18 December 2018
EMA/879309/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Namuscla (mexiletine hydrochloride)
Treatment of myotonic dysorders
EU/3/14/1353 (EMA/OD/074/14)
Sponsor: Lupin Europe GmbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substance	Mexiletine hydrochloride
International Non-Proprietary Name	Mexiletine hydrochloride
Orphan indication	Treatment of myotonic disorders
Pharmaceutical form	Capsule, hard
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	Cardiac therapy, antiarrhythmics, class Ib (C01BB02)
Sponsor's details:	Lupin Europe GmbH Hanauer Landstraße 139-143 60314 Frankfurt am Main Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Lupin Europe GmbH - Germany
COMP opinion date	9 October 2014
EC decision date	19 November 2014
EC registration number	EU/3/14/1353
Post-designation procedural history	
Transfer of sponsorship	Transfer from Temmler Pharma GmbH & Co. KG to Hormosan Pharma GmbH – EC decision 9 October 2015. Transfer from Hormosan Pharma GmbH to Lupin (Europe) Limited - EC decision of 18 August 2016. Transfer from Lupin (Europe) Limited to Lupin Europe GmbH – EC decision of 18 May 2018.
Marketing authorisation	
Rapporteur / co-Rapporteur	B. Sepodes, K. Dunder
Applicant	Lupin Europe GmbH - Germany
Application submission date	26 June 2017
Procedure start date	18 August 2017
Procedure number	EMA/H/C/004584/0000
Invented name	Namuscla
Therapeutic indication	Symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders. Further information on Namuscla can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/namuscla
CHMP opinion date	18 October 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	A. Magrelli/ A. Lorence
Sponsor's report submission date	28 August 2018
COMP discussion and adoption of list of questions	11-13 September 2018
COMP opinion date	8 November 2018

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the orphan medicinal product designation in 2014 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing mexiletine hydrochloride was considered justified based on a bibliographic compilation of clinical studies which have reported the effect of this product in the proposed condition;
- the condition is chronically debilitating due to pain with muscle stiffness associated with disability. The muscle stiffness can be very debilitating leading to falls associated with fractures and serious injury;
- the condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made; this was based on a literature search which was conducted by the sponsor;
- in addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mexiletine hydrochloride may be of significant benefit to those affected by the condition. The satisfactory methods of treatment authorised include mexiletine hydrochloride being authorised in two EU Member States, which due to its limited coverage does not offer sufficient access for patients affected by the condition. The potential increased availability through a centralised authorisation is accepted as a justification for a significant benefit based on a major contribution to patient care.

3. Review of criteria for orphan designation at the time of marketing authorisation

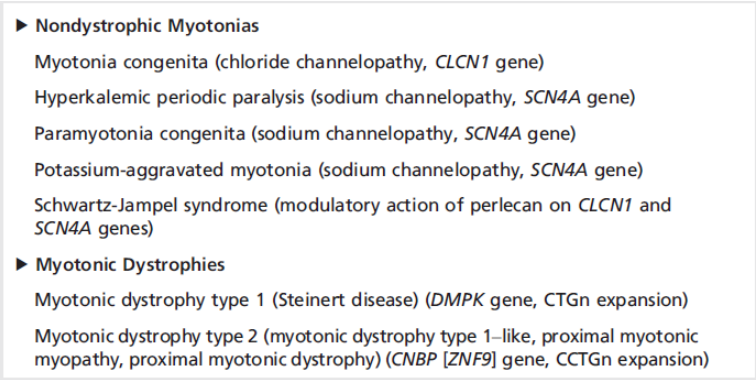
Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor is proposing that myotonic disorders is a distinct medical entity and thus continues to be a condition that can be maintained for this marketing procedure. Myotonic disorders cover two forms: myotonic dystrophies (DMs) and non-dystrophic myotonias (NDMs).

Figure 1.



