European Heart Journal

Continued misuse of orphan drug legislation: a life-threatening risk for mexiletine

--Manuscript Draft--

Manuscript Number:	EURHEARTJ-D-20-00133
Article Type:	CardioPulse
Keywords:	Ventricular tachycardia Ventricular fibrillation Mexiletine European Medicines Agency Orphan drugs Pharmaceutical industry Misuse
Corresponding Author:	Pieter Postema, MD, PhD AMC Amsterdam, NETHERLANDS
First Author:	Pieter G. Postema, MD, PhD
Order of Authors:	Pieter G. Postema, MD, PhD
	Peter J Schwartz, MD
	Elena Arbelo, MD, PhD
	Wilbert J Bannenberg, MD, MSc
	Elijah R Behr, MA, MBBS, MD
	Bernard Belhassen, MD
	Josep Brugada, MD, PhD
	Pedro Brugada, MD, PhD
	A John Camm, MD
	Ruben Casado-Arroyo, MD, PhD
	Ellen 't Hoen, LLM, PhD
	Carla E.M. Hollak, MD, PhD
	Stefan Kääb, MD, PhD
	Pier D Lambiase, MRCP, PhD
	Antoine Leenhardt, MD
	Silvia G Priori, MD, PhD
	Vincent Probst, MD, PhD
	Bas C Stunneberg, MD
	Jacob Tfelt-Hansen, MD, DMSc
	Baziel G.M. Van Engelen, MD, PhD
	Christian Veltmann, MD
	Sami Viskin, MD
	Arthur A.M. Wilde, MD, PhD
Abstract:	Mexiletine, a class 1b sodium channel blocker, has been used in cardiology since the 1970's, and is still in use for the prevention of (recurrent) ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients with cardiomyopathy and in patients with Long QT syndrome. In addition, Mexiletine has been successfully used since the 1980's in neurology, and specifically for non-dystrophic myotonia. The use

	of Mexiletine in non-dystrophic myotonia has received renewed interest, also from the pharmaceutical industry, since randomised, placebo-controlled studies published in 2012 and 2018. This finally resulted in a marketing authorisation of Mexiletine as an orphan drug for non-dystrophic myotonia in 2018 by the European Medicines Agency, and consequently resulted both in withdrawal of generic Mexiletine, prohibiting of import, and in an exorbitant price increase, for both neurology and cardiology patients. Likewise, European healthcare systems are forced to either accept, negotiate or deny this price rise, and risk (further) problems in Mexiletine availability for patients who depend on this drug for VT/VF prevention and risk problems in the delivery of other care. This is just another example of continued misuse of orphan drug legislation and should be prevented.

Position

References online

Title: Continued misuse of orphan drug legislation: a life-threatening risk for mexiletine.

Introduction

Recently, patient access to mexiletine for the prevention of ventricular tachycardia (VT) and ventricular fibrillation (VF) has become critically endangered. This follows from the marketing authorisation by the European Medicines Agency (EMA) in December 2018 of mexiletine hydrochloride, now sold as 'Namuscla' by Lupin Europe GmbH, as an orphan drug for non-dystrophic myotonias.[1] As such, the price of mexiletine has skyrocketed to about €65,000 per patient per year in European countries (price varying with dose and geographic location from €17,000 to €85,000), not only for patients with non-dystrophic myotonia but also for cardiology patients who, since the 1970's,[2] use mexiletine to prevent VT/VF. As a consequence, our social healthcare systems are suddenly burdened with another tremendous increase in healthcare costs for a drug previously priced at about €450-4400 per patient per year (either import or production). Noteworthy, this case only adds to our continuing troubles with drugs to prevent VT/VF (e.g. quinidine[3]).

