Accepted Manuscript

The possibility of obtaining marketing authorization of orphan pharmaceutical compounding preparations: 3,4-DAP for Lambert-Eaton Myasthenic Syndrome

Sofieke de Wilde, Maria G.H. de Jong, Alexander F. Lipka, Henk-Jan Guchelaar, Kirsten J.M. Schimmel

PII: S0928-0987(17)30654-1
DOI: doi:10.1016/j.ejps.2017.11.025
Reference: PHASCI 4314

To appear in: *European Journal of Pharmaceutical Sciences*

Received date: 5 October 2017
Revised date: 20 November 2017
Accepted date: 27 November 2017

Please cite this article as: Sofieke de Wilde, Maria G.H. de Jong, Alexander F. Lipka, Henk-Jan Guchelaar, Kirsten J.M. Schimmel , The possibility of obtaining marketing authorization of orphan pharmaceutical compounding preparations: 3,4-DAP for Lambert-Eaton Myasthenic Syndrome. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Phasci(2017), doi:10.1016/j.ejps.2017.11.025

[TITEL PAGE]

The possibility of obtaining marketing authorization of orphan pharmaceutical compounding preparations: 3,4-DAP for Lambert-Eaton Myasthenic Syndrome

Sofieke de Wilde, MSc [1] s.de_wilde@lumc.nl; Maria G.H. de Jong, BSc[2] m.g.h.dejong@students.uu.nl; Alexander F. Lipka, MSc[3] a.f.lipka@lumc.nl; Prof. Henk-Jan Guchelaar[1] h.j.guchelaar@lumc.nl; Kirsten J.M. Schimmel, PhD[1#] k.j.m.schimmel@lumc.nl

1] Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands

2] Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands

3] Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

Corresponding author: *#Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, P.O. Box 9600, Post zone L0-172, 2300 RC Leiden, The Netherlands. E-mail: k.j.m.schimmel@lumc.nl Tel.: +31 71 526 2612, Fax: +31 71 526 6866*

[ABSTRACT]

Background. Pharmaceutical compounding preparations, produced by (hospital) pharmacies, usually do not have marketing authorization. As a consequence, some of these pharmaceutical compounding preparations can be picked-up by a pharmaceutical company to obtain marketing authorization, often leading to price increases. An example is the 3,4-diaminopyridine slow release (3,4-DAP SR) tablets for Lambert-Eaton Myasthenic Syndrome (LEMS). In 2009 marketing authorization was given for the commercial immediate release phosphate salt of the drug, including a fifty-fold price increase compared to the pharmaceutical compounding preparation. Obtaining marketing authorization for 3,4-DAP SR by academia might have been a solution to prevent this price increase. To determine whether the available data of a pharmaceutical compounding preparation with long-term experience in regular care are adequate to obtain marketing authorization, 3,4-DAP SR is used as a case study.

Methods. A retrospective qualitative case-study was performed. Initially, document analysis was executed by collecting the required data for marketing authorization in general and whether data of Firdapse® and 3,4-DAP SR met these requirements. Secondly, the (non-) available data of the two formulations were compared with each other to determine the differences in availability.

Results. At the time of approval, almost all data were available for both Firdapse® and 3,4-DAP SR. Conversely, much of the data used for the approval of Firdapse® originated from the 3,4-DAP immediate release (3,4-DAP IR) formulation. Only two bioequivalence studies and one pharmacology safety study was performed with Firdapse® before marketing authorization application.

Conclusions. In conclusion, at time Firdapse® obtained approval, the data available did not differ substantially from 3,4-DAP SR, indicating that approval with 3,4-DAP SR would have

been possible. We make a plea for approval of orphan medicinal products developed and manufactured by academic institutions as to keep utilization of these products affordable.

[KEYWORDS]

- Decision making
- Hospital medicines
- Pharmaceutical compounding preparations
- Orphan drugs
- LEMS
- 3,4-DAP

Background

The Lambert-Eaton Myasthenic Syndrome (LEMS) is an ultra-orphan autoimmune disease of the neuromuscular junction(Gilhus, 2011; Hülsbrink and Hashemolhosseini, 2014) with a prevalence of 0·35:100 000(Orphanet, n.d.; Schuller et al., 2015). Currently, due to lacking curing treatment of LEMS, symptoms can be relieved by preferably symptomatic or immunomodulating treatment(Quartel et al., 2010). 3,4-Diaminopyridine (3,4-DAP) is the most frequently prescribed symptomatic treatment and is used globally(Tarr et al., 2015).