Continuum (Minneap Minn) 2016;22(6):1889–1915

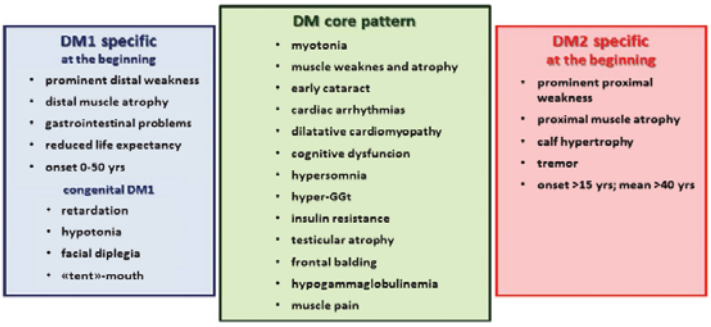
Myotonia is clinically defined as a difficulty in relaxation of a muscle after maximum voluntary contraction. It can affect muscles to varying degrees as well as be aggravated by specific conditions. Myotonia may not only affect skeletal muscle but also smooth muscle. Smooth muscle involvement is not a typical feature of nondystrophic myotonias but of myotonic dystrophies.

The spectrum of DMs includes two types: type 1 (DM1) and type 2 (DM2) which are caused by mutations in two different genes. The age of onset of DMs ranges from congenital forms at birth to late onset at ~70 years.

DM1 causing mutations are an expansion of a CTG repeat in the 3' UTR of the DMPK gene. Repeats consisting of more than 1,000 CTG-triplets result in congenital DM, the most severe expression of the disease. The sexual inheritance also affects the severity of the disease: maternal inheritance results in more severe clinical features than paternal inheritance. Additional symptoms described in classical DM1 include distal muscle weakness, fatigue, cardiac conduction defects, neuropathy, endocrinopathies (on top of diabetes mellitus), and alopecia. Age of onset for the classical phenotype ranges between 10 and 30 years. In congenital DM1 affected children suffer severe and generalized weakness, hypotonia and respiratory problems after birth. One study further found that DM1 patients may have an increased risk of skin cancer.

DM2 mutations are located within intron 1 of the CNBP gene: more than 75 CCTG repeats have been described as disease causing. DM2 is considered a clinically more benign disorder than DM1 and can be distinguished by a proximal muscular dystrophy and sparing of facial muscles, and the lack of a congenital form or the severe central nervous system involvement observed in DM1. The diagram below taken from *Journal of Neuromuscular Diseases 2 (2015) S59–S71* summarises this.

Figure 2.



Myotonic dystrophies are multisystemic diseases with a core pattern of clinical presentation which also presents a number of dissimilar features making them clearly separate diseases

The nondystrophic myotonias are channelopathies caused by mutations in voltage-gated ion channels on the skeletal muscle membrane resulting in episodic muscle weakness or myotonia. Three types of channelopathies have been described (*Continuum (Minneap Minn) 2016;22(6):1889–1915*):

- Sodium channelopathies is associated with an autosomal dominant allelic disorder.
- Chloride channelopathies are associated with two types of genetic mutations. One is transmitted as a autosomal dominant namely myotonia congenita described by Thomsen in 1876 and the second as a recessive namely myotonia congenital described by Becker.
- Scwartz-Jampel Syndrome which is linked to anautosomal recesive trait leading to perlecan deficiency. Perlecan deficiency is associated with modification of channel function (both sodium and chloride channel function) leading to nondystrophic myotonia.

The condition continues to be described as distinct in a recent literature search and there does not seem to be any major changes in classification or description of the condition just more detail regarding the different presentations.

The condition can be considered a distinct medical entity and has not been significantly changed since the initial orphan designation.

The approved therapeutic indication “symptomatic treatment of myotonia in adult patients with myotonic disorders” falls within the scope of the designated orphan indication “myotonic disorders”.

Intention to diagnose, prevent or treat

Based on a positive CHMP assessment, the intention to treat the condition is acceptable.

Chronically debilitating and/or life-threatening nature

The condition, while not life-threatening, is chronically debilitating. The most common problems are stiffness and pain. There is very little data available in the public domain regarding these problems. However, one publication cited by the author discussed the average severity of stiffness which was rated at 3.85 on a 1-9 scale with a standard deviation of 1.82 between subjects and within subjects of 1.50 thus demonstrating the variability. Pain is a frequent symptom that may have been previously under-recognized and possibly undertreated in the non-dystrophic myotonias. In addition to pain and stiffness, permanent and debilitating muscle weakness can develop. This spectrum of disorders is not fatal, but has a variable degree of disease severity. The more severe forms may be considered chronically debilitating in particular due to pain and muscle stiffness which may lead to impairment in daily functioning.

Number of people affected or at risk

The sponsor had conducted a literature search which produced articles covering the following countries: Croatia, England, Finland, Germany, Ireland, Italy, Spain and Sweden. The articles range in publication data from 1982 to 2017. The reporting of prevalence in several of the articles covers subtypes of the condition.

