

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Namuscla 83 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains mexiletine hydrochloride corresponding to 83.31 mg mexiletine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Namuscla capsules are Swedish orange (cap) and white (body) 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 NaMuscla is 167 mg daily. After at least 1 week of treatment, based on the clinical response, the daily dose can be increased up to 333 mg daily. After at least 1 further week of treatment, based on clinical response, the dose can be further increased up to a maximal 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 83mg 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 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.

Drug screening

Mexiletine may cross-react in various amphetamine screening assays, which can lead to a false-positive urine test for amphetamines when Mexiletine is taken.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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.

<i>Blood and lymphatic system disorders</i> Not known: leukopenia, thrombocytopenia
<i>Immune system disorders</i> Very rare: drug reaction with eosinophilia and systemic symptoms Not known: lupus-like syndrome, dermatitis exfoliative, Stevens-Johnson syndrome
<i>Psychiatric disorders</i> Very common: insomnia Common: somnolence Not known: hallucinations, confusional state
<i>Nervous system disorders</i> Common: headache, paraesthesia, vision blurred Uncommon: seizure, speech disorders Not known: diplopia, dysgeusia
<i>Ear and labyrinth disorders</i> Common: vertigo

<p><i>Cardiac disorders</i> Common: tachycardia Uncommon: bradycardia Not known: atrioventricular block</p>
<p><i>Vascular disorders</i> Common: flushing, hypotension Not known: circulatory collapse, hot flush</p>
<p><i>Respiratory, thoracic and mediastinal disorders</i> Not known: pulmonary fibrosis</p>
<p><i>Gastrointestinal disorders</i> Very common: abdominal pain Common: nausea Not known: diarrhoea, vomiting, oesophageal ulcers and perforation</p>
<p><i>Hepatobiliary disorders</i> Rare: hepatic function abnormal Very rare: drug-induced liver injury, liver disorder, hepatitis</p>
<p><i>Skin and subcutaneous tissue disorders</i> Common: acne</p>
<p><i>Musculoskeletal and connective tissue disorders</i> Common: pain in the extremities</p>
<p><i>General disorders and administration site conditions</i> Common: fatigue, asthenia, chest discomfort, malaise</p>

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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 \geq 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		

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

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		
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)

PLGB 54289/0005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/05/2025

10. DATE OF REVISION OF THE TEXT

14/01/2026