Until 2009, two formulations of 3,4-DAP tablets used to be available as pharmaceutical compounding preparations: 3,4-DAP base immediate release (3,4-DAP IR) and 3,4-DAP base slow release (3,4-DAP SR)[1] (Lundh et al., 1983). However, in 2009 a third type of 3,4-DAP received marketing authorization in Europe, Firdapse® (European Medicines Agency, 2009), an immediate release phosphate salt, see table 1. Due to the licensed status of Firdapse® and the obtained orphan designation status, including ten years of market exclusivity, the two other 3,4-DAP formulations were not allowed anymore for treating LEMS in most countries despite the fact that before the licensed Firdapse® appeared, 3,4-DAP IR had obtained long-term experience in LEMS patients (Lundh et al., 1983; Sanders, 1998). Likewise, the SR variant of 3,4-DAP has been produced and used for over 20 years at the Leiden University Medical Center (LUMC) in The Netherlands.

For Firdapse®, obtaining complete data for marketing authorization submission was not possible due to the rarity of the disease. Therefore, this medicinal product is approved ‘under exceptional circumstances’ (European Medicines Agency, 2009). After the approval of Firdapse®, a substantial increase in pricing occurred compared to the costs for the available pharmaceutical compounding preparations 3,4-DAP SR and IR(Boer, 2011). This rise in costs negatively influenced regular LEMS patient care: e.g. in the United Kingdom, due to

[1] *Contents of 3,4-DAP SR can be given upon request*

the 50-fold increase in costs, health care insurances were not willing to pay these extra costs, while the pharmaceutical formulations were forbidden to be provided to patients, resulting in inaccessibility of 3,4-DAP as a treatment for LEMS patients (Goldberg, 2010; Nicholl et al., 2010). Alternatively, in The Netherlands the Dutch Minister of Health, Welfare and Sport decided that due to the modified release profile of the SR formulation and the undesirable additional costs of Firdapse®, estimated at €1·8 million per year for the 40-70 treated patients, 3,4-DAP SR was still allowed for the treatment of LEMS patients(Boer, 2011).

Several pharmaceutical compounding preparations, such as 3,4-DAP IR and SR, are produced in the (fully Good Manufacturing Practices (GMP) licensed hospital) pharmacies. In most cases, these are medicinal products for (ultra-) orphan diseases and arise from *ad hoc* preparations. Sometimes, in case such *ad hoc* preparation is prescribed more frequently, these preparations can be scaled up to (small) for-stock preparations(Minghetti et al., 2014). These for-stock preparations increase the requirements for documentation of the product and its quality assurance and lead to substantial experience with such medicinal products in regular care (de Wilde, n.d.; Minghetti et al., 2014). However, these unlicensed pharmaceutical compounding preparations can easily be picked up by the pharmaceutical industry, and in some cases receive a license with a substantially higher price tag in comparison with the pharmaceutical compounding preparation formulation(Nicholl et al., 2010). 3,4-DAP SR is an example of such pharmaceutical compounding preparation which was picked-up by the industry and for which the costs increased tremendously, but other examples exist, such as ibuprofen for neonatal patent ductus arteriosus and zinc acetate for Wilson's disease(Dooms et al., 2013).

Licensing of a medicinal product guarantees a level of quality, efficacy, and safety of the product. Moreover, industrial production is more rigidly monitored compared to pharmaceutical compounding(Minghetti et al., 2014), including authorized patient

information and pharmacovigilance which are not always available for the pharmaceutical compounding preparations. Due to this extra monitoring, it is reasonable that costs for treatment increase compared to the regular therapy with pharmaceutical compounding preparations (de Wilde, n.d.). However, due to the ten years market exclusivity and the small market size, prices for (ultra-) orphan drugs often rise more than desired(Editorial, 2015; Mizoguchi et al., 2016). In some cases, the increase can be disproportionate to the limited efforts required for authorization("The rising cost of orphan drugs," 2015), especially when (hardly) no original research is performed by the pharmaceutical company to obtain marketing authorization.

To determine whether the available data of a pharmaceutical compounding preparation with long-term experience in regular clinical care are sufficient to apply for marketing authorization, 3,4-DAP by LEMS is used as a case study. The available data of 3,4-DAP SR will be compared with the data of the licensed Firdapse®, to investigate whether 3,4-DAP SR could have been licensed at the same time as Firdapse® did and/or which additional studies are still required to obtain marketing authorization with 3,4-DAP SR. The goal of investigating marketing authorization possibilities for the pharmaceutical compounding preparation 3,4-DAP SR is to guarantee regular patient care at a reasonable price. Recommendations will be provided to ensure reasonable pricing and possibilities of pharmaceutical compounding preparations towards marketing authorization.

Methods

Study design

A retrospective qualitative case-study was performed with 3,4-DAP SR and Firdapse®. Initially, a document analysis was conducted to collect the required data for marketing authorization and whether Firdapse® and 3,4-DAP SR met these requirements. Secondly, the available data for the two formulations were compared with each other, to determine at which points the data of 3,4-DAP SR differed from the data of Firdapse®.