Table 1. Overview of EU studies on the prevalence of DM and NDM.

Country	Subtype	Prevalence	Reference
Croatia	DM1	1.8 per 10,000	Medica et al. 1997
England	NDM (MC) (PC) (SCM)	0.08 per 10,000 (0.05 per 10,000) (0.01 per 10,000) (0.02 per 10,000)	Horga et al. 2013
England	DM (DM1) (DM2)	1.0 per 10,000 (1.0 per 10,000) (0.02 per 10,000)	Norwood et al. 2009
Finnland	MC	0.7 per 10,000	Baumann et al. 1997
Germany	DM2	≥0.1 per 10,000	Udd et al. 2003
Germany	MC (Thomsen) (Becker)	0.05 per 10,000 (0.02 per 10,000) (0.03 per 10,000)	Baumann et al. 1997
Ireland	DM1 MC PC	0.7 per 10,000 0.03 per 10,000 0.02 per 10,000	Lefter et al. 2017
Ireland	DM	0.9 per 10,000	Hughes et al. 1996
Ireland	DM	1.2 per 10,000	Magee et al. 1999
Italy	DM (DM1) (DM2)	1.1 per 10,000 (1.0 per 10,000) (0.1 per 10,000)	Vanacore et al. 2016
Italy	DM1	0.9 per 10,000	Siciliano et al. 2001
Italy	MC	0.1 per 10,000	Pinessi et al. 1982
Spain	DM	2.6 per 10,000	López de Munain et al. 1993
Sweden	DM	2.0 per 10,000	Ahlström et al. 1993
Sweden	DM1	1.8 per 10,000	Lindberg & Bjerkne 2017

The sponsor highlighted a review article by Theadom and colleagues [2014] which was authored by epidemiologists in New Zealand covering different muscular dystrophies worldwide. This included 10 studies from EU countries on myotonic dystrophy. The prevalence range reported for DM was 0.2 – 1.8 per 10,000 with the vast majority of studies indicating a prevalence in the range of 1 per 10,000 (i.e. 0.7 – 1.1 per 10,000). A review publication by Deenen J et al 2015 from the Netherlands narrowed the prevalence for Europe to 10 in 100,000 in myotonic dystrophies and 1 in 100,000 in nondystrophic myotonia. A recent paper by Lindberg C et al 2017 gives some indication of the geographical distribution of the myotonic disorders highlighting that Croatia had prevalence reported of 18 in 100,000 with Finland reporting the highest at 44.2 in 100,000. It would therefore appear that there is some variability of the condition across Europe. Myotonic Dystrophies DM1 and DM2 are reportedly more prevalent than nondystrophic myotonias.

Following a request by the COMP the sponsor provided an updated prevalence calculation based on the most recent published sources (Suetterlin et al. 2015, Wood et al. 2018) as well as information from

recently created National registries. The later provide information primarily on dystrophic myotonia patients. From these publications the sponsor created the following tables.

Table 1.

Country	Registry	Reported number of patients in registry
Bulgaria	www.nmd-bg.com; accessed 26.Sept 2018	84 patients with DM; NDM not reported. Source: Wood 2018 (data as of April 2017)
Czech Republic	www.ready.registry.cz; accessed 26.Sept 2018	612 patients with DM; NDM not reported - number as of Sept 2018.
France	www.dmscope.fr;	2914 patients with DM (2777 with DM1 and 137 with DM2) – number reported as of April 2018.
Germany	Myotonic Dystrophy Patient Registry (Germany and	508 patients with DM; NDM not reported. Source: Wood 2018 (data as of April 2017)
Poland	Polish Registry of Patients with Neuromuscular Diseases	>200 patients with NDM Source: Dr Anna Lusakowska custodian of registry (Unpublished Data Jan 2018). ---- 378 patients with DM. Source: Wood 2018 (data as of April 2017)
United Kingdom (DM)	Myotonic Dystrophy Patient Registry	610 patients with DM – number reported as of July 2016.
United Kingdom (NDM)	Non-dystrophic Patient Registry	122 patients identified from the registry for study purposes – number reported by Suetterlin et al in 2015
Netherlands	CRAMPS	482 patients with DM; NDM not reported. Source: Wood 2018 (data as of April 2017)
Spain	Spanish Registry of neuromuscular diseases	278 patients with DM, NDM not reported. Source: Wood 2018 (data as of April 2017)
Italy	The Italian registry for Myotonic Dystrophy	538 patients with DM; NDM not reported. Source: Wood 2018 (data as of April 2017)
Sweden	NMiS	211 patients with DM; NDM not reported. Source: Wood 2018 (data as of April 2017)

And data from the most recent publications which are summarised below.