Commercial interest and regulatory incapability

Regretfully, the mexiletine case (figure 1) is just another example of our regulatory incapability to withstand misuse of orphan drug legislation and regulation by exorbitant commercial interests in the treatment of patients with rare or common disease.[3–7] Such interference of commercial interest with society healthcare can be illustrated as follows:

- A healthcare's inability to pay for excessive commercial prices of patented/novel or out-of-patent/conventional drugs with (regulated or effective) market exclusivity
- A healthcare's need to cut on other care to pay for excessive commercial prices of patented/novel or out-of-patent/conventional drugs with (regulated or effective) market exclusivity
- 'Evergreening' of drug patents (e.g. by changing administration route, obtaining additional patents for new use or combinations) to prolong patent exclusivity.
- Repurposing of drugs to new (orphan) indications, providing new patents or market exclusivity
- Price gouging of out-of-patent drugs for (orphan) indications
- Production stops of commercially unfavourable (orphan) drugs

These commercial interferences with healthcare jeopardise any type of healthcare system throughout the world, and now mexiletine is threatened by commercial misuse of orphan drug regulation by appropriation of medical knowledge in the public domain.

Insert figure 1.

The cardiology case of mexiletine

Mexiletine is one of the Vaughan Williams class 1b anti-arrhythmic drugs (a sodium channel blocker) that is available for the prevention of (recurrent) VT/VF in both ischemic and non-ischemic cardiomyopathies and, more mechanism-specific, in Long QT syndrome (LQTS). Mexiletine had been developed in the late 1960's, early 1970's, by Boehringer Ingelheim and was quickly and successfully tested for the prevention of ventricular arrhythmias.[2] However, subsequent studies in the 1980's showed that not all patients post myocardial infarction

received benefit from mexiletine, limiting its use at that time.[8,9] In 1995, mexiletine's late sodium current blocking properties were successfully explored to decrease the QT-interval in LQTS-patients (in particular LQTS-type 3 based on an increased late inward sodium current[10] and later also in LQTS-type 2[11]), to decrease their risk of VT/VF.[11,12]

Although other anti-arrhythmic drugs have now widely surpassed mexiletine, it is currently still successfully, but incidentally, used for VT/VF prevention in patients with a cardiomyopathy and recurrent VT/VF when other pharmacological and/or invasive interventions fail. This life-saving potential of mexiletine is also very clear in LQTS-patients with severely prolonged QTc-intervals despite beta-blocker therapy and is used to avoid cardioverter defibrillator implantations. Consequently, mexiletine is still acknowledged in both European and United States guidelines for VT/VF and sudden cardiac death prevention, either as monotherapy or escalation therapy in addition to other anti-arrhythmic drugs and/or interventions.[13,14]

The neurology case of mexiletine

Non-dystrophic myotonias (prevalence <2:100,000 with distinct geographic variation) form a heterogenous group of rare diseases caused by mutations in skeletal muscle ion channels. The most striking hallmark of non-dystrophic myotonias is delayed skeletal muscle relaxation after voluntary contraction (the symptom of myotonia), resulting in functional limiting muscle stiffness, pain, fatigue, weakness and social impairment.[15]

Due to the clear overlap of the electrophysiology of cardiac and skeletal muscle, it is of no surprise that anti-arrhythmic drugs can be used to treat neurological disorders. Similarly, neurological (and also psychotropic) drugs may result in cardiac (side-)effects[16,17] and vice versa, because of their organ-unspecific impact on ion channels. As such, since the 1980's many anti-arrhythmic drugs have been studied in small case series for the treatment of different types of myotonic disorders, with mexiletine as the most successful anti-myotonic drug.[18] Ever since, off-label mexiletine is considered the first drug of choice for patients with non-dystrophic myotonias.

In two recent, randomised, placebo-controlled studies in patients with non-dystrophic myopathy, published in 2012 and 2018, mexiletine was indeed effective for decreasing symptoms, increasing functional abilities and increasing social participation with less discomfort.[15,19] Since, many more patients (from children to adults) with non-dystrophic myopathy are treated with mexiletine.

Mexiletine as a commercial interest

The European orphan drug legislation was launched in 2000 to stimulate development of medicinal products for rare diseases.[20] Apart from protocol assistance and other incentives, 10-year market exclusivity has indeed resulted in a considerable number of new treatments for rare disease that have frequently been accompanied by very high to outrageous prices.[6,7] Although meant to stimulate development of new drugs, this legislation has also enabled authorisation of old drugs for new indications that are subsequently sold at monopoly prices. It appears that the randomised study with mexiletine, published in 2012,[15] spurred commercial interest in mexiletine due to its promise as a formal orphan drug with huge potential financial profits.

