatrial block necessitates the interruption of the mexiletine treatment.
Risk factors and risk groups	Patients with Dystrophic myotonia and patients with existing conduction abnormalities will be at a risk of developing cardiac arrhythmias. Mexiletine should be administered with caution in patients with pre-existing cardiac conduction anomalies. The benefit-risk ratio needs to be assessed on case by case basis for the benefit on the myotonia versus the risk of rhythm complication. The concomitant use of mexiletine and antiarrhythmic drug inducing torsade de pointes is contraindicated. Co-administration of hepatic enzymes (CYP1A2 and CYP2D6) inhibitors (such as ciprofloxacin, fluvoxamine, propafenone or quinidine) may significantly increase mexiletine exposure and thus the associated risk of side effects of mexiletine including arrhythmias.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3, 4.4, 4.5 and 4.8. PL section 2 and 4. Additional risk minimisation measures: 1. Educational guide for Healthcare Professional 2. Patient card
Additional pharmacovigilance activities	PASS - LUP/MEX/2018/001 See section II.C of this summary for an overview of the post-authorisation development plan.

Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine	
Evidence for linking the risk to the medicine	Mexiletine is a potent inhibitor of CYP1A2; therefore, co-administration of mexiletine with a medicinal product metabolised by CYP1A2 (such as theophylline, caffeine or tizanidine) may be associated with elevations in plasma concentrations of the concomitant medicine that could increase or prolong the therapeutic efficacy and/or adverse events, especially if mexiletine is co-administered withCYP1A2 substrate with narrow therapeutic window. A study in eight normal subjects showed a 65% mean increase in plasma theophylline levels when mexiletine was used concomitantly. In a clinical study in 12 subjects (5 healthy subjects and 7 patients with cardiac arrhythmias), the clearance of caffeine was decreased by 50% following the administration of mexiletine.

Risk factors and risk groups	During the treatment with mexiletine patient might require treatment other concomitant medications and they can inform their healthcare professionals about ongoing treatment with mexiletine before starting any other medication. Increased concentrations of caffeine occurring with the co-administration of mexiletine may be of concern in patients with cardiac arrhythmia. It is, therefore, recommended to reduce caffeine intake during treatment with mexiletine. Patients with myotonic disorder and respiratory disorders and/ or requiring co-administration of CYP1A2 substrate might be at risk of increased exposure to these drugs more so for the drugs with narrow therapeutic window.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.5. PL section 2. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment	
Evidence for linking the risk to the medicine	Mexiletine is mainly (90%) metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. In severe hepatic impairment such as liver cirrhosis total clearance was diminished by approximately 4 times which can lead to considerable increase in plasma levels of Mexiletine and associated risk of side effects of mexiletine. Cirrhosis of the liver markedly alters the pharmacokinetics of mexiletine. The steady state serum concentration of mexiletine is significantly higher in patients with cirrhosis of the liver compared with patients without liver disease. Following administration of a single intravenous dose of mexiletine hydrochloride 200mg to patients with cirrhosis or healthy controls, the clearance and elimination rate constant were significantly lower in patients with cirrhosis compared with the control group. Indeed, the mean half-life of mexiletine in patients with cirrhosis was 2.9 times that found in the control group.
Risk factors and risk groups	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.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 and 4.8. PL section 2. Additional risk minimisation measures: Educational guide for Healthcare Professionals
Additional pharmacovigilance activities	PASS - LUP/MEX/2018/001 See section II.C of this summary for an overview of the post-authorisation development plan.

Increased frequency of seizure episodes in patients with epilepsy	
Evidence for linking the risk to the medicine	Common elements of pathogenesis create a basis for the assumption that antiarrhythmic drugs (AADs) may affect seizure phenomena and interact with antiepileptic drugs (AEDs). There are no studies to demonstrate this however considering the pharmacological properties of mexiletine and pathophysiology of epilepsy potential for increase in frequency of seizure episodes in epileptic patients cannot be excluded.
Risk factors and risk groups	Patients with known history of epilepsy and on antiepileptic drugs (AEDs).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8. PL section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS - LUP/MEX/2018/001 See section II.C of this summary for an overview of the post-authorisation development plan.