Table 2.

Country	Subtype	Prevalence	Reference
England	NDM	0.08 per 10,000	Horga et al. 2013
Ireland	DM1 NDM (MC) (PC)	0.7 per 10,000 0.05 per 10,000 (0.03 per 10,000) (0.02 per 10,000)	Lefter et al. 2017
Italy	DM (DM1) (DM2)	1.1 per 10,000 (1.0 per 10,000) (0.1 per 10,000)	Vanacore et al. 2016
Sweden	DM1	1.8 per 10,000	Lindberg & Bjerkne 2017

With the exception of the numbers from Sweden, there is general consensus that the prevalence of DM in EU is no more than 1-1.3 per 10,000. There are certain regional differences, such as higher prevalence in the Nordic countries (for example western Sweden) and differences in the prevalence of DM2 in Germany, Finland and Czech Republic

Prevalence for non dystrophic myotonia is significantly less (estimated to be 0.1 per 10,000). However, studies and registries in this population are scarce.

The applicant considered that although prevalence studies for in particular NDM are not exhaustive or robust, it can be considered more correctly estimated that prevalence for DM in EU is on average 1.1 per 10,000 and for NDM 0.1 per 10,000. Overall prevalence for dystrophic myotonia would thus be 1.2 per 10,000 in EU.

The COMP accepted this revised prevalence calculation for the basis of the maintenance of the orphan designation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Mexiletine has been authorised for the treatment of myotonic disorders in France for limited use in a hospital setting. There are no other medicines authorised in Europe for this condition.

There are no pan-European Guidelines on how to manage and treat myotonic disorders. There is however a position paper from a working group which has just recently been published in *Neuromuscular Disorders · February 2018: 222nd ENMC International Workshop: Myotonic dystrophy, developing a European consortium for care and therapy, Naarden, The Netherlands, 1–2 July 2016 Libby Wood, Guillaume Bassez, Baziel van Engelen, Hanns Lochmüller, Benedikt Schoser on behalf of the 222nd ENMC workshop participants.*

There are also recent National/Regional Guidelines (many listed in the sponsor's survey MyoPath):

- Scotland: Guideline for the management of Myotonic Dystrophy in adults 2017. Recommendation of the use of mexilitene.

- England: Mexilitene for the symptomatic treatment of myotonic disorders – first line NHS 2017.
- Netherlands: Guidelines for myotonic dystrophy type1 and focused on cardiac complications and respiratory function but not for the treatment of myotonia symptoms.
- Germany: Guidelines in place from the German Society of Neurology recommendation of the use of mexilitene.
- Greece: Guidelines used by expert but no specific national guidelines.
- France: Draft guidelines in progress.
- Spain: Consensus on treatment of myotonic dystrophy type 1 and guidelines in press.

It appears that the guideline landscape for myotonic disorders in Europe is evolving and that there are a substantial number of national guidelines with the release of the recent position paper in 2018 mentioned above. This is a significant change from the time of the initial orphan designation.

Significant benefit

The sponsor claims lack of availability of mexiletine across Europe as the basis of significant benefit.

The only country where this product has a national licence for the designated condition is France.

Mexiletine as an antiarrhythmic had previously been available in Europe as Boehringer Ingelheim's MEXITIL which was discontinued in 2008. In order to allow patients in France with myotonic disorders to continue benefiting from mexiletine following the withdrawal of the product from France, on 12 October 2010, the marketing authorisation ownership was transferred from Boehringer Ingelheim to AP-HP (Assistance Publique Hôpitaux de Paris, France). Since 2010, the product has been available on the French market for the "symptomatic treatment of myotonic syndromes (myotonic dystrophies and non-dystrophic myotonias or channelopathies)" based on a literature review.

Mexiletine also has a national licence in Hungary, however the authorisation is for cardiac arrhythmias only.

In Italy, the Agenzia Industrie Difesa-Stabilimento Chimico Farmaceutico Militare took over manufacturing mexiletine at the request of national authorities. This is provided to myotonia patients on the basis of a "named patient program" but without the presence of a marketing authorisation.