This story supposedly starts in 2010 when the mexiletine marketing authorisation in France was transferred from Boehringer Ingelheim France to Etablissement Pharmaceutique de l'AP-HP (Assistance Publique - Hôpitaux de Paris) and labelled for symptomatic treatment of myotonic syndromes instead of ventricular arrhythmias.[21] The French example, labelling mexiletine for myotonic disorders, was utilised by Temmler Pharma GmbH & Co. KG , Germany (now known as Aenova Group), to acquire an European orphan drug designation in 2014 for mexiletine for the treatment of myotonic disorders.[1] In 2015, when Lupin announced the acquirement of the specialty product portfolio of Temmler, which apparently included mexiletine, the product designation was transferred from Temmler to Hormosan Pharma GmbH, Germany (already acquired in 2008 by Lupin Group).[1] In 2016 the product designation was transferred from Hormosan to Lupin (Europe) Limited, United Kingdom, and in 2018 it was transferred to Lupin Europe GmbH, Germany.[1] Then, in December 2018, EMA granted marketing of Namuscla for the treatment of adult patients with non-dystrophic myotonia. Subsequently, in January 2019, the Etablissement Pharmaceutique de l'AP-HP ceased mexiletine delivery and transferred to Namuscla.[22] Strikingly, the price of mexiletine skyrocketed when being sold as Namuscla.

Catch 22

Regretfully, the European marketing authorisation of Namuscla for non-dystrophic myotonia, now jeopardises the >40-year-old cardiological indication of mexiletine. In several European countries, mexiletine to prevent VT/VF is now only available as Namuscla at this outrageous price. Ironically, the official contra-indications of Namuscla[1] list ventricular tachyarrhythmias, previous myocardial infarction and heart failure – mirroring one of the cardiology indications for mexiletine.

Importantly, there are no alternative (outpatient) class 1b anti-arrhythmic drugs for the same indication to prevent VT/VF. Lidocaine only has similar properties and effects when administered intravenously (which is also one of the ways to quickly test the potency of mexiletine to decrease risk for arrhythmias), and is therefore no outpatient alternative, and phenytoin is solely indicated for arrhythmias due to digitalis intoxication.

Orphan drugs in Europe—leaving no patient behind?

'Leaving no patient behind' is one of EMA's mottos. In this case, however, there are important consequences that may not have been clear to the authorities – although previous warnings have been provided.[4–6] The rationale of the orphan drug legislation has been to promote commercial interest for new products for rare diseases and conditions, because without commercial interest the assumption is that such solutions will not be developed. Allowing labelling of (long) known drugs for orphan indications is only one of the caveats that terrorises healthcare systems on a large scale due to the, often exorbitant, price increases that accompany the commercial benefits associated with 10-year (orphan) drug market exclusivity.[6,7] In addition, when drugs are used for multiple indications (e.g. non-dystrophic myotonia versus myotonic disorders in general), let alone in multiple specialties (e.g. neurology versus cardiology), market exclusivity for one indication translates to the same exorbitant price rises for the other indications – which easily doubles or triples the impact of such decisions. Because a healthcare budget is restricted, money spent on excessively priced orphan drugs cannot be spent on, e.g., wages of nurses, elderly or primary care initiatives, etc.

The EMA recommendation, and European Commission decision, made with Namuscla therefore very much leaves patients behind, not only patients with non-dystrophic myotonia who live in a European Union member state that is not able to comply with mexiletine's

outrageous price increase, as well as patients with other neurological or cardiology indications for mexiletine, as well as patients without a mexiletine indication who receive less net healthcare funding due to the drain of a budget by such price increase. Compellingly, the party that receives the financial benefits of this market exclusivity was not involved in the development of the drug nor in the investigations that led to the indications thereof (although it will probably have paid a significant price for this future asset).