Processing and analysis of the data

Based on the requirements for an assessment report (AR)(European Medicines Agency, 2016a, 2016b, 2016c), data of Firdapse® in the AR were scored on availability(European Medicines Agency, 2009). When data were adopted in the AR, a check on the origin of the data was performed, including whether data came from the phosphate salt (Firdapse®) or from the 3,4-DAP IR. In case data were not available but were required after approval by the European Medicines Agency (EMA), this was also scored, see figure 1 for a schematic overview of the analysis.

Above described method was also used for the unlicensed 3,4-DAP SR. Not only the pharmaceutical product dossier of 3,4-DAP SR was examined "Unpublished obeservations, M.G.H. de Jong, S de Wilde, K.J.M. Schimmel" but also the sources PubMed and Scopus were used to search for additional data, such as non-clinical and clinical pharmacokinetics and non-clinical toxicology.

Finally, data for both formulations were compared to determine whether the available data of 3,4-DAP SR differed from the data used for licensing of Firdapse®. Eventually, it was determined whether additional research would have been necessary for marketing authorization of 3,4-DAP SR, see figure 1.

The scored data were subcategorized in quality (see additional file 1), non-clinical (see additional file 2) and clinical aspects (see additional file 3) like the AR of Firdapse®.

Results

Overviews of the available data of Firdapse® in the AR and of 3,4-DAP in the product dossiers are listed in additional files 1-3, and a summary of missing data for both products is shown in table 2.

Quality

All required quality data, according to the requirements for marketing authorization, were available for both Firdapse® and 3,4-DAP SR (see additional file 1). For 3,4-DAP SR, the data were less extensively described compared to Firdapse® but the data met the requirements (see additional file 1).

Non-clinical

The primary and secondary pharmacodynamic data were available for both formulations. However, data about the pharmacodynamic drug interactions for both medicinal products were lacking, see additional file 2. Moreover, for 3,4-DAP SR the safety pharmacology programme was also missing. For both medicinal products data were adopted from the IR formulation of 3,4-DAP and both in vitro data and secondary pharmacodynamic data acquired from 3,4-DAP IR were described in the AR of Firdapse® and could be extended for 3,4-DAP SR. Also, data from 3,4-DAP IR, obtained from literature, was used for the in vivo data of 3,4-DAP SR (Harvey and Marshall, 1977; Mori et al., 2012).

Limited pharmacokinetic data were available for both product formulations, and absorption data were available for both medicinal products, see additional file 2. As for metabolism and excretion, no studies have been performed. Distribution data were only available for Firdapse®.

For Firdapse®, only carcinogenicity data were lacking from the toxicology data. On the contrary, since 3,4-DAP SR did not contain much toxicology data, data were adopted from the IR formulation, like for Firdapse®. The genotoxicity data were conducted from studies with 3,4-DAP IR and given in the AR of Firdapse®. The lacking data about the single-dose toxicity of 3,4-DAP SR were obtained from literature(Schafer et al., 1983). The pharmaceutical company of Firdapse® conducted the reproduction toxicity study after approval; this toxicity study was a requirement of approval along with the carcinogenicity study (see additional file 2).

The ecotoxicity/environmental risk assessment for both medicinal products was acquired from 3,4-DAP IR (see additional file 2). The results of this study were presented in the AR of Firdapse®.

Clinical

Overall, the clinical data for both Firdapse® and 3,4-DAP SR also contained data adopted from 3,4-DAP IR. A pharmacokinetic study in healthy volunteers was conducted after approval of Firdapse® and published in 2014 (Haroldsen et al., 2015a), see additional file 3. At the time of approval, these data were not yet provided, thus the available data were similar to 3,4-DAP SR. Data about the pharmacokinetic interactions and pharmacokinetics using human biomaterials were not available for both products.

The presented pharmacodynamic data of 3,4-DAP SR were the same as Firdapse® (see additional file 3). The primary pharmacology, the relation between plasma concentration and effect, and the pharmacodynamic interactions with other medicinal products or substances were acquired from 3,4-DAP IR for both products. For the clinical efficacy and safety almost all required data were available for both Firdapse® and 3,4-DAP SR, with the exception of data for special populations, such as patients with hepatic or renal impairment (see additional

file 3). Due to the long-term availability of 3,4-DAP SR, more experience in patients has been established compared to Firdapse®.

Discussion

In this study, the AR of the licensed Firdapse® and the product dossier of the pharmaceutical compounding preparation 3,4-DAP SR were analysed to investigate whether data fulfilled the requirements for marketing authorization as described by the EMA or which studies should be initiated to complete the lacking data. Since not all required data were available at the time of marketing authorization, due to the small LEMS patient cohort, Firdapse® was approved 'under exceptional circumstances' (European Medicines Agency, 2009). At the time of approval, most of the data were equally available for both Firdapse® and 3,4-DAP SR. Furthermore, most of the data used for the approval of Firdapse® originated from 3,4-DAP IR (Boer, 2011).