There are no other products authorised in Europe for the treatment of myotonic disorders. Mexiletine is imported to some EU countries (see below) but the source of this import is reported to be from outside the EU (Israel, Canada, USA and Japan).

To support their significant benefit claim the sponsor has conducted a European Survey to substantiate that lack of availability of mexiletine results in patient harm. The survey is called "*Myotonia Observation Survey of Patient Access to therapy avoiding Harm" (MyoPath).*

MyoPath consists of two key elements: (1) a qualitative assessment on the basis of interviews with clinical experts and patients/patient advocates in 12 of the 15 Member States targeted across the EU (France, Italy, Hungary, Spain, Poland, Netherlands, Germany, Sweden, Belgium, Portugal, Greece and Romania;in the UK, Finland and Austria no interviews were conducted and (2) a quantitative analysis on the basis of an online survey among patients and caregivers. Eighteen Member States were targeted in the second survey (Germany, Italy, Poland, France, Romania, Belgium, Spain, Austria, Ireland, Slovakia, UK, Estonia, Finland, Greece, Hungary, the Netherlands, Portugal and Sweden). The largest proportion of respondents was from Germany, Italy, Poland, France and Romania. Responses

from Belgium, Spain, Austria, Ireland, Slovakia and UK were low, ranging from 1-4. No responses were received from the remaining Member States.

The full report is included in Annex 2 of the submission.

Reported availability of mexiletine in the European Union

Aspects of the availability of mexiletine across Europe are captured in both elements of the survey done by the sponsor.

In the Qualitatively Analysis, a series of interviews with clinical experts and patient representatives was performed to obtain more insight in the local treatment habits. The objective of these interviews was to evaluate awareness and access of mexiletine. A total of seventeen interviews spanning across twelve out of the planned 15 Member States (see above) were completed. Twelve of these interviews were held with healthcare professionals and five with patient representatives. The sponsor stated that the rationale to select those Member States was (a) to cover a representative sample of the EU population, (b) to have for this purpose information from the main geographical areas and finally (c) to involve those Member States where mexiletine is known to be available at least to a certain extent (specifically France, Italy and Hungary) as well as those where such supply would not be expected. This rationale is well understood and supported, even though it would have been even more useful for the purpose of assessment to have all EU Member States included.

From the interviews it is reported that even for those patients who have a source of mexiletine the supply is not always dependable and continuous.

The interviews focus to a large extent on the awareness of the use of mexiletine in myotonic disorders as well as on the access tothe product. It was noted that the awareness of the use of mexiletine in this condition is not optimal and thus if awareness was improved this could benefit patients.

As regards the French national licence for mexiletine, the COMP noted that the marketing authorisation was held by a hospital which produced limited amounts of mexiletine solely aimed at satisfying the national needs of French patients with the condition. The COMP could not find any record that the hospital was exporting the product to other Member States. Indeed it was noted that Member States were importing the product from countries outside of the European Union (Canada, USA, Israel and Japan).

The sponsor summarised the statements regarding availability in 12 different Member States in the table below.

Table 3.

Country	Availability	Comment
France	Mexiletine is authorised as treatment for myotonic disorders, marketing authorisation available, manufactured and distributed through the Assistance Publique – Hôpitaux de Paris	The only member state with a marketing authorisation, and a relatively consistent supply of mexiletine. Despite high level of activities and awareness it is estimated that up to 40% of myotonia patients are not covered by the national network.
Italy	Agenzia Industrie Difesa-Stabilimento Chimico Farmaceutico Militare manufactures mexiletine. No marketing authorisation.	Product is distributed under a "named patient program". Still there is only limited awareness with inconsistent supply and drug shortage being experienced.
Hungary	National marketing authorisation for mexiletine in antiarrhytmic indication. Accessible in local pharmacies.	Supply problems sometimes occur that might last for several months. Burden to patients is mainly financial.
Spain	Intermittently available via import to some patients who reach experts (that are aware of mexiletine)	Laborious procedure requiring coordinated effort from physician/patient and pharmacy to gain approval from the Ministry of Health for import.
Poland	Available to some patients via import (e.g. from Canada)	Laborious procedure requiring coordinated efforts from physician/patient as well as two levels of approval from health authorities and participation from pharmacy performing the import. Patients experience discontinuation in supply.
Netherlands	Available to some patients via import (usually from Japan, Israel, US, or Canada, occasionally from Hungary).	Not much experience among neurologists. Frequently anti-epileptics are prescribed. Laborious procedure requiring coordinated effort from physician/patient and participation from pharmacy performing the import.
		Delays in refill orders may result in interrupted treatment with mexiletine
Germany	Available to some patients via import (usually from Canada)	Laborious procedure requiring coordinated effort from physician/patient and participation from pharmacy performing the import. Because access is difficult physicians rarely prescribe the product.
Sweden	Available to some patients via import	Laborious procedure requiring coordinated effort from physician/patient and participation from pharmacy performing the import.
Belgium	Available to some patients via import	Laborious procedure requiring coordinated effort from physician/patient and participation from pharmacy performing the import. Some reluctance among physicians to prescribe mexiletine due to difficult access.
Portugal	Available in one center based on importation from Japan.	Limited awareness of mexiletine Since it is available in one centre only high travel burden for patients.
Greece	Mexiletine is not available	Essentially no awareness of mexiletine among experts and hence no steps taken for import it. Patients are treated with anti-epileptic drugs (specifically carbamazepine).
Romania	Mexiletine is not available	Experts do not take steps to import mexiletine.

