ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Namuscla 167 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains mexiletine hydrochloride corresponding to 166.62 mg mexiletine .

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Namuscla capsules are Swedish orange hard shell gelatin capsules (20 mm) filled with white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The recommended starting dose of mexiletine is 167 mg daily (1 capsule per day). After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333 mg daily (2 capsules per day). After at least 1 further week of treatment, based on clinical response, dose can be further increased to 500 mg daily (3 capsules per day).
Maintenance treatment is between 167 mg – 500 mg daily (1 to 3 capsules per day), according to the intensity of symptoms and the clinical response, taken regularly throughout the day.

The dose should not exceed 500 mg/day. Regular reassessment should be implemented, not to continue long-term treatment in a patient not responding or not experiencing benefit of the treatment. Before starting mexiletine treatment, detailed and careful cardiac evaluation should be carried out; throughout treatment with mexiletine, cardiac monitoring needs to be continued and adapted as a function of the heart condition of the patient (see contraindications in section 4.3 and warning in section 4.4).

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

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

Hepatic impairment
Mexiletine should be used with caution in patients with mild or moderate hepatic impairment. In these patients, it is recommended that the dose should only be increased after at least 2 weeks of treatment. Mexiletine should not be used in patients with severe hepatic impairment (see section 4.4).

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

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

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

Method of administration

Oral use.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Cardiac arrhythmogenic effects

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

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

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

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

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

For cardiac disorders not listed in section 4.3, the benefit of the antimyotonic effects of mexiletine needs to be balanced against the risk of cardiac complications on a case by case basis.
Mexiletine should be stopped immediately in case any cardiac conduction abnormalities or any of the contraindications listed in the section 4.3 are detected.

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

Drug reaction with eosinophilia and systemic symptoms (DRESS)

DRESS refers to a syndrome which includes in its complete form severe cutaneous eruptions, fever, lymphadenopathy, hepatitis, haematological abnormalities with eosinophilia and atypical lymphocytes, and can involve other organs. Symptoms typically occur 1-8 weeks after exposure to the medicinal product. Severe systemic manifestations are responsible for a 10% mortality rate. Incidence of DRESS has been reported between 1:100 and 1:10.000 patients treated.
Several medicinal products including anticonvulsants, antibiotics and also mexiletine have been identified as possible causes. Patients with known hypersensitivity to mexiletine or any other ingredients of this product or to any local anaesthetic are at high risk of developing DRESS and should not receive mexiletine.

Hepatic impairment

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

Renal impairment

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

Epilepsy

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

CYP2D6 polymorphism

CYP2D6 polymorphism may affect mexiletine pharmacokinetics (see section 5.2). Higher systemic exposure is expected in patients who are CYP2D6 poor metabolisers or who take medicinal products

that inhibit CYP2D6 (see section 4.5). A period of at least 7 days before dose increase must be respected to ensure that steady-state levels are reached and that mexiletine is well tolerated in all patients, irrespective of CYP450 polymorphism.

Smoking

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

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

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

Pharmacokinetic interactions

Effect of other medicinal products on mexiletine

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

CYP1A2 & CYP2D6 inhibitors
Co-administration of mexiletine with a hepatic enzyme inhibitor (CYP1A2 inhibitor: ciprofloxacin, fluvoxamine, propafenone; CYP2D6 inhibitor: propafenone, quinidine) significantly increases mexiletine exposure and thus the associated risk of adverse reactions to mexiletine.
In a single-dose interaction study, the clearance of mexiletine was decreased by 38% following the co-administration of fluvoxamine, an inhibitor of CYP1A2.
Therefore, clinical and ECG monitoring, as well as adaptation of mexiletine dosage may be indicated throughout and after treatment with a CYP1A2 or CYP2D6 inhibitor.

