Part VI: Summary of the risk management plan

Summary of risk management plan for Namuscla (Mexiletine hydrochloride)

This is a summary of the risk management plan (RMP) for Namuscla. The RMP details important risks of Namuscla, how these risks can be minimised, and how more information will be obtained about Namuscla's risks and uncertainties (missing information).

Namuscla's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Namuscla should be used.

This summary of the RMP for Namuscla should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Namuscla's RMP.

I. The medicine and what it is used for

Namuscla is authorised for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders. It contains mexiletine hydrochloride as the active substance and it is given orally.

Further information about the evaluation of Namuscla's benefits can be found in Namuscla EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/namuscla.*

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

Important risks of Namuscla, 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;

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

In the case of Namuscla, 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 PSUR 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 Periodic Safety Update Reports (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 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. 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 children 7. Off-label use in DM1 and DM2 patients
Missing information	8. Long term use in adult patients with myotonic disorders 9. Effect on fertility and use in pregnancy 10. Safety in elderly 11. Use in patients with severe renal impairment

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	<u>Routine risk minimisation measures</u> SmPC section 4.3 and 4.8. PL section 2 and 4. <u>Additional risk minimisation measures</u> 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.
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 alert 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.
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.
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.
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 4.4. PL section 2. Additional risk minimisation measures: Educational guide for Healthcare Professional
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).
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 children	
Evidence for linking the risk to the medicine	Non-dystrophic myotonic disorders are congenital, and their onset may occur at all ages, including infancy, childhood and adolescence. Therefore, the possibility of off-label use in the paediatric population cannot be excluded.
Risk factors and risk groups	Children presenting early with myotonic symptoms may be at risk of off-label use as paediatric clinicians may want to use mexiletine in the paediatric population (children and adolescent aged 0 to 18 years).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2. PL section 2. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

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: None. 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.

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.

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.