In order to complete the results of the survey carried out by the sponsor, the COMP reviewed the availability in the remaining 16 Member States not covered by the sponsor's survey (Austria, Denmark, Finland, Estonia, Lithuania, Latvia, the Czech Republic, Slovenia, Slovakia, Croatia, United Kingdom,

Ireland, Luxembourg, Cyprus, Malta and Finland). The review was done by the COMP members from each of the remaining 16 Member States by checking import status and use of mexiletine in their respectiveMember States . Denmark and Slovenia clearly indicated that they had the product available on a name patient basis. In Finland, the United Kingdom and Ireland mexiletine is also used on a named patient basis, but it was impossible to separate out the use for patients with myotonic disorders and the uses in anti-arrhythmic indications. Very limited amounts of mexiletine were requested in Estonia (7 boxes for 2017) and Croatia (2 boxes in 2017). In Luxembourg, Malta, Slovakia, the Czech Republic, Cyprus, Latvia and Bulgaria, there was no name patient use of mexiletine for the condition. There was no response from Austria and Lithuania.

The findings from the COMP members' review of their national situation are in line with the findings from the sponsor's MyoPath survey and can be considered to confirm the representativeness of the results from the MyoPath survey of the situation across the EU. They also confirm that the French authorised product is not being exported to any of these Member States.

Based on the MyoPath survey and the COMP members' national review, the availability of mexiletine across the EU for the treatment of myotonic disorders can be summarised as follows:

- No information from Austria and Lithuania (2 Member States).
- Not available in Luxembourg, Malta, Slovakia, the Czech Republic, Cyprus, Latvia, Bulgaria, Greece and Romania (9 Member States).
- Very limited availability for use (condition unverifiable) in Estonia and Croatia (2 Member States).
- Limited availability for use (condition unverifiable) in Finland, Ireland and the United Kingdom. (3 Member States)
- Limited and intermittent availability for use (condition verifiable) in Belgium, Poland, Spain, Sweden and the Netherlands (5 Member States).
- Limited availability for use (condition verifiable) with reports of single tertiary care use in Portugal (1 Member States).
- Name patient programmes with clearly described availability of the product for use in the condition in specialised tertiary care units in Denmark, Germany, Italy and Slovenia (4 Member States).
- Off-label use in Hungary.
- National Licence in France with product limited to a hospital pharmacy.

The sponsor's MyoPath quantitative online survey had as an objective the verification of the conclusions from the qualitative interviews, amongst a larger group of patients and caregivers. The survey was carried out in the same 15 Member States selected for interviews with the addition of Ireland, Slovakia and Estonia (18 countries in total). The survey respondents included participants from 11 out of the 18 Member States targeted. A total of 390 patients responded to the survey.

Notably and in support of the above considerations regarding lack of availability: 80% (n=312) of the participants had never received mexiletine for the treatment of their symptoms of myotonia. Seventy-eight patients (20%) were either currently on mexiletine or had tried mexiletine in the past (n=78;). At the time the survey was conducted 54 patients were being treated with mexiletine (~14% of the patients surveyed). Those patients were asked if they experienced any difficulty obtaining mexiletine. Thirty-seven percent 37% (n=20) confirmed this difficulty.