Firdapse®

Only two medium-sized bioequivalence studies (one in animals and one in healthy volunteers) and one small pharmacology safety study was performed with Firdapse® before applying for marketing authorization (European Medicines Agency, 2009). Due to the demonstrated bioequivalence studies, with equal areas under the curves (AUC) for both Firdapse® and 3,4-DAP IR, bridging of (non-) clinical data from 3,4-DAP IR was justified for Firdapse®. The equal AUCs support the assumption that efficacy between those two medicinal products is identical (Zorginstituut Nederland, n.d.).

After marketing authorization approval, additional studies were required by the EMA. For non-clinical data, a carcinogenicity and a reproduction toxicity study still had to be performed. Furthermore, a clinical pharmacokinetic study, concerning the effects of food intake (Haroldsen et al., 2015b) and genetic variation in aryl N-acetyltransferase (Haroldsen et al., 2015a), was required. All required additional studies were conducted, except for the non-clinical carcinogenicity study (European Medicines Agency, 2009). At last, more data about the clinical efficacy and safety had to be obtained, which was achieved by executing a

phase III, randomised, double-blinded clinical trial (Oh et al., 2016), on the company's own initiative, and by the establishment of an LEMS patient registry in Europe (Mantegazza et al., 2015). With the patient registry, additional long-term efficacy and safety data is provided and the exposure to Firdapse® can be monitored (Mantegazza et al., 2015). Furthermore, this patient registry may collect additional data about special populations, such as patients with hepatic or renal impairment (European Medicines Agency, 2009; Mantegazza et al., 2015).

3,4-DAP SR

Many characteristics of 3,4-DAP SR originated from the IR, like Firdapse®. Data from 3,4-DAP IR can be used for the SR formulation, since both pharmaceutical formulations contain the same active ingredient, as shown in figure 2. It is also expected that the exposure is the same as 3,4-DAP IR (in case the active ingredient is completely absorbed) (European Medicines Agency, 2014; Zorginstituut Nederland, n.d.). To confirm these assumptions, a pharmacokinetic study should be conducted to determine whether the AUC of 3,4-DAP SR equals the AUC of Firdapse®, and thus 3,4-DAP IR. By using the same study design as the pharmacokinetic study of Firdapse® (Haroldsen et al., 2015b), the results can be compared without using the expensive medicinal product in a study design. By using this strategy, no study is required that directly compares the pharmacokinetics of Firdapse® with 3,4-DAP SR. In case the AUC of 3,4-DAP SR equals the AUCs of the IR and Firdapse®, non-clinical data of Firdapse® can be used for 3,4-DAP SR as well.

3,4-DAP SR has been used for over 20 years in regular clinical care in The Netherlands, which means long-term experience in patients. Up to now, no severe, likely related adverse events have been reported at the Dutch pharmacovigilance database (Lareb) taking into account that no official pharmacovigilance has been performed yet.

Scoring of the availability of the aspects, "yes" or "no", in the AR or in the product dossier do not reflect the extensiveness of the available data. An extensive amount of the required

data for marketing authorization was discussed in the AR of Firdapse®, but sometimes the data were only briefly described. Also for 3,4-DAP SR, not all the data are comprehensively described, for example, the quality part is not as extensively described as Firdapse®. Whereas parts of the guideline are very descriptive about the requirements of quality, non-clinical and clinical aspects of the marketing authorisation application, these requirements were not always met by Firdapse® (and 3,4-DAP SR). Still, our analysis provides a good overview of the data required for approval and which data can be collected after approval for 3,4-DAP SR.

Furthermore, we have to keep in mind that the Firdapse® and 3,4-DAP SR is a specific case of a pharmaceutical compounding preparation, and in order to apply for licensing a high level of documentation is needed, which might be a hurdle for compounded products. However, we think that this example clarifies the possibilities of pharmaceutical compounding preparations towards licensing as a possibility to keep treatment available at reasonable costs. Also, it seems that currently the initiatives for orphan medicinal products are focused on the development of new drugs which impairs the availability of existing pharmaceutical compounding preparations (Editorial, 2010).

Another possibility to avoid tremendous increases in pricing after licensing former pharmaceutical compounding preparations can be established by more involvement from the government in protecting the purpose of the (ultra-) orphan drug designation. For example, in case the (ultra-)orphan medicinal product exceeds the number of 50 000 patients using it (Schuller et al., 2015), the qualification of an (ultra-) orphan drug expires and the exclusivity period can be decreased (Daniel et al., 2016). In Japan, pharmaceutical companies pay a 1% sales tax on orphan drugs with annual profits exceeding 100 million Japanese yen (approximately €900 000) (Daniel et al., 2016). Moreover, the price transparency can be

increased. In the EU, the pricing of (ultra-) orphan drugs is completely confidential which leads to unanswered questions (Hyry et al., 2015).

