

## Update on Amifampridine as a Drug of Choice in Lambert-Eaton Myasthenic Syndrome

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### Abstract

Lambert-Eaton myasthenic syndrome (LEMS) is a disabling autoimmune disorder involving impairment of neuromuscular transmission and producing serious muscle weakness, for which few effective medications are currently available. 3,4-diaminopyridine (3,4-DAP, INN/USAN: amifampridine) is the leading treatment for LEMS and has been available for over 25 years as an unapproved drug under treatment and expanded access protocols filed with the US Food and Drug Administration (FDA) or from compounding pharmacies in the US. Administering the correct dose of 3,4-DAP is critical—overdosing can increase the risk for seizures and other adverse events, while underdosing can result in a substantial loss of efficacy or even treatment failure. Two recent studies have shown a wide variation in the 3,4-DAP content of compounded preparations. A tablet formulation of 3,4-DAP phosphate salt (FIRDAPSETM) has been licenced in Europe with orphan medicinal product status since 2009 and appears to be as efficacious as the base in relieving the symptoms of LEMS. The product has also received orphan drug status in the US and is currently being evaluated in a multicenter, double-blind, placebo-controlled phase III trial to support New Drug Application (NDA) approval in the US. A recent safety trial in healthy volunteers using doses at and above normal levels has shown no effect on QT intervals, heart rate, or cardiac depolarization. Based on available clinical trial data, amifampridine phosphate was recently given Breakthrough Therapy designation by the FDA, which may enable fast-track NDA approval, thus increasing the potential for more patients with LEMS to receive an effective therapy.

### Keywords

Amifampridine/3,4-diaminopyridine/3,4-DAP, Lambert-Eaton myasthenic syndrome, potassium ion channel blockers, compounded drugs clinical trial evidence, treatment, expanded access protocols

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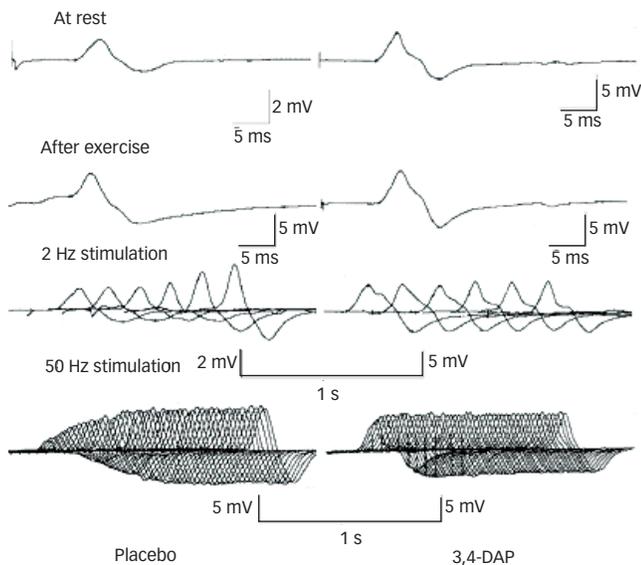
Lambert-Eaton myasthenic syndrome (LEMS) is a uncommon, but debilitating, neuromuscular disorder that is estimated to affect 2.32 people per million in Europe<sup>1</sup> with a prevalence of up to 3,000 cases in the US.<sup>2</sup> The disease has an autoimmune etiology in which autoantibodies bind to P/Q-type voltage-gated calcium channels (VGCCs) and decrease the release of acetylcholine at the synapses affecting peripheral cholinergic neurotransmission.<sup>3</sup> The impaired function of the VGCCs decreases the secretion of acetylcholine and disrupts synaptic transmission at neuromuscular junctions and certain autonomic nerve terminals leading to muscular weakness and symptoms of autonomic dysfunction.<sup>2,4-6</sup>

More than half the patients with LEMS, particularly male smokers aged over 50 years, present with an underlying malignancy, usually small cell lung cancer (SCLC).<sup>7,8</sup> However, there are also case reports on a wide

variety of lung and non-lung malignancies observed in LEMS patients. The peak age of onset of non-tumor LEMS is 35 years with a second peak at 60 years, whereas paraneoplastic LEMS occurs primarily in middle-aged and older adults, with a median age of onset of 58 years.<sup>9</sup> Non-paraneoplastic LEMS can be associated with other organic-specific autoimmune disorders.<sup>10</sup> Paraneoplastic cerebellar degeneration can also occur in cancer-associated LEMS cases.<sup>11</sup>

The diagnosis of LEMS can be challenging since the clinical presentation of sub-acute progressive fatigue and weakness is nonspecific. As a result, diagnosis is often delayed from many months up to even decades.<sup>10</sup> Clinical suspicion is the key for the diagnosis of LEMS. The symptoms of LEMS are frequently mistaken for those of myasthenia gravis (MG). In contrast to MG, oculo-bulbar paresis is rare and reflexes are reduced or absent in LEMS.