The sponsor also submitted a survey which was performed by the Myotonia Subgroup of German Muscle Association (DMG) in Germany in 2017 (hereafter "DMG survey"). This included data from 171 patients with myotonic disorders. Of these, only 17 patients (10%) were taking mexiletine. Several of

these patients reported that they obtained mexiletine from non-EU countries such as Canada, USA or Japan.

Based on the above considerations it can be concluded that there is varied and limited availability of mexiletine across the EU. Mexiletine is authorised for the treatment of myotonic disorders in only one EU Member State (France) and none of the other Member States have access to the French authorised product. According to the qualitative survey, approximately 80% (312 of 390 respondents in the survey) of patients with the condition were not receiving treatment with this product.

It is also noted that in those countries with access to mexiletine, the supply is often disrupted. This confirms that there is lack of availability of mexiletine in the EU.

Patient harm:

In order to justify significant benefit, the sponsor claims that lack of availability of mexiletine in the EU results in patient harm. The qualitative survey offered patient and expert testimonials which confirm the debilitation of the disease and the need for a treatment.

The MyoPath survey also presented data on patient harm associated with lack of availability and disruption to access to mexiletine. In the interviews described in the qualitative part of the survey various situations of interrupted treatment are discussed:

- Discontinuation of mexiletine as a marketed product in 2008 (Boehringer Ingelheim's MEXITIL): Many patients experienced worsening of symptoms and quality of life that could not be adequately improved with alternative therapies.
- Mexiletine treatment interrupted: These examples describe the impact that interruptions in treatment with mexiletine have on patients' symptoms and quality of life. For those patients who succeed in finding a source of mexiletine, the supply is not always dependable and continuous. As a result, patients experience a worsening of symptoms and quality of life when treatment with mexiletine is interrupted.

The findings are further supported by the data from the on-line survey where 390 patients participated (the quantitative analysis). In this survey eighteen Member States were targeted (Germany, Italy, Poland, France, Romania, Belgium, Spain, Austria, Ireland, Slovakia, UK, Greece, Portugal, Sweden, Finland, Netherlands, Estonia, Hungary, Estonia and Finland). The largest proportion of respondents was from Germany, Italy, Poland, France and Romania. Responses from Belgium, Spain, Austria, Ireland, Slovakia and UK were low, ranging from 1-4. No responses were received from the remaining Member States. For the patients who confirmed interruptions in their supply, over two thirds of the respective patients experienced this as harmful interruption of their treatment, with type of harm described for example as worsened muscle stiffness, mobility, fatigue, falling, pain, swallowing, breathing, digestion and sleep quality. Some key results are presented below:

Figure 3. Level of harm observed on typical myotonia symptoms when treatment with mexiletine is interrupted (DM1 and DM2 patients currently or in the past on mexiletine)