Increased supervision of the Health Technology Assessment (HTA) might also positively influence the price tag (World Health Organization, n.d.). The HTA should supervise the data on which a product received marketing authorization. In the case of a sudden and extreme price increase, without significant research performed by the pharmaceutical company to justify this increase in pricing, it is advisable that the HTA can impose restrictions to stop the tremendous price increase.

In the procedure of obtaining marketing authorization, orphan drugs are accompanied by less difficulties compared to conventional drugs (Editorial, 2010). Since the available data from 3,4-DAP SR did not differ substantially from Firdapse® at the time of approval, there is a possibility that academic institutions can obtain marketing authorization for pharmaceutical compounding preparations after long-term use. As shown in the case of Firdapse®, a medicinal product can receive marketing authorization with hardly any original research and some small additional studies. However, in academic institutions, applying for marketing authorization is not a priority: since the focus is more science and care-driven instead of product-driven (de Wilde et al., 2016). A commencement can be made by ensuring good documentation and quality controls to guarantee safety of the product for the patients. Where some companies claim that this guarantee on safety is not feasible for academic centers without collaborations with industry, in France a government agency produces unlicensed pharmaceutical compounding preparations (Editorial, 2010). In The Netherlands several academic (and non-academic) GMP licensed pharmacies produce drugs for patients with otherwise unmet medical needs. Subsequently, registration of all safety and efficacy data can be obtained via good documentation, such as an LEMS patient registry, and can be used for applying for marketing authorization with such a product. Another possibility is to

collaborate with a pharmaceutical company, to ensure safety for patients against affordable prices.

Conclusions

In conclusion, at time Firdapse® obtained marketing authorization approval, the available data did not differ much from 3,4-DAP SR, indicating that marketing authorization approval with 3,4-DAP SR would have been possible, most likely 'Under Exceptional Circumstances'. Such approval requires post-marketing additional studies like it was the case for Firdapse®. To license 3,4-DAP SR, a pharmacokinetic study in healthy volunteers is necessary and investigation of long-term safety and efficacy could be established by collecting data in a patient registry. To avoid the tremendous price increases of pharmaceutical compounding preparations like 3,4-DAP SR, the involvement of the government and HTA can lead to more control over the data used for marketing authorization by a commercial company. Furthermore, 3,4-DAP shows the possibility of obtaining marketing authorization with a pharmaceutical compounding preparation by academic GMP licensed institutions.

List of abbreviations

3,4 – DAP	3,4 aminodypyridine
AR	Assessment report
AUC	Area under the curve
EMA	European Medicines Agency
GMP	Good Manufacturing Practices
HTA	Health Technology Assessment
IM	Immediate release
LEMS	Lambert-Eaton Myasthenic Syndrome
LUMC	Leiden University Medical Center
PDA	Patent ductus arteriosus
SR	Slow release

[DECLARATIONS]

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests

Funding

All authors, except for M.G.H. de Jong who was an intern at the LUMC, were financially supported by the Leiden University Medical Center, The Netherlands.

Authors' contributions

SdW, MdJ, HJG and KS made substantial contributions to conception and design and all authors were involved in the data interpretation. MdJ performed all the data collection. SdW and MdJ contributed to the literature search, figure finalization, and data analysis. All authors contributed to the writing of this manuscript, and all authors read and approved the final manuscript.

Acknowledgements

Not applicable

References

Boer, A., 2011. Letter: subject: CHF-rapport 11/37: amifampridine (Firdapse).

Daniel, M.G., Pawlik, T.M., Fader, A.N., Esnaola, N.F., Makary, M.A., 2016. The Orphan Drug Act: Restoring the Mission to Rare Diseases. Am. J. Clin. Oncol. 39, 210–213. doi:10.1097/COC.0000000000000251

de Wilde, S., n.d. Unlicensed pharmaceutical preparations for clinical patient care: ensuring safety. Pharmacoepidemiology and Drug Safety.

de Wilde, S., Guchelaar, H.-J., Herberts, C., Lowdell, M., Hildebrandt, M., Zandvliet, M., Meij, P., 2016. Development of cell therapy medicinal products by academic institutes. Drug Discov. Today 21, 1206–1212. doi:10.1016/j.drudis.2016.04.016

Dooms, M., Pincé, H., Simoens, S., 2013. Do we need authorized orphan drugs when compounded medications are available? J Clin Pharm Ther 38, 1–2. doi:10.1111/jcpt.12006

Editorial, 2015. Reducing the cost of rare disease drugs. Lancet 385, 746. doi:10.1016/S0140-6736(15)60420-2

Editorial, 2010. Stop exploiting orphan drugs. BMJ, Editor's choice c:6587. doi:10.1136/bmj.c6587

European Medicines Agency, 2016a. D80 assessment report - Quality guidance rev 10.16 - WC500004808.pdf.