Off-label use in DM1 and DM2 patients	
Evidence for linking the risk to the medicine	Given that Mexiletine is already approved for symptomatic management of myotonia in DM1 and DM2 in France and the pharmacological properties of mexiletine, the possibility of off-label use in DM1 and DM2 patients cannot be excluded. Mexiletine is already being used in DM1 and DM2 patients.
Risk factors and risk groups	1) There is currently no symptomatic treatment for myotonia in DM1 and DM2 patients in Europe, hence clinicians may consider Namuscla as a treatment option. 2) DM1 and DM2 patients primarily presenting with myotonias.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1. PL section 1. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

Long term use in patients with myotonic disorders	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 Additional risk minimisation measures: None.
Additional pharmacovigilance activities	PASS - LUP/MEX/2018/001 See section II.C of this summary for an overview of the post-authorisation development plan.

Effect on fertility and use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6. PL section 2. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

Safety in elderly	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	PASS - LUP/MEX/2018/001 See section II.C of this summary for an overview of the post-authorisation development plan.

Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2. Additional risk Minimisation Measures: None.
Additional pharmacovigilance activities	PASS - LUP/MEX/2018/001 See section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety in paediatric population	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and 4.8 PL Section 2 Additional risk Minimisation Measures: None.
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation.

There are no studies which are conditions to the marketing authorisation or specific obligation of Namuscla 42 mg, 62 mg, 83 mg and 167 mg hard capsules.

II.C.2 Other studies in post-authorisation development plan

PASS - LUP/MEX/2018/001

Purpose of the study: To date, randomised studies conducted for mexiletine have assessed only short-term efficacy and safety data with little supporting data for long-term use from observational research.
This non-interventional study will collect data on the long-term (12 months to 3 years) safety of Namuscla in a real-world setting. This study is ongoing.

Part VII: Annexes

Annex 4	Specific adverse drug reaction follow-up forms	Not Changed Targeted follow-up questionnaire for reports of Cardiac arrhythmia Version Dec. 2018
Annex 6	Details of proposed additional risk minimisation activities	Not changed 1. Educational guide for Healthcare Professional (Annex 6a) Version 1.1 2. Patient card (Annex 6b) Version 1.1
Annex 7	Other supporting data (including referenced material)	Not changed

Annex 4 Specific adverse drug reaction follow-up forms

Annex 4 - Specific adverse drug reaction follow-up forms

Targeted Follow-up Questionnaire – Cardiac arrhythmia

Note: Information provided in the initial adverse drug reaction (ADR) report need not be refilled in this form. Please write all dates in the following format: (DD Mmm YYYY)

1. Patient details:

Initials (First name / family name): .....

Date of Birth/ Age: .....

Gender: M ☐ F ☐ Weight (in kg):.....

Reported event term: .....Start of the ADR (date): _____ / _____ / _____

2. Type of Myotonic disorder (Please tick √ for applicable type)

Please specify the type of indication:

Non-dystrophic myotonia Yes ☐ No ☐

If yes, please specify sub-type:

Myotonia congenita	
Paramyotonia congenita	
Sodium channel myotonia	
Other (please specify):	

If no, please specify:

Outcome of ADR:			Date (DD Mmm YYYY)
- Complete recovery:	No ☐	Yes ☐	_____ / _____ / _____
- Recovered with sequelae:	No ☐	Yes ☐	_____ / _____ / _____
- Ongoing:	No ☐	Yes ☐	_____ / _____ / _____
- Death:	No ☐	Yes ☐	_____ / _____ / _____
- Unknown	☐		

Annex 4 - Specific adverse drug reaction follow-up forms

3. Suspect Medication - Mexiletine:

Suspect medication information	Status	Details
Mexiletine start date (DD Mmm YYYY) _____ / _____/ _____ Dose of the drug given: Strength: _____ _____ times a day	Ongoing ☐ Stopped ☐ Restarted ☐ Dose modified ☐	If stopped, date of stop: _____ / _____ / _____ If restarted, date of restart: _____ / _____ / _____ If dose is modified, Strength: _____ , _____ times a day

Co-suspect medications: No ☐ Yes ☐ Unknown ☐

If yes, please specify:

Substance	Brand name / generic name	Dose	Route	Start date	End date / Ongoing	Duration

Concomitant medications:

Substance	Brand name / generic name	Dose	Route	Start date	End date / Ongoing	Duration
Antiarrhythmic drugs (such as amiodarone, ibutilide, procainamide, quinidine, cibenzoline, flecainide, lidocaine, propafenone)						
Others						

Annex 4 - Specific adverse drug reaction follow-up forms

4. Prior history / underlying disorders:

4.1 Co-factors / risk factors:

- Smoking: No ☐ Yes ☐ Unknown ☐
  If yes, please specify: no. of cigarettes and duration of smoking: .....
- Exposure to asbestos / silica: No ☐ Yes ☐ Unknown ☐
  If yes, please specify:.....
- Other conditions: No ☐ Yes ☐ Unknown ☐
  If yes, please specify:.....

