

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

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1 **Introduction**

2 Recently, patient access to mexiletine for the prevention of ventricular tachycardia (VT) and
3 ventricular fibrillation (VF) has become critically endangered. This follows from the marketing
4 authorisation by the European Medicines Agency (EMA) in December 2018 of mexiletine
5 hydrochloride, now sold as 'Namuscla' by Lupin Europe GmbH, as an orphan drug for non-dystrophic
6 myotonic disorders.¹ As such, the price of mexiletine has skyrocketed to about €80,000 per patient
7 per year in many European countries, not only for patients with non-dystrophic myotonic disorders
8 but also for cardiology patients who, since the 1970's,^{2,3} use mexiletine to prevent VT/VF. As a
9 consequence, our social healthcare systems are suddenly burdened with another tremendous
10 increase in healthcare costs for a drug (previously) priced at about €450-4400 per patient per year
11 (either import or production).

12

13 ***Commercial interest and regulatory incapability***

14 Regretfully, this is just another example of our current regulatory incapability to withstand misuse of
15 orphan drug legislation and regulation by exorbitant commercial interests in the treatment of
16 patients with rare or common disease.⁴⁻⁸ Such interference of commercial interest with society
17 healthcare can be illustrated as follows:

18

- 19 • A healthcare's inability to pay for excessive commercial prices of patented/novel or out-of-
20 patent/conventional drugs with (regulated or effective) market exclusivity
- 21 • A healthcare's need to cut on other care to pay for excessive commercial prices of
22 patented/novel or out-of-patent/conventional drugs with (regulated or effective) market
23 exclusivity
- 24 • 'Evergreening' of drug patents (e.g. by changing administration route, obtaining additional
25 patents for new use or combinations) to prolong patent exclusivity.

1 • Repurposing of drugs to new (orphan) indications, providing new patents or market
2 exclusivity

3 • Price gouging of out-of-patent drugs for (orphan) indications

4 • Production stops of commercially unfavourable (orphan) drugs

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

8

9 ***The cardiology case of mexiletine***

10 Mexiletine is one of the Vaughan Williams class 1b anti-arrhythmic drugs (a sodium channel blocker)
11 that is available for the prevention of (recurrent) VT/VF in both ischemic and non-ischemic
12 cardiomyopathies and, more mechanism-specific, in Long QT syndrome (LQTS). Mexiletine has been
13 developed in the late 1960's, early 1970's, by Boehringer Ingelheim and was quickly and successfully
14 tested for the prevention ventricular arrhythmias.² However, subsequent studies in the 1980's
15 showed that not all patients post myocardial infarction received benefit from mexiletine, limiting its
16 use at that time.^{9,10} In 1995, the late sodium current blocking properties of mexiletine were
17 successfully explored to decrease the QT-interval in LQTS-patients (in particular LQTS-type 3 based
18 on an increased late inward sodium current), and, subsequently, to decrease their risk of VT/VF.^{3,11,12}

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

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The neurology case of mexiletine

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^{15,16} 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 for the treatment of different types of myotonic disorders, including successful treatments with mexiletine.¹⁷

Non-dystrophic myopathies (prevalence 1:100,000) are a conglomerate of very rare diseases caused by mutations in skeletal muscle ion channels. The most striking hallmark of the non-dystrophic myopathies is delayed muscle relaxation, causing functional limiting stiffness, pain, fatigue, weakness and social impairment.¹⁸ In two recent, randomized, placebo-controlled studies in patients with non-dystrophic myopathy, published in 2012 and 2018, mexiletine was indeed effective for decreasing symptoms.^{18,19} Since, many patients (from children to adults) with non-dystrophic myopathy are treated with mexiletine enabling increased functional abilities and increased social participation with less discomfort.

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. 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 since the recent randomized clinical study with mexiletine, published in 2012,¹⁸ the commercial interest in mexiletine developed due to its promise as a formal orphan drug with huge potential financial profits.