European Medicines Agency, 2016b. D80 assessment report - Non Clinical Guidance rev 10.16 - WC500206988.pdf.

European Medicines Agency, 2016c. D80 assessment report - Clinical Guidance rev 10.16 - WC500206987.pdf.

European Medicines Agency, 2014. Guideline on the pharmacokinetic and clinical evaluation 4 of modified release dosage forms 5 (EMA/CPMP/EWP/280/96 Corr1) - WC500177884.pdf.

European Medicines Agency, 2009. Assessment Report for Zenas.

Gilhus, N.E., 2011. Lambert-eaton myasthenic syndrome; pathogenesis, diagnosis, and therapy. Autoimmune Dis 2011, 973808. doi:10.4061/2011/973808

Goldberg, A., 2010. Drug firms accused of exploiting loophole for profit. BBC News.

Haroldsen, P.E., Garovoy, M.R., Musson, D.G., Zhou, H., Tsuruda, L., Hanson, B., O'Neill, C.A., 2015a. Genetic variation in aryl N-acetyltransferase results in significant differences in the pharmacokinetic and safety profiles of amifampridine (3,4-

diaminopyridine) phosphate. Pharmacol Res Perspect 3, e00099. doi:10.1002/prp2.99

Haroldsen, P.E., Musson, D.G., Hanson, B., Quartel, A., O'Neill, C.A., 2015b. Effects of Food Intake on the Relative Bioavailability of Amifampridine Phosphate Salt in Healthy Adults. Clin Ther 37, 1555–1563. doi:10.1016/j.clinthera.2015.05.498

Harvey, A.L., Marshall, I.G., 1977. The actions of three diaminopyridines on the chick biventer cervicis muscle. Eur. J. Pharmacol. 44, 303–309.

Hülsbrink, R., Hashemolhosseini, S., 2014. Lambert-Eaton myasthenic syndrome - diagnosis, pathogenesis and therapy. Clin Neurophysiol 125, 2328–2336. doi:10.1016/j.clinph.2014.06.031

Hyry, H.I., Manuel, J., Cox, T.M., Roos, J.C.P., 2015. Compassionate use of orphan drugs. Orphanet J Rare Dis 10, 100. doi:10.1186/s13023-015-0306-x

Lindquist, S., Stangel, M., 2011. Update on treatment options for Lambert-Eaton myasthenic syndrome: focus on use of amifampridine. Neuropsychiatr Dis Treat 7, 341–349. doi:10.2147/NDT.S10464

Lundh, H., Nilsson, O., Rosén, I., 1983. Novel drug of choice in Eaton-Lambert syndrome. J. Neurol. Neurosurg. Psychiatr. 46, 684–685.

Mantegazza, R., Meisel, A., Sieb, J.P., Le Masson, G., Desnuelle, C., Essing, M., 2015. The European LEMS Registry: Baseline Demographics and Treatment Approaches. Neurol Ther 4, 105–124. doi:10.1007/s40120-015-0034-0

Minghetti, P., Pantano, D., Gennari, C.G.M., Casiraghi, A., 2014. Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe. Health Policy 117, 328–333. doi:10.1016/j.healthpol.2014.07.010

Mizoguchi, H., Yamanaka, T., Kano, S., 2016. Research and drug development activities in rare diseases: differences between Japan and Europe regarding influence of prevalence. Drug Discov. Today 21, 1681–1689. doi:10.1016/j.drudis.2016.06.014

Mori, S., Kishi, M., Kubo, S., Akiyoshi, T., Yamada, S., Miyazaki, T., Konishi, T., Maruyama, N., Shigemoto, K., 2012. 3,4-Diaminopyridine improves neuromuscular transmission in a MuSK antibody-induced mouse model of myasthenia gravis. J. Neuroimmunol. 245, 75–78. doi:10.1016/j.jneuroim.2012.02.010

Nicholl, D.J., Hilton-Jones, D., Palace, J., Richmond, S., Finlayson, S., Winer, J., Weir, A., Maddison, P., Fletcher, N., Sussman, J., Silver, N., Nixon, J., Kullmann, D., Embleton, N., Beeson, D., Farrugia, M.E., Hill, M., McDermott, C., Llewelyn, G.,

Leonard, J., Morris, M., 2010. Open letter to prime minister David Cameron and health secretary Andrew Lansley. BMJ 341, c6466.

Oh, S.J., Shcherbakova, N., Kostera-Pruszczyk, A., Alsharabati, M., Dimachkie, M., Blanco, J.M., Brannagan, T., Lavrnić, D., Shieh, P.B., Vial, C., Meisel, A., Komoly, S., Schoser, B., Sivakumar, K., So, Y., LEMS Study Group, 2016. Amifampridine phosphate (Firdapse(®)) is effective and safe in a phase 3 clinical trial in LEMS. Muscle Nerve 53, 717–725. doi:10.1002/mus.25070

Orphanet, n.d. Orphanet [WWW Document]. The portal for rare diseases and orphan drugs. URL http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=10583&Disease_Disease_Search_diseaseGroup=Lambert-Eaton-myasthenic-syndrome&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Lambert-Eaton-myasthenic-syndrome&title=Lambert-Eaton-myasthenic-syndrome&search=Disease_Search_Simple (accessed 5.9.17).