Possible solutions

There are several possible solutions to this problem of misusing orphan drug legislation to gain orphan drug status for old drugs and/or known indications and charge high prices as a consequence of an orphan market exclusivity;

1) exclude known indications or known use of existing drugs from orphan designation eligibility,

2) introduce a 'sufficiency test' to define the line between sufficient and excessive profitability (the latter leading to withdrawal of orphan exclusivity),

3) introduce sanctions by competition authorities against companies that abuse their (orphan) market position and/or engage in excessive pricing practices, and

4) warrant that import or production of an affordable generic product (including active pharmaceutical ingredient) remains possible.

In 2016, the European Council announced a review of the pharmaceutical incentives in the European Union. Suggestions have been made to re-instate a 'withdrawal clause' into orphan drug legislation to protect quite specifically against pharmaceutical firms charging excessively high prices or making excessive profits.[7] One should note that a company that obtains an (orphan) market exclusivity is under no obligation to demand an exorbitant price for its product. Indeed, a company that takes its responsibility in healthcare serious, would not.

As an example of a potential solution, in South Korea the delivery and pricing problems with orphan and essential drugs has resulted in the national Korea Orphan Drug Centre which delivers drugs at a fraction of international prices; mexiletine for example is priced at about US $0,17/100mg, circa 200 times cheaper than Namuscla. In the USA, advanced legislation on exorbitant drug pricing has recently been put forward.[23]

Conclusions

Mexiletine has been used since the 1970's for the prevention of (recurrent) VT/VF. The 2018 EMA marketing authorisation of mexiletine as an orphan drug for non-dystrophic myotonia resulted both in withdrawal of generic mexiletine, prohibiting of import and in an exorbitant price increase, for both neurology and cardiology patients. Likewise, European healthcare systems are forced to either accept, negotiate or deny this price rise, and risk (further) problems in mexiletine availability for patients who depend on this drug for VT/VF prevention and risk problems in the delivery of other care. This is just another example of continued misuse of orphan drug legislation and should be prevented.

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Authors

1. Pieter G. Postema, MD, PhD, Department of Cardiology, Heart Center, Amsterdam University Medical Centers, Amsterdam, The Netherlands. Member of the European Reference Network (ERN) GUARD-Heart

2. Peter J. Schwartz, MD, Instituto Auxologico Italiano, IRCCS, Center for Cardiac Arrhythmias of Genetic Origin, Milan, Italy. Member of the European Reference Network (ERN) GUARD-Heart
3. Elena Arbelo, MD, PhD, Arrhythmia Section, Cardiology Department, Hospital Clínic, Universitat de Barcelona and Institut d'Investigació August Pi i Sunyer (IDIBAPS), Barcelona, Spain, and Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain.
4. Wilbert J. Bannenberg, MD, MSc (CHDC), Pharmaceutical Accountability Foundation, The Netherlands
5. Elijah R. Behr, MA, MBBS, MD, Cardiology Clinical Academic Group, Institute of Molecular and Clinical Sciences, St. George's, University of London, St. George's University Hospitals NHS Foundation Trust, London, United Kingdom. Member of the European Reference Network (ERN) GUARD-Heart
6. Bernard Belhassen, MD, Heart Institute, Hadassah University Hospital, Jerusalem, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.
7. Josep Brugada, MD, PhD, Cardiology Department, Hospital Clinic, University of Barcelona, Barcelona, Spain
8. Pedro Brugada, MD, PhD, Cardiovascular Division, Free University of Brussels, Brussels, Belgium
9. A. John Camm, MD, Cardiology Clinical Academic Group, Molecular & Clinical Sciences Institute, St, George's University of London, London, United Kingdom
10. Ruben Casado-Arroyo, MD, PhD, Department of Cardiology, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium.
11. Ellen 't Hoen, LLM, PhD, Medicines Law & Policy, Amsterdam, The Netherlands, and Global Health Unit, University Medical Centre Groningen, The Netherlands
12. Carla E.M. Hollak, MD, PhD, Department of Endocrinology and Metabolism, Amsterdam University Medical Centers, Amsterdam, The Netherlands
13. Stefan Kääb, MD, PhD, Department of Medicine I, University Hospital Munich, Campus Großhadern, Ludwig-Maximilians University Munich (LMU), Munich, Germany, and DZHK (German Centre for Cardiovascular Research), Partner Site Munich, Munich Heart Alliance (MHA), Munich, Germany
14. Pier D. Lambiase, MRCP, PhD, Electrophysiology Department, Barts Heart Centre, Barts Health NHS trust, London, United Kingdom. Member of the European Reference Network (ERN) GUARD-Heart
15. Antoine Leenhardt, MD. Unité de Rythmologie, Centre de Référence Maladies Cardiaques Héréditaires, Service de Cardiologie, Université de Paris, AP-HP Hôpital Bichat, Paris, France. Member of the European Reference Network (ERN) GUARD-Heart.
16. Silvia G. Priori, MD, PhD. Department of Molecular Medicine University of Pavia, Cardiology & Molecular Cardiology, IRCCS Fondazione Salvatore Maugeri, Pavia, Italy. Member of the European Reference Network (ERN) GUARD-Heart
17. Vincent Probst, MD, PhD. L'institut du thorax, service de cardiologie du CHU de Nantes, Nantes, France. Member of the European Reference Network (ERN) GUARD-Heart
18. Bas C. Stunnenberg, MD. Department of Neurology, Donders Institute for Brain Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands.
19. Jacob Tfelt-Hansen, MD, DMSc. Department of Cardiology, Heart Centre, Copenhagen University Hospital, Rigshospitalet, and Department of Forensic