CYP1A2 & CYP2D6 inducers
Co-administration of mexiletine with a hepatic enzyme inducer (CYP1A2 inducer: omeprazole; CYP2D6 inducer: phenytoin, rifampicin) may increase the clearance and elimination rate of mexiletine due to an increased hepatic metabolism, resulting in decreased plasmatic concentrations and half-life of mexiletine.
In a clinical study, co-administration of mexiletine with phenytoin resulted in a significant decrease in exposure to mexiletine ($p < 0.003$) due to enhanced clearance as reflected in significantly decreased elimination half-life (17.2 to 8.4 hours, $p < 0.02$).
Therefore, based on the clinical response, the mexiletine dosage should be adapted during and after treatment with the enzyme inducer.

After the oral administration of single (167 mg) and multiple (83 mg twice a day during 8 days) doses of mexiletine, total clearance of mexiletine is significantly increased in smokers (1.3 to 1.7-fold) due to induction of CYP1A2, resulting in a correspondingly decreased elimination half-life and drug

exposure. Mexiletine dose may need to be increased if a patient starts to smoke during mexiletine treatment and decreased if a patient stops smoking.

Effect of mexiletine on other medicinal products

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

CYP1A2 substrates
Mexiletine is a potent inhibitor of CYP1A2; therefore, co-administration of mexiletine with medicinal products metabolised by CYP1A2 (such as theophylline, caffeine, lidocaine or tizanidine) may be associated with elevations in plasma concentrations of the concomitant medicine that could increase or prolong the therapeutic efficacy and/or the adverse reactions, especially if mexiletine is co-administered with CYP1A2 substrates with narrow therapeutic window, e.g. theophylline and tizanidine.
The CYP1A2 substrate blood levels should be monitored, particularly when the mexiletine dose is changed. An appropriate adjustment in the dose of the CYP1A2 substrate should be considered.

Caffeine
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. 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.

OCT2 substrates
The organic cation transporter 2 (OCT2) provides an important pathway for the uptake of cationic compounds in the kidney. Mexiletine may interact with drugs transported by OCT2 (such as metformin and dofetilide).
If mexiletine and other OCT2 substrates are to be used concurrently, the OCT2 substrate blood levels should be monitored, particularly when the mexiletine dose is changed. An appropriate adjustment in the dose of the OCT2 substrate should be considered.

Substrates of other enzymes and transporters
The potential interactions between mexiletine and substrates of other common enzymes and transporters have not yet been assessed; it is currently contra-indicated to use mexiletine with any substrate having a narrow therapeutic window such as digoxin, lithium, phenytoin, theophylline or warfarin (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

Mexiletine is excreted in human milk. There is insufficient information on the effects of mexiletine in newborns/infants. A decision must be made whether to discontinue breast-feeding or to

discontinue/abstain from mexiletine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients treated with mexiletine are abdominal pain (12%), vertigo (8%) and insomnia (12%).
The most serious reported adverse reactions in patients treated with mexiletine are drug reaction with eosinophilia and systemic symptoms and arrhythmia (atrioventricular block, arrhythmia, ventricular fibrillation).

Tabulated list of adverse reactions

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

Blood and lymphatic system disorders Not known: leukopenia, thrombocytopenia
Immune system disorders Very rare: drug reaction with eosinophilia and systemic symptoms Not known: lupus-like syndrome, dermatitis exfoliative, Stevens-Johnson syndrome
Psychiatric disorders Very common: insomnia Common: somnolence Not known: hallucinations, confusional state
Nervous system disorders Common: headache, paraesthesia, vision blurred Uncommon: seizure, speech disorders Not known: diplopia, dysgeusia
Ear and labyrinth disorders Common: vertigo
Cardiac disorders Common: tachycardia Uncommon: bradycardia Not known: atrioventricular block
Vascular disorders Common: flushing, hypotension Not known: circulatory collapse, hot flush
Respiratory, thoracic and mediastinal disorders Not known: pulmonary fibrosis

Gastrointestinal disorders Very common: abdominal pain Common: nausea Not known: diarrhoea, vomiting, oesophageal ulcers and perforation
Hepatobiliary disorders Rare: hepatic function abnormal Very rare: drug-induced liver injury, liver disorder, hepatitis
Skin and subcutaneous tissue disorders Common: acne
Musculoskeletal and connective tissue disorders Common: pain in the extremities
General disorders and administration site conditions Common: fatigue, asthenia, chest discomfort, malaise

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

Fatal outcomes have been reported for acute overdoses at 4.4 g of mexiletine hydrochloride ingestion but survival has also been reported following acute overdose of approximately 4 g of oral mexiletine hydrochloride.