1 This story supposedly starts in 2010 when the mexiletine marketing authorisation in France
2 was transferred from Boehringer Ingelheim France to Etablissement Pharmaceutique de l'AP-HP
3 (Assistance Publique - Hôpitaux de Paris) and labelled for “symptomatic treatment of myotonic
4 syndromes”.²¹ The French example labelling mexiletine for myotonic disorders, was utilised by
5 Temmler Pharma GmbH & Co. KG , Germany (now known as Aenova Group), to acquire an EU orphan
6 drug designation in 2014 for mexiletine for the treatment of myotonic disorders.¹ In 2015, when
7 Lupin announced the acquirement of the specialty product portfolio of Temmler, which apparently
8 included mexiletine, the product designation was transferred from Temmler to Hormosan Pharma
9 GmbH, Germany (already acquired in 2008 by Lupin Group).¹ In 2016 the product designation was
10 transferred from Hormosan to Lupin (Europe) Limited, United Kingdom, and in 2018 it was
11 transferred to Lupin Europe GmbH, Germany.¹ Then, in December 2018, EMA recommended a
12 marketing authorisation for Namuscla for the treatment of adult patients with non-dystrophic
13 myotonia, which was granted. Subsequently, in January 2019, the Etablissement Pharmaceutique de
14 l'AP-HP ceased mexiletine delivery and transferred to Namuscla.²² Strikingly, the price of mexiletine
15 skyrocketed when being sold as Namuscla, to €80,000 per patient per year.

16

17 **Catch 22**

18 Regretfully, the European marketing authorisation of Namuscla for non-dystrophic myotonia, now
19 jeopardises the >40-year-old cardiological indication of mexiletine. In several European countries,
20 mexiletine to prevent VT/VF is now only available as Namuscla at this outrageous price. Interestingly,
21 the official contra-indications of Namuscla¹ list ventricular tachyarrhythmias, previous myocardial
22 infarction and heart failure – mirroring one of the cardiology indications for mexiletine.

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

1 for arrhythmias), and is thus no outpatient alternative, and phenytoin is effectively solely indicated
2 for arrhythmias due to digitalis intoxication.

3

4 **Orphan medicines in the EU—leaving no patient behind?**

5 'Leaving no patient behind' is one of EMA's mottos. In this case, however, there are important
6 consequences that may not have been clear to the authorities – although previous warnings have
7 been provided.^{4,6,7} The rationale of the orphan drug legislation has been to promote commercial
8 interest for new products for rare diseases and conditions, because without commercial interest the
9 assumption is that such solutions will not be developed. Allowing labelling of (long) known drugs for
10 orphan indications is only one of the caveats that terrorises healthcare systems on a large scale due
11 to the, often exorbitant, price increases that accompany the commercial benefits associated with 10-
12 year (orphan) drug market exclusivity. In addition, when drugs are used for multiple indications (e.g.
13 non-dystrophic myotonia versus myotonic disorders in general), let alone in multiple specialties (e.g.
14 neurology versus cardiology), market exclusivity for one indication translates to the same exorbitant
15 price rises for the other indications – which easily doubles or triples the impact of such decisions.
16 Because healthcare budget is restricted, money spend on excessively priced orphan drugs cannot be
17 spend on, e.g., wages of nurses, elderly or primary care initiatives etc. The EMA recommendation,
18 and the EU Commission decision, made with Namuscla therefore very much leaves patients behind,
19 not only patients with non-dystrophic myotonia who live in a European member state that is not able
20 to comply with the outrageous price increase of mexiletine, as well as patients with other
21 neurological or with cardiology indications for mexiletine, as well as patients without an indication
22 for mexiletine who receive less net healthcare funding due to the drain of budget by such price
23 increase. Compellingly, the party that receives the financial benefits of this market exclusivity was in
24 no way involved in the development of the drug nor in the investigations that led to the indications
25 thereof (although it will probably have paid a significant price for this future asset).