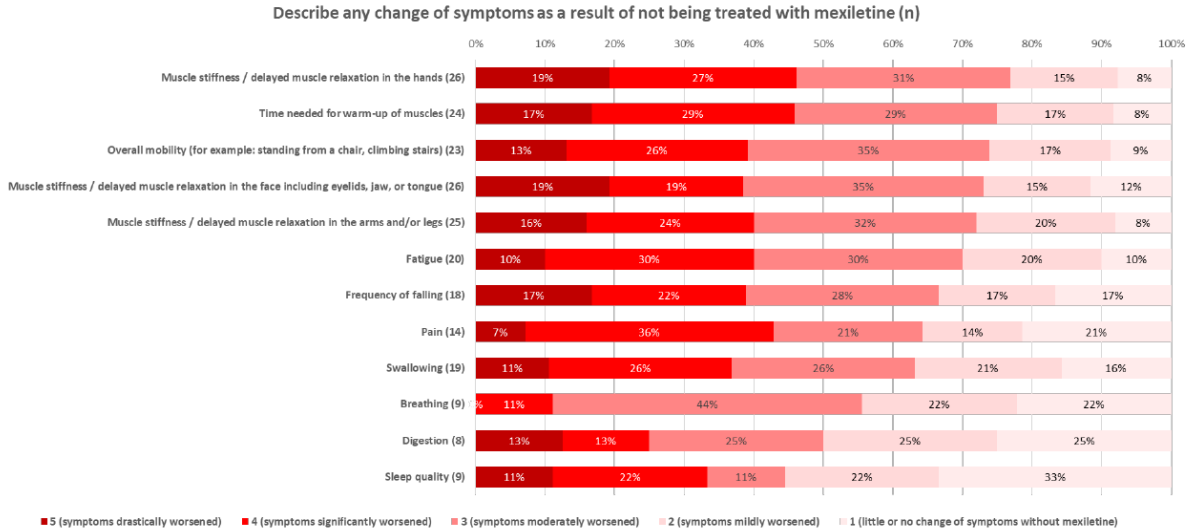
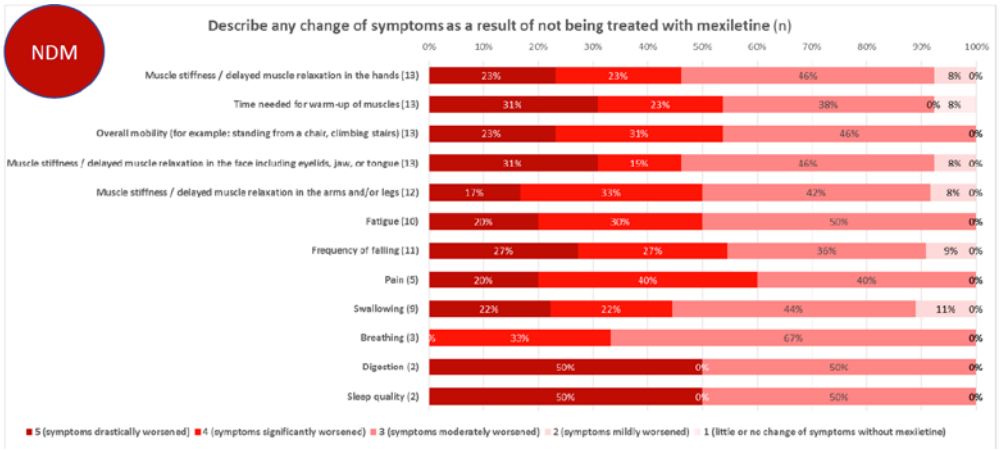


Figure 4. Level of harm observed on typical myotonia symptoms when treatment with mexiletine is interrupted (DM1 patients currently or in the past on mexiletine)



Similar deterioration of symptom control was seen in the DMG Survey.

Myotonia is a clinical phenomenon, which refers to a delayed muscle relaxation after voluntary or evoked muscle contraction. It is a cardinal feature of myotonic disorders including myotonic dystrophy and the non-dystrophic myotonias.

The Cochrane Review (Trip J, Drost GG, van Engelen BGM, Faber CG. Drug treatment for myotonia. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004762) states "*In the case of the nondystrophic patients it is noted in the literature that the major clinical manifestation of the non-dystrophic myotonias is muscle stiffness as a consequence of the myotonia. Additional common symptoms include pain, weakness and fatigue. Morbidity in the non-dystrophic myotonias is associated with painful myotonia and fatigue which are associated with the best predictors of poor general health perception and physical functioning (Brain 2010: 133; 9–22)*".

The data generated in the online survey showed that withdrawal of mexiletine caused a particularly pronounced harm in patients who have nondystrophic myotonia (NDM). The level of harm is higher in particular with regards to the recording of pain, digestion, frequency of falling, breathing and muscle stiffness as compared with DM1. This is plausible recognizing the use in clinical practice, and based on the mechanism of action as a sodium channel blocker. It is also in line with the indication the CHMP

has given to the product specifically focused on the treatment of patients with non-dystrophic myotonia (NDM). The patient harm confirmed in patients who have discontinued treatment with mexiletine can be extrapolated to patients who have never been treated with the product. It can therefore be considered that patients with NDM not treated with mexiletine are harmed.

The COMP concluded that the sponsor's structured survey which used a well-defined methodology together with the review done by COMP members demonstrated that there is limited and disrupted availability of mexiletine in the EU that results in patient harm, particularly in patients with nondystrophic myotonia. It is therefore established that Namuscla will bring significant benefit to those affected by the condition.

4. COMP position adopted on 8 November 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of myotonic disorders (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 1.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to pain with muscle stiffness associated with disability. The muscle stiffness can be very debilitating leading to falls associated with fractures and serious injury;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, Namuscla is of significant benefit to those affected by the orphan condition. The sponsor established that the lack of availability of mexiletine and disruption to treatment causes patient harm in patients with non dystrophic myotonia.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Namuscla, mexiletine hydrochloride, EU/3/14/1353 for treatment of myotonic dysorders is not removed from the Community Register of Orphan Medicinal Products.