The symptoms of mexiletine overdose include neurological disorders (paresthesia, confusion, hallucination, seizure) and cardiac disorders (sinusal bradycardia, hypotension, collapse, and in extreme cases, cardiac arrest).

Overdose management

The treatment is mainly symptomatic. The seriousness of the symptoms may require hospital supervision. In case of bradycardia with hypotension, intravenous atropine should be used. In case of seizure, benzodiazepines should be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, antiarrhythmics, class Ib, ATC code: C01BB02.

Mechanism of action

Mexiletine blocks sodium channels with a stronger potency in situations of excessive burst of action potentials (use-dependent block) and/or prolonged depolarization (voltage-dependent block), as occurring in diseased tissues, rather than on physiological excitability (resting or tonic block). Mexiletine is, therefore, mostly active on muscle fibres subject to repeated discharges (such as skeletal muscles). It improves myotonic symptoms by decreasing muscle stiffness through reduction of the delay of muscle relaxation.

Clinical efficacy and safety

The efficacy and safety of mexiletine in non-dystrophic myotonia was evaluated in MYOMEX, a multi-centre, double-blind, placebo-controlled, cross-over (2 treatment periods of 18 days) study with a 4-day wash-out period in 13 patients with myotonia congenita (MC) and 12 patients with paramyotonia congenita (PC). Age of the overall study population ranged from 20 to 66 years old and about 2/3 of the patients were male. Patients who experienced myotonic symptoms that involved at least 2 segments and that had an impact on at least 3 daily activities were included into the study. The patients were randomized according to a cross-over design to a sequence including the 2 following treatments: a) mexiletine, started at 167 mg/day and titrated by increments of 167 mg every 3 days to reach a maximum dose of 500 mg/day in 1 week or b) placebo.[1]
The primary efficacy measure for both MC and PC was the score of stiffness severity as self-reported by the patients on a Visual Analogue Scale (VAS). The VAS is constructed as an absolute measure, with a 100 mm straight horizontal line having the endpoints "no stiffness at all" (0) and "worst possible stiffness" (100). The main secondary endpoints were changes in health–related quality of life as measured by individualised neuromuscular quality of life (INQoL) scale and the time needed to stand up from a chair, walk around the chair and sit down again (chair test).
Results for the primary and key secondary endpoints are summarised in the table below.

	Mexiletine	Placebo
Primary Analysis **Stiffness score (VAS) (mm)**		
Number of subjects	25	25
Median VAS value at Baseline	71.0	81.0
Median VAS value at Day 18	16.0	78.0
Median VAS absolute change from baseline	-42.0	2.0
Percentage of Patients with an Absolute VAS Change from Baseline ≥ 50 mm at Day 18	12/21 (57.1%)	3/22 (13.6%)
Effect of treatment (Mixed Effect Linear Model)	p < 0.001	
Secondary Analysis **Chair test (s)**		
Number of subjects	25	25
Mean (SD) value at Baseline	7.3 (3.5)	
Mean (SD) value at Day 18	5.2 (1.6)	7.5 (4.1)
Mean (SD) absolute change from baseline	-2.1 (2.9)	0.2 (1.6)
Effect of treatment (Wilcoxon signed-rank test)	p = 0.0007	
Secondary Analysis **Individualised neuromuscular quality of life – Overall quality of life**		
Number of subjects	25	25
Median value at Baseline	51.1	
Median value at Day 18	23.3	48.3
Median absolute change from baseline	-25.0	1.1
Effect of treatment (linear mixed model)	p < 0.001	
Secondary Analysis **Clinical Global Impression (CGI) Efficacy index**		
Number of subjects	25	25
CGI as judged efficient by the investigators	22 (91.7%)	5 (20.0%)
CGI as judged efficient by the patients	23 (92.0%)	6 (24.0%)
Effect of treatment (Mc Nemar test)	p < 0.001	
Secondary Analysis		