26

1 **Possible solutions**

2 There are several possible solutions to this problem of misusing orphan drug legislation to gain
3 orphan drug status for old drugs and/or known indications and charge high prices as a consequence
4 of an orphan market exclusivity; 1) exclude known indications or known use of non-novel drugs from
5 orphan designation eligibility, 2) introduce a 'sufficiency test' to define the line between sufficient
6 and excessive profitability (the latter leading to withdrawal of orphan exclusivity), 3) introduce
7 sanctions by competition authorities against companies that abuse their (orphan) market position
8 and/or engage in excessive pricing practices, and 4) warrant that import or production of affordable
9 generic product (including active pharmaceutical ingredient) remains possible.

10 In 2016, the Council of the EU announced a review of the pharmaceutical incentives in the EU
11 and its member states. Suggestions have been made to re-instate a 'withdrawal clause' into orphan
12 drug legislation to protect quite specifically against pharmaceutical firms charging excessively high
13 prices or making excessive profits.⁸ One should note that a company that obtains an (orphan) market
14 exclusivity is under no obligation to demand an exorbitant price for its product. Indeed, a company
15 that takes its responsibility in healthcare serious would not.

16 As a potential solution example, in South Korea the delivery and pricing problems with
17 orphan and essential drugs has resulted in the national Korea Orphan Drug Center which delivers
18 drugs often at a fraction of international prices; mexiletine for example is priced at about
19 \$0,17/100mg, over 200 times cheaper than Namuscla.

20

21 **Conclusions**

22 Mexiletine has been used since the 1970's for the prevention of (recurrent) VT/VF. The 2018 EMA
23 marketing authorisation of mexiletine as an orphan drug for non-dystrophic myotonia resulted both
24 in withdrawal of generic mexiletine, prohibiting of import and in an exorbitant price rise, for both
25 neurology and cardiology patients. Likewise, healthcare systems throughout Europe are forced to
26 either accept, negotiate or deny this price rise, and risk (further) problems in mexiletine availability

1 for patients who depend on this drug for VT/VF prevention and risk problems in the delivery of other
2 care. This is just another example of continued misuse of orphan drug legislation and should be
3 prevented.

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5 **References**

- 6 1. European Medicines Agency. Namuscla [Internet]. [cited 2019 Nov 12]; Available from:
7 <https://www.ema.europa.eu/en/medicines/human/EPAR/namuscla>
- 8 2. Talbot RG, Nimmo J, Julian DG, Clark RA, Neilson JM, Prescott LF. Treatment of ventricular
9 arrhythmias with mexiletine (Kö 1173). *Lancet* 1973;2(7826):399–404.
- 10 3. Schwartz PJ, Priori SG, Locati EH, et al. Long QT syndrome patients with mutations of the SCN5A
11 and HERG genes have differential responses to Na⁺ channel blockade and to increases in heart
12 rate. Implications for gene-specific therapy. *Circulation* 1995;92(12):3381–6.
- 13 4. Hoen E 't, Berger J, Calmy A, Moon S. Driving a decade of change: HIV/AIDS, patents and access
14 to medicines for all. *J Int AIDS Soc* 2011;14:15.
- 15 5. Viskin S, M Wilde AA, Guevara-Valdivia ME, et al. Quinidine, a life-saving medication for
16 Brugada syndrome, is inaccessible in many countries. *J Am Coll Cardiol* 2013;61(23):2383–7.
- 17 6. Alpern JD, Stauffer WM, Kesselheim AS. High-cost generic drugs--implications for patients and
18 policymakers. *N Engl J Med* 2014;371(20):1859–62.
- 19 7. Luzzatto L, Hyry HI, Schieppati A, et al. Outrageous prices of orphan drugs: a call for
20 collaboration. *Lancet* 2018;392(10149):791–4.
- 21 8. Boulet P, Garrison C, 't Hoen E. European Union review of pharmaceutical incentives:
22 suggestions for change. Amsterdam, The Netherlands: Medicines Law & Policy; 2019.
- 23 9. Chamberlain DA, Jewitt DE, Julian DG, Campbell RW, Boyle DM, Shanks RG. Oral mexiletine in
24 high-risk patients after myocardial infarction. *Lancet Lond Engl* 1980;2(8208–8209):1324–7.
- 25 10. Impact Research Group. International mexiletine and placebo antiarrhythmic coronary trial: I.
26 Report on arrhythmia and other findings. *J Am Coll Cardiol* 1984;4(6):1148–63.
- 27 11. Mazzanti A, Maragna R, Faragli A, et al. Gene-Specific Therapy With Mexiletine Reduces
28 Arrhythmic Events in Patients With Long QT Syndrome Type 3. *J Am Coll Cardiol*
29 2016;67(9):1053–8.
- 30 12. Bos JM, Crotti L, Rohatgi RK, et al. Mexiletine shortens the QT Interval in patients with
31 potassium channel-mediated type 2 Long QT syndrome. *Circ Arrhythm Electrophysiol*
32 2019;12(5):e007280.
- 33 13. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management
34 of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task
35 Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of