4.2 History of cardiac disorder: No ☐ Yes ☐ Unknown ☐
If yes, please specify: .....

4.3 History of electrolyte imbalance: No ☐ Yes ☐ Unknown ☐
If yes, please specify: .....

4.4 Cardiac evaluation done before start of treatment: No ☐ Yes ☐ Unknown ☐
If yes, please specify
(i) Date _____ / _____ / _____
(ii) Any significant finding: .....

4.5 Latest cardiac evaluation done on _____ / _____ / _____
If done, please specify any significant finding:.....

4.6 History of any renal disease
If yes, please specify:.....

4.7 History of any hepatic disease
If yes, please specify:.....

4.8 Treatment history of the underlying disorder

5. Onset, duration and progress of ADR:

5.1 Time to onset (Interval between drug start and first symptoms):
Days:___ Months:___ Year:___

5.2 Time to recovery (Duration until symptoms subsided):
Days:___ Months:___ Year:___

5.3 Previous exposure with Mexiletine: No ☐ Yes ☐ Unknown ☐
Start Date: _____ / _____ / _____ Stop Date_____ / _____ / _____
Duration of past exposure:.....
Adverse reaction with past exposure: No ☐ Yes ☐ Unknown ☐

Annex 4 - Specific adverse drug reaction follow-up forms

If yes, please specify: .....

6. Review of signs / symptoms:

6.1 General signs / symptoms:

- Fatigue No ☐ Yes ☐ Unknown ☐ If yes, start date:.....
- Dizziness No ☐ Yes ☐ Unknown ☐ If yes, start date:.....
- Lightheadedness No ☐ Yes ☐ Unknown ☐ If yes, start date:.....

6.2 Cardiac signs / symptoms:

- Palpitations: No ☐ Yes ☐ Unknown ☐ If yes, start date:.....
- Tachycardia: No ☐ Yes ☐ Unknown ☐ If yes, start date:.....
- Bradycardia: No ☐ Yes ☐ Unknown ☐ If yes, start date:.....
- Chest pain: No ☐ Yes ☐ Unknown ☐ If yes, start date:.....
- Shortness of breath: No ☐ Yes ☐ Unknown ☐ If yes, start date:.....
- Sweating: No ☐ Yes ☐ Unknown ☐ If yes, start date:.....
- Fainting or near fainting: No ☐ Yes ☐ Unknown ☐ If yes, start date:.....
- Others (please specify): .....

7. Relevant diagnostic tests:

Name of Test: ECG/ Holter monitoring/ 2D Echo Date: ____ / ____ / ____

Result:

Name of Test: Hepatic function test Date: ____ / ____ / ____

Result:

Name of Test: Renal function test Date: ____ / ____ / ____

Result:

Name of Investigation: Others Date: ____ / ____ / ____

Result:

8. Reporting Physician:

Name: ..... E-mail: ..... Phone no. .....

Address: ..... Fax no. .....

Date: ..... Signature: .....

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Annex 6 Details of proposed additional risk minimisation activities

Annex 6a - Educational guide for Healthcare Professionals

Educational guide for Healthcare Professionals

Namuscla hard capsules (Mexiletine hydrochloride) and the risk of cardiac arrhythmia and the increased risk of adverse reactions of mexiletine in patients with hepatic impairment

Content

- Objective
- General information about Namuscla
- Risk of cardiac arrhythmia
- Cardiac effect related to Namuscla pharmacological properties
- Patients who are at higher risk of developing cardiac arrhythmia
- Contraindications
- Cardiac evaluation
- When should Namuscla be stopped?
- Risk of adverse reactions of mexiletine in patients with hepatic impairment
- Patient counselling

Objective

- To make healthcare professionals aware of the risk of cardiac arrhythmia, associated with use of Namuscla.
- To help healthcare professionals to identify patients who are at higher risk of developing cardiac arrhythmia while on treatment with Namuscla.
- To educate healthcare professionals on 'Key Risk Minimization Activities' to mitigate risk of cardiac arrhythmia while using Namuscla.
- To explain the risk of decreased Mexiletine clearance in patients with hepatic impairment and guide how to treat those patients.