Medicine, Faculty of Medical Sciences, University of Copenhagen, Copenhagen, Denmark. Member of the European Reference Network (ERN) GUARD-Heart.
20. Baziel G.M. Van Engelen, MD, PhD. Department of Neurology, Donders Institute for Brain Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands
21. Christian Veltmann, MD. Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany
22. Sami Viskin, MD. Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.
23. Arthur A.M. Wilde, MD, PhD, Department of Cardiology, Heart Center, Amsterdam University Medical Centers, Amsterdam, The Netherlands. Member of the European Reference Network (ERN) GUARD-Heart.

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Correspondence:
Dr. Pieter G. Postema, MD, PhD.
Department of Cardiology, Heart Center
Amsterdam University Medical Centers
Academic Medical Center
PO-Box 22700, 1100DE, Amsterdam, The Netherlands.
Tel:+31-20-5663072,
Fax:+31-20-6971385
Email: p.g.postema@amsterdamumc.nl

Disclosures:
Dr. Postema reports receiving speaker fees (2018: <€500) from Abbvie, outside the submitted work.
Dr. Hollak reports to be involved in premarketing studies in the field of lysosomal storage disorders with Sanofi, Protalix and Idorsia, outside the submitted work.
Dr. Veltmann reports personal fees from Medtronic, Abbott, Zoll, Boston Scientific, Biotronik, Boehringer-Ingelheim, BMS, Bayer, CVRx, and Daiichi Sankyo, outside the submitted work.
Dr. Casado-Arroyo reports receiving speaker fees from Abbott and Boston Scientific, outside the submitted work.
Dr. Probst reports grants and personal fees from Boston scientific and personal fees from Medtronic, outside the submitted work.
Dr. Schwartz, Dr. Arbelo, Dr. Behr, Dr. Belhassen, Dr. J. Brugada, Dr. P. Brugada, Dr. Camm, Ms. ‘t Hoen, Dr. Kääb, Dr. Lambiase, Dr. Leenhardt, Dr. Priori, Dr. Stunnenberg, Dr. Tfelt-Hansen, Dr. Van Engelen, Dr. Viskin and Dr. Wilde, report no conflicts of interest.

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Figure and Legend

Figure 1. Illustration of the Mexiletine case. Mexiletine has been long known to have life-saving properties in patients with cardiomyopathy and recurrent VT, and in patients with Long QT syndrome, to decrease their risk of recurrent malignant arrhythmia. In addition, it has also successfully been used in neurology for non-dystrophic myotonia since decades, which was confirmed in a detailed 2012 publication in JAMA. Since the European marketing authorisation for neurology by EMA, its price skyrocketed.