- 1 Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for
2 European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;36(41):2793–867.
- 3 14. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for
4 Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac
5 Death. *Circulation* 2018;138(13):e272–391.
- 6 15. Postema PG, Wolpert C, Amin AS, et al. Drugs and Brugada syndrome patients: review of the
7 literature, recommendations, and an up-to-date website (www.brugadadrugs.org). *Heart*
8 *Rhythm* 2009;6(9):1335–41.
- 9 16. Postema PG, Neville J, de Jong JSSG, Romero K, Wilde AAM, Woosley RL. Safe drug use in long
10 QT syndrome and Brugada syndrome: comparison of website statistics. *Europace*
11 2013;15(7):1042–9.
- 12 17. Trip J, Drost G, van Engelen BGM, Faber CG. Drug treatment for myotonia. *Cochrane Database*
13 *Syst Rev* 2006;(1):CD004762.
- 14 18. Statland JM, Bundy BN, Wang Y, et al. Mexiletine for symptoms and signs of myotonia in
15 nondystrophic myotonia: a randomized controlled trial. *JAMA* 2012;308(13):1357–65.
- 16 19. Stunnenberg BC, Raaphorst J, Groenewoud HM, et al. Effect of Mexiletine on Muscle Stiffness
17 in Patients With Nondystrophic Myotonia Evaluated Using Aggregated N-of-1 Trials. *JAMA*
18 2018;320(22):2344–53.
- 19 20. Fontaine N, Hemila K. Regulation (EC) No 141/2000 of the European Parliament and of the
20 Council of 16 December 1999 on orphan medicinal products. *Off J Eur Communities*
21 2000;43(L18):1–5.
- 22 21. French National Authority for Health (HAS). Medical, Economic and Public Health Assessment
23 Division, Transparency Committee. Transparency Committee opinion 19 January 2011;
24 MEXILETINE AP-HP 200 mg, capsule [Internet]. Available from: [https://www.has-](https://www.has-sante.fr/upload/docs/application/pdf/2012-08/mexiletine_ap-hp_ct_9407.pdf)
25 [sante.fr/upload/docs/application/pdf/2012-08/mexiletine_ap-hp_ct_9407.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2012-08/mexiletine_ap-hp_ct_9407.pdf)
- 26 22. Assistance Hopitaux publique de Paris. A l'attention des professionnels de sante. Mexiletine AP-
27 HP 200 mg, gelule: rupture de stock et arret de commercialisation. Importation de Namuscla.
28 [Internet]. 2019 [cited 2019 Nov 25]; Available from:
29 [https://www.ansm.sante.fr/content/download/169377/2214097/version/1/file/rs-191118-](https://www.ansm.sante.fr/content/download/169377/2214097/version/1/file/rs-191118-Mexiletine.pdf)
30 [Mexiletine.pdf](https://www.ansm.sante.fr/content/download/169377/2214097/version/1/file/rs-191118-Mexiletine.pdf)

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