Quartel, A., Turbeville, S., Lounsbury, D., 2010. Current therapy for Lambert–Eaton myasthenic syndrome: development of 3,4-diaminopyridine phosphate salt as first-line symptomatic treatment. Current Medical Research and Opinion 26, 1363–1375. doi:10.1185/03007991003745209

Sanders, D.B., 1998. 3,4-Diaminopyridine (DAP) in the treatment of Lambert-Eaton myasthenic syndrome (LEMS). Ann. N. Y. Acad. Sci. 841, 811–816.

Schafer, E.W., Bowles, W.A., Hurlbut, J., 1983. The acute oral toxicity, repellency, and hazard potential of 998 chemicals to one or more species of wild and domestic birds. Arch. Environ. Contam. Toxicol. 12, 355–382.

Schuller, Y., Hollak, C.E.M., Biegstraaten, M., 2015. The quality of economic evaluations of ultra-orphan drugs in Europe – a systematic review. Orphanet Journal of Rare Diseases 10. doi:10.1186/s13023-015-0305-y

Tarr, T.B., Wipf, P., Meriney, S.D., 2015. Synaptic Pathophysiology and Treatment of Lambert-Eaton Myasthenic Syndrome. Mol. Neurobiol. 52, 456–463. doi:10.1007/s12035-014-8887-2

The rising cost of orphan drugs, 2015. . Lancet Haematol 2, e456. doi:10.1016/S2352-3026(15)00229-X

World Health Organization, n.d. WHO | HTA activities at WHO [WWW Document]. WHO. URL http://www.who.int/health-technology-assessment/activities/en/ (accessed 5.9.17).

Zorginstituut Nederland, n.d. Farmacokinetiek [WWW Document]. Farmacologie. URL https://www.farmacotherapeutischkompas.nl/farmacologie/farmacokinetiek (accessed 5.9.17).

[FIGURE LEGENDS]

Figure 1. Schematic overview of the methodological analysis. 3,4-DAP = 3,4-diaminopyridine; IR = immediate release; SR = slow release; Green = 'yes'; Red = 'No'.

Figure 2. Chemical structures of 3,4-diaminopyridine base and 3,4-diaminopyridine phosphate (Firdapse®). Figure adapted from Lindquist, 2011**(Lindquist and Stangel, 2011)**. Both 3,4-DAP base and 3,4-DAP phosphate (Firdapse®) contain the same active ingredient. 3,4-DAP = 3,4-diaminopyridine; SR = Slow release.