[1] Clinical Study Report refers to 200 mg dose which is the amount of mexiletine hydrochloride (corresponding to 166.62mg mexiletine base)

Preference between the 2 treatment periods		
Number of subjects	25	25
Period preferred	20 (80.0%)	5 (20.0%)
Effect of treatment (binomial test)	p = 0.0041	
Secondary Analysis **Clinical Myotonia Scale – Severity Global Score**		
Number of subjects	25	25
Mean (SD) value at Baseline	53.8 (10.0)	
Mean (SD) value at Day 18	24.0 (17.1)	47.6 (23.3)
Mean (SD) absolute change from baseline	-29.8 (16.0)	-6.2 (19.0)
Effect of treatment (linear mixed model)	p < 0.001	
Secondary Analysis **Clinical Myotonia Scale – Disability Global Score**		
Number of subjects	25	25
Mean (SD) value at Baseline	7.8 (2.8)	
Mean (SD) value at Day 18	2.7 (2.6)	7.0 (3.8)
Mean (SD) absolute change from baseline	-5.1 (3.1)	-0.8 (3.4)
Effect of treatment (linear mixed model)	p < 0.001	

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Namuscla in all subsets of the paediatric population in the symptomatic treatment of myotonic disorders (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Mexiletine is rapidly and almost completely absorbed following oral administration with a bioavailability of about 90% in healthy subjects. Peak plasma concentrations following oral administration occur within 2 to 3 hours. No notable accumulation of mexiletine was observed after repeated administration.
Food does not affect the rate or extent of absorption of mexiletine. Therefore, mexiletine can be taken with or without food.

Distribution

Mexiletine is rapidly distributed in the body; its volume of distribution is large and varies from 5 to 9 L/kg in healthy individuals.
Mexiletine is weakly bound to plasma proteins (55%).
Mexiletine crosses the placental barrier and diffuses into breast milk.

Biotransformation

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

resulting in prolonged elimination half-life, higher exposure, and lower volume of distribution in poor metabolisers compared to extensive metabolisers.

Approximately 10% is excreted unchanged by the kidney.

Elimination

Mexiletine is eliminated slowly in humans (with a mean elimination half-life of 10 hours, ranging from 5 to 15 hours).
Excretion of mexiletine essentially occurs through the kidney (90% of the dose, including 10% as unchanged mexiletine).

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

Linearity/non-linearity

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

Special populations

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

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

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

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development. The main observed effects in rats and/or dogs were vomiting, diarrhoea, tremor, ataxia, convulsions and tachycardia. However, these studies were not performed in accordance with contemporary standards and are, hence, of unclear clinical relevance.
The studies in rats on carcinogenic potential were negative, but not performed in accordance with current standards and therefore of unclear clinical relevance. The negative genotoxicity potential does not indicate an increased carcinogenic risk of treatment with mexiletine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Maize starch
Colloidal anhydrous silica
Magnesium stearate

Capsule shell

Iron (III) oxide (E 172)
Titanium dioxide (E 171)
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Capsules are packed in Aluminium/PVC/PVDC blisters containing 30, 50, 100 or 200 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Lupin Europe GmbH
Hanauer Landstraße 139-143,
60314 Frankfurt am Main
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1325/001 - 004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18.12.2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Hormosan Pharma GmbH
Hanauer Landstraße 139-143,
60314 Frankfurt am Main
Germany

Lupin Healthcare (UK) Ltd
The Urban Building, second floor, 3-9 Albert Street
SL1 2BE Slough, Berkshire,
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Namuscla in each Member State (MS) the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

In order to prevent and / or minimise the important identified risks of Cardiac Arrhythmia in patients with Dystrophic Myotonia (off-label use) and Decreased Namuscla clearance, thus the risk of adverse reactions in patients with hepatic impairment, the MAH shall ensure that in each MS where Namuscla is marketed, all healthcare professionals (HCPs) and patients are provided, respectively, with:

- Educational guide for HCPs;
- Patient alert card

The Educational guide for HCPs, which should always be read in conjunction with the Summary of Product Characteristics (SmPC) before prescribing Namuscla, should contain the following key elements:

- Information about the risk of cardiac arrhythmias in patients using Namuscla;
- Guidance to identify (and exclude) patients at a greater risk of developing arrhythmias due to Namuscla treatment;
- Contraindications with Namuscla which may increase the susceptibility to arrhythmias;
- Before starting treatment, HCPs should perform a detailed and careful cardiac evaluation in all patients, in order to determine the cardiac tolerability of Namuscla. A cardiac evaluation is also recommended shortly after starting Namuscla (e.g. within 48 hours).
- Throughout treatment with Namuscla:
    - 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, a 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.
- Namuscla should be stopped immediately if the patient develops cardiac abnormalities, is not responding or experiencing benefit within Namuscla long-term treatment;
- Highlight the risk of decreased Namuscla clearance in patients with hepatic impairment and provide guidance on how to treat those patients in order to prevent it, ensuring Namuscla cautious titration in patients with mild or moderate hepatic impairment (increasing the dose after at least 2 weeks of treatment). Namuscla should not be used in patients with severe hepatic impairment;
- HCPs should counsel patients on:
    - The risk of cardiac arrhythmias (informing about symptoms of arrhythmias, advising patients to contact immediately their HCP, or emergency centres, if they experience any of these symptoms);

- The risk of decreased Namuscla clearance in patients with hepatic impairment (advising patients to inform their HCP if they have any underlying hepatic disorder);

- Reporting of adverse reactions in patients using Namuscla.

The patient alert card (wallet size), to be handed by prescribing specialist and to be read in conjunction with the patient leaflet, should contain the following key messages:

- Patients should carry the card at all times, and show it at all medical visits to HCPs other than the prescriber (e.g. emergency HCPs);

- Prompts to enter the contact details of the patient, the treating physician, and Namuscla treatment starting date;

- Inform patients that, before starting and throughout treatment with Namuscla, HCPs should perform a detailed and careful cardiac evaluation;

- Patients should inform the HCP about any ongoing medications or before starting any new medication, while on treatment with Namuscla;

- Information about symptoms of cardiac arrhythmias, which can be life-threatening, and when patients should seek HCP attention;

- Patients should not take more than 3 capsules of Namuscla per day or a double dose to make up for a forgotten dose;

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Namuscla 167 mg hard capsules
mexiletine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains mexiletine hydrochloride corresponding to 166.62 mg of mexiletine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
50 hard capsules
100 hard capsules
200 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lupin Europe GmbH
Hanauer Landstraße 139-143,
60314 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Namuscla 167

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Namuscla 167 mg capsules
mexiletine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lupin Europe GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Namuscla 167 mg hard capsules
mexiletine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

There is an **Alert Card** distributed with Namuscla, to remind you and medical staff of the risk of cardiac arrythmias. **Read the Alert Card in conjunction with this leaflet and keep the card it with you at all times**.

What is in this leaflet

1. What Namuscla is and what it is used for

Namuscla is a medicine that contains the active substance mexiletine.

Namuscla is used to treat the symptoms of myotonia (when muscles relax slowly and with difficulty after they are used) in adults with non-dystrophic myotonic disorders, which are caused by genetic defects that affect muscle function.

2. What you need to know before you take Namuscla

Do not take Namuscla
- if you are allergic to mexiletine or to any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to any local anaesthetic
- if you have had heart attack
- if your heart does not work well enough
- if you have certain disorders of the heart rhythm
- if your heart beats too fast
- if the blood vessels of your heart are damaged
- if you also take certain medicines to treat disorders of the heart rhythm (see Other medicines and Namuscla)
- if you also take certain medicines which have a narrow therapeutic window (see Other medicines and Namuscla).