General information about Namuscla

- Namuscla capsules contain the active ingredient Mexiletine hydrochloride and is indicated for symptomatic treatment of Myotonia in adults and children (from 6 to 18 years of age) with Non-Dystrophic Myotonic Disorders.
- 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.
- Before starting treatment with Namuscla, detailed and careful cardiac evaluation should be carried out; throughout treatment with Namuscla, cardiac monitoring needs to be continued and adapted as a function of the heart condition of the patient.

Risk of Cardiac Arrhythmia

- Namuscla may cause cardiac effects: possible increased QRS, decreased QTc,

increased PR intervals, tachycardia are likely to occur, which are related to the its pharmacological properties.

- Given the pro-arrhythmogenic effect of class I anti-arrhythmics, notably at the ventricular level, Namuscla treatment of myotonic syndromes in subjects with cardiac disorders needs to be associated with a full cardiac evaluation before the start of the treatment and after start of treatment (e.g. 48 hours after start of treatment) to evaluate the good cardiologic tolerability.
- Caution to be exercised while using Namuscla along with other anti-arrhythmic agents, especially those known to induce Torsades de pointes.

Patients who are at higher risk of developing cardiac arrhythmia

- Patients with history of cardiac disorder
- Patients with presenting symptoms of arrhythmias:
  - fainting
  - palpitations
  - chest pain
  - light headedness
  - shortness of breath
  - lipothymia
  - syncope
- Patients with anti-arrhythmic medication
- Patients taking medicines with interacting potential

Contraindications

- Hypersensitivity to mexiletine, or to any of the excipients
- 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

Cardiac Evaluation

- Namuscla is a class I b antiarrhythmic drug according to the Vaughan Williams classification, and as such, it may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed.
- In patients without cardiac abnormalities, an electrocardiogram (ECG) monitoring should be performed periodically (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.

When should Namuscla be stopped?

- If patient (under Namuscla therapy) develops cardiac abnormalities e.g. an atrioventricular block, a permanent complete heart block, or a sinoatrial block, it necessitates the **interruption** of mexiletine treatment.
- If a patient is not responding or experiencing benefit of the Namuscla long-term treatment, Namuscla should be discontinued.

Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment

- Mexiletine should be used with caution in patients with mild or moderate hepatic impairment.
- The hepatic impairment may decrease mexiletine clearance and therewith to increase plasma concentrations of mexiletine, thus increasing the risk to develop mexiletine associated adverse reactions.
- In patients with mild or moderate hepatic impairment, it is recommended that the dose should only be increased after at least 2 weeks of treatment.
- The experience with mexiletine in patients with severe hepatic impairment is limited.
- Mexiletine **should not be used** in patients with **severe hepatic impairment.**

Patient counselling

- Patients should be counselled for risk of cardiac arrhythmia; patient card should be given to patient before treatment initiation.
- Patients should be informed about the symptoms of arrhythmia and advise to immediately contact HCP or emergency center if they experience any of these symptoms.
- Patients should be advised to inform their HCP if they have any underlying hepatic disorders.

Adverse event reporting

If your patient taking Namuscla experiences any signs or symptoms of cardiac arrhythmia or any other Adverse Event you become aware of, these Adverse Events should be reported.

Reporting forms and information can be found at *<To be updated>*

Annex 6b - Patient Card

PATIENT CARD for Namuscla

Namuscla (mexiletine hydrochloride)
Patient Card for patients, parents and caregivers

read in conjunction with the patient leaflet

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**. You or your parents/caregivers should be aware of the risks associated with the use of Namuscla.

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/ nurse/ pharmacist about your ongoing medications and show them this card **before starting any new medication** while on treatment with Namuscla

What are signs of cardiac arrhythmia?

Typical signs and symptoms of cardiac arrhythmia are:

- feel like your heart is beating too hard or too fast (palpitations)
- chest pain
- unusual headache
- sweating
- shortness of breath
- lightheadedness, dizziness or fainting

Contact an emergency center immediately if you experience any of these signs!

- *See reverse of card*

Write your treatment and doctor's details below:

Start Date of taking Namuscla:_____

Patient Name: _____

Doctor's Name: _____

Doctor's contact number: _____

What else do I need to know?

Before starting treatment with Namuscla and regularly during treatment you will undergo tests to evaluate your heart function, including electrocardiogram (ECG). Depending on your heart function you may also need testing before and after any dose adjustment. Follow all the instructions given by your doctor.

Do not take more than the prescribed dose 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

Annex 7 Other supporting data (including referenced material)

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