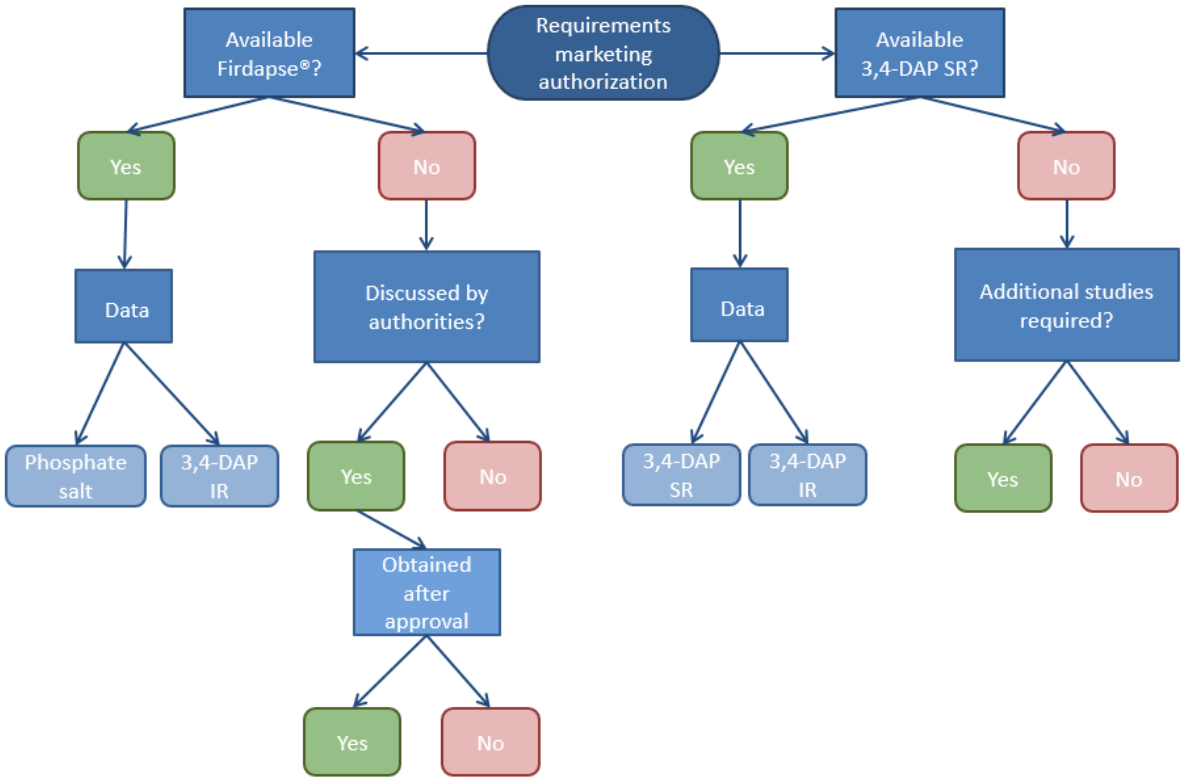
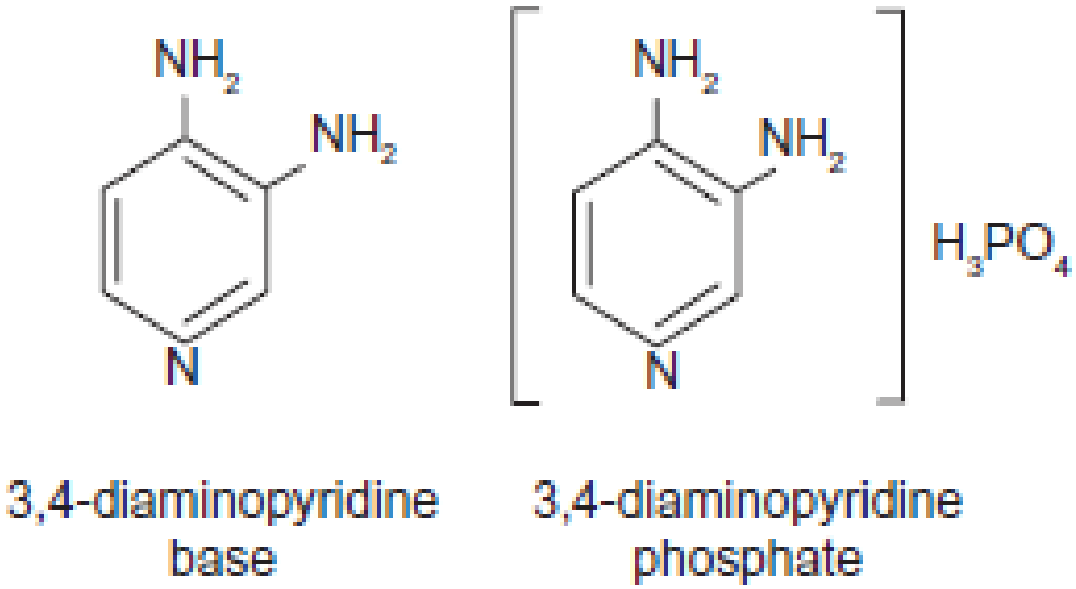


Fig. 1



3,4-diaminopyridine base

3,4-diaminopyridine phosphate

Fig. 2

Table 1. Different formulations of 3,4-diaminopyridine. 3,4-DAP IR = 3,4-diaminopyridine immediate release, 3,4-DAP SR = 3,4-diaminopyridine slow release

Name	**Base/phosphate**	**Immediate/slow release**	**Trade Name**
3,4-DAP IR	Base	Immediate	NA (pharmaceutical preparation)
3,4-DAP SR	Base	Slow	NA (pharmaceutical preparation)
3,4-DAP phosphate	Phosphate	Immediate	Firdapse®

Table 2. Missing data of Firdapse® and 3,4-DAP SR in the EPAR or product dossier. 3,4-DAP = 3,4-diaminopyridine; EPAR = European public assessment report; IR = immediate release; SR = slow release.

		Missing data	
		Firdapse®	**3,4-DAP SR**
Quality		-	-
Non-clinical	*Pharmacology*	Pharmacodynamic drug interactions	Safety pharmacology programme Pharmacodynamic drug interactions
	Pharmacokinetics	Metabolism Excretion Pharmacokinetic drug interactions	Distribution Metabolism Excretion Pharmacokinetic drug interactions
	Toxicology	Carcinogenicity	Carcinogenicity Reproduction toxicity Toxicokinetic
Clinical	*Pharmacokinetics*	Data obtained after approval	No data
	Pharmacodynamics	Secondary pharmacology	Secondary pharmacology
	Efficacy and safety	Available data and 3,4-DAP IR data	Available data and 3,4-DAP IR data

Graphical abstract