If you have any doubt, ask your doctor or pharmacist.

Warnings and precautions
Talk to your doctor or pharmacist or nurse before taking Namuscla if you have:
- heart problems

- liver problems
- kidney problems
- low or high potassium blood levels
- low magnesium blood levels
- epilepsy

Heart function
Before starting treatment with Namuscla, you will have tests to check how well your heart is working, including ECG (Electrocardiogram). These tests will also be performed regularly during treatment with Namuscla, and before and after your dose of Namuscla is modified. How often these tests will be performed depends on your heart function.
If you or your doctor detects any heart rhythm disturbances or any of the conditions stated in section "Do not take Namuscla", your doctor will stop your treatment with Namuscla.

If you notice that the rhythm of your heart changes (the heart beats faster or slower), if you feel fluttering or pain in your chest, if you have difficulty breathing, if you feel dizzy, if you sweat or if you faint, you have to **contact an emergency centre immediately**.

Some patients may have higher blood levels of Namuscla because of slower break down in the liver and the dose may need to be adjusted accordingly.

Children and adolescents
Namuscla should not be used in children and adolescents younger than 18 years old.

Other medicines and Namuscla
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Namuscla with certain medicines for treating heart rhythm disorders (quinidine, procainamide, disopyramide, ajmaline, encainide, flecainide, propafenone, moricizine, amiodarone, sotalol, ibutilide, dofetilide, dronedarone, vernakalant). See section "Do not take Namuscla". Taking Namuscla together with any of these medicines increases the risk of a serious heart rhythm disturbance called torsades de pointes.

Do not take Namuscla with certain medicines which have a so called narrow therapeutic window (these are medicines where small differences in dose or blood concentration may impact the effect of the medicine or side effects). Examples of such medicines are digoxin (for heart problems), lithium (mood stabiliser), phenytoin (for treating epilepsy), theophylline (against asthma) and warfarin (against blood clots).

Tell your doctor or pharmacist if you are taking any of the following since these medicines may affect or be affected by Namuscla:
- medicines for heart problems (lidocaine, tocainide, propranolol, esmolol, metoprolol, atenolol, carvedilol, bisoprolol, nebivolol, verapamil, diltiazem),
- certain other medicines:
    - timolol for treating high pressure in the eye (glaucoma),
    - certain antibiotics (ciprofloxacin, rifampicin),
    - certain antidepressants (fluvoxamine),
    - tizanidine (used to relax the muscles),
    - metformin (used against diabetes)
    - omeprazole (to treat stomach ulcer and gastric acid reflux).

Smoking and Namuscla
Tell your doctor or pharmacist if you start to smoke or quit smoking while taking Namuscla because smoking impacts the Namuscla blood levels and your dose may need to be adjusted accordingly.

Namuscla with drink
It is recommended to reduce your caffeine intake by half while on treatment with mexiletine because the medicine can increase caffeine levels in your blood.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. If you become pregnant while taking Namuscla, see your doctor immediately as it is preferable not to take Namuscla while you are pregnant. If you become pregnant while taking Namuscla, see your doctor immediately.

Mexiletine passes into human milk. You should talk to your doctor about this, together you will make a decision whether to abstain breast-feeding or to discontinue/abstain from mexiletine therapy.

Driving and using machines

Namuscla may in rare cases cause tiredness, confusion, blurred vision: If you have these effects do not drive, cycle and use machines.

3. How to take Namuscla

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended starting dose is 1 capsule per day. The doctor will increase the dose gradually depending on how well the medicine is working. The maintenance dose is 1 to 3 capsules daily taken at regular intervals throughout the day.

Do not take more than 3 capsules a day.

Check of heart function
Before starting treatment with Namuscla and regularly during treatment, you will have tests to check how well your heart is working,. Depending on your heart function you may also need testing before and after any dose adjustment. See section “Warnings and precautions”. Your doctor will also regularly reassess your treatment to make sure Namuscla is still the best medicine for you.

Method of administration
Namuscla is for oral use.

Swallow the capsule with a glass of water, while standing or sitting up. You may take Namuscla during a meal to avoid belly pain (see section “Possible side effects”).

If you take more Namuscla than you should
Contact your doctor if you take more than the recommended dose of Namuscla. This could be very harmful to your health. You or your companion should contact the doctor immediately if you have tingling in the arms and legs, if you feel unable to think clearly or concentrate, if you have hallucinations, convulsions, if you feel that your heart beats slower, if you feel dizzy and faint, if you collapse or if your heart stops beating.

If you forget to take Namuscla
If you have forgotten a dose, do not take a double dose and take the next dose at your regular schedule.

If you have further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effects are:
Contact your doctor or go to your nearest emergency center **immediately** if you experience any of the following side effects:
- severe allergy to mexiletine (with symptoms such as severe rash with fever); this is a very rare side effect, may affect up to 1 in 10,000 people.
- disorders of heart rhythm, see section "Warnings and precautions" for symptoms and more information; this is a common side effect, may affect up to 1 in 10 people.

Other side effects that may occur:
Very common side effects (may affect more than 1 in 10 people):
- Abdominal (belly) pain
- Insomnia (difficulty sleeping)

Common side effects (may affect up to 1 in 10 people):
- Somnolence (sleepiness)
- Headache
- Tingling in the arms and legs
- Blurred vision
- Vertigo (sensation of feeling off balance)
- Rapid heart rate
- Flushing
- Low blood pressure (which can cause dizziness and feeling faint)
- Nausea (feeling sick)
- Acne
- Pain in the arms and legs
- Tiredness
- Weakness
- Chest discomfort
- Malaise (a feeling of general discomfort and illness)

Uncommon side effects (may affect up to 1 in 100 people):
- Convulsions (fits)
- Speech disorders
- Slow heart rate

Rare side effects (may affect up to 1 in 1,000 people):
- Abnormal functioning of the liver (observed after blood analysis).

Very rare side effects (may affect up to 1 in 10,000 people):
- Liver injury including inflammation (hepatitis)
- Severe reaction to the medicine (with rash and fever)

Not known (frequency cannot be estimated from the available data):
- Decrease in white blood cells or in platelets
- Lupus syndrome (disease of the immune system)
- Redness and peeling of the skin
- Stevens-Johnson syndrome: a severe allergic reaction with skin rashes, often in the form of blisters and sores in the mouth and eyes, and other mucous membranes
- Blisters of the skin, malaise and fever in the context of a condition called DRESS
- Hallucinations (seeing or hearing something that is not present).
- Transient confusion (a temporary inability to think clearly or concentrate)
- Double vision
- Altered sense of taste
- Disorders of heart rhythm
- Collapse
- Hot flushes

- Pulmonary fibrosis (disease of the lung)
- Diarrhoea
- Vomiting
- Injury of the oesophagus (food pipe)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Namuscla

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister. The expiry date refers to the last day of that month.

Store below 30°C. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Namuscla contains
Each hard capsule contains:
- mexiletine hydrochloride corresponding to 166.62 mg of mexiletine (active substance)
- Other ingredients (maize starch, colloidal anhydrous silica, magnesium stearate, gelatin, iron oxide [E 172], titanium dioxide [E 171]).

What Namuscla looks like and contents of the pack
Namuscla hard capsules are reddish hard gelatin capsules filled with white powder.
Namuscla is available in blister packs containing 30, 50, 100 or 200 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Lupin Europe GmbH
Hanauer Landstraße 139-143,
60314 Frankfurt am Main
Germany

Manufacturer
Hormosan Pharma GmbH
Hanauer Landstraße 139-143,
60314 Frankfurt am Main
Germany

Lupin Healthcare (UK) Ltd
The Urban Building, second floor, 3-9 Albert Street
SL1 2BE Slough, Berkshire,
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

AT, BE, BG, CZ, CY, DK, EE, EL, ES, FR, FI, HR, IE, IS, IT, LV, LT, LU, HU, MT, NL, NO, PL, PT, RO, SI, SK, SE

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.