**Figure 1: Improvement in Repetitive Nerve Stimulation Test in the Abductor Digiti Quinti Muscle on Administration of 3,4-diaminopyridine Compared with Placebo**



Compound muscle action potential (CMAP) at rest: 2 mV in placebo versus 6.3 mV in 3,4-diaminopyridine (3,4-DAP); post-exercise facilitation: +275 % in placebo versus +19 % in 3,4-DAP; 2 Hz response: +100 % in placebo versus +7 % in 3,4-DAP; 50 Hz response: +650 % in placebo versus 0 % in 3,4-DAP.

At placebo, the repetitive nerve stimulation (RNS) pattern (except 2 Hz response) typical of presynaptic neuromuscular transmission block is observed: low CMAP, post-exercise facilitation and incremental response at high rate (50 Hz) stimulation. Decremental response at low (2 Hz) stimulation is typical of presynaptic block. With 3,4-DAP, the RNS test is normalized.

The most common clinical presentation of LEMS is proximal muscle weakness (more pronounced in the hip girdle than in the shoulder girdle) and easy fatigability. The classic triad of LEMS includes proximal leg weakness, hyporeflexia or areflexia, and cholinergic dysautonomia (dry mouth, impotence, and orthostatic hypotension).<sup>12</sup> Tendon reflexes are reduced or absent, but it is important to note that they may be preserved early in the course of the illness. Cranial muscles may also be involved with symptoms such as ptosis, facial weakness, dysphagia, dysarthria, and difficulty chewing. Cranial muscle weakness is usually milder and rarer than in MG and it occurs after the onset of limb-girdle weakness. Additional symptoms of autonomic dysfunction include reduced salivation, erectile dysfunction, dryness of the eyes, and reduced sweating.<sup>13</sup> The presence of an annoying dry mouth in patients with unexplained muscular fatigability is characteristic of LEMS. A transient improvement in muscle strength and reflexes immediately after brief exercise is classically observed in LEMS patients and is pathognomonic of LEMS.<sup>14</sup>

Diagnosis of LEMS is based on an assessment of clinical symptoms in conjunction with electrophysiologic parameters and antibody testing. Repetitive nerve stimulation (RNS) test is the electrophysiologic study of choice for the diagnosis of LEMS. RNS test demonstrates the characteristic so-called 'LEMS triad', including (see *Figure 1*):

- Low Compound Muscles Action Potential (CMAP) amplitude.
- Decremental responses in the low-rate (2–5 Hz) stimulation.

- Marked incremental responses (facilitation) of the CMAP amplitudes in the high-rate stimulation (HRS) (50 Hz) in the RNS test or after voluntary muscle contraction over a brief (10 second) period of time.<sup>12</sup>

For the brief exercise test, 10-second exercise is critical.<sup>15</sup> A more than 100 % increase in the CMAP in the HRS or after brief exercise is almost pathognomonic of LEMS. A recent study showed that a more than 60 % increment after brief exercise or during HRS is sufficient for the diagnosis of LEMS.<sup>12</sup> The diagnosis of LEMS may be confirmed by radioimmunoassay of VGCC antibodies, which are believed to be the main pathogenic factors in LEMS,<sup>16</sup> and P/Q VGCC antibodies are detected in 85 % of patients with clinically and electrophysiologically defined LEMS.<sup>17,18</sup> In seronegative LEMS patients, without detectable VGCC antibodies, the electrophysiologic findings are less pronounced.<sup>19</sup>

Because of the high prevalence of SCLC in LEMS, it is mandatory to perform a careful tumor screening, especially in patients with a history of smoking. SCLC is usually identified within 2 years of the diagnosis of LEMS. Computed tomography (CT)-thorax scans detected most of the tumors found and was far more sensitive than chest X-rays.<sup>20</sup> [18F] fluorodeoxyglucose positron emission tomography (FDG-PET) may have an additive value in tumor screening in selected cases.

## The Advent of an Effective Treatment Symptomatic Treatment

A range of medications have been tried with varying success as treatments for LEMS, but due to the rarity of the condition, few randomized controlled trials (RCTs) have been conducted apart from 3,4-diaminopyridine (3,4-DAP), which has been more thoroughly investigated and is discussed in the next section.

### Acetylcholinesterase Inhibitors

Pyridostigmine has been used for symptomatic treatment in more than 80 cases since 1953, when the first case of LEMS was reported. A double-blind, placebo-controlled, crossover study found significant improvement of CMAP amplitude and muscle strength with intravenous (IV) administration of 3,4-DAP but not with pyridostigmine (see *Table 1*).<sup>21</sup> A minimal to moderate response was reported in five patients among more than 80 treated cases in an extensive review.<sup>22</sup> In a few anecdotal cases, pyridostigmine alone is enough to induce a satisfactory symptomatic improvement in mild cases. Often pyridostigmine is used together with guanidine and 3,4-DAP.<sup>23-26</sup>

### Guanidine Hydrochloride

The potassium channel blocker, guanidine hydrochloride, is currently the only drug approved for use in LEMS<sup>27,28</sup> in the US, but was approved by the US Food and Drug Administration (FDA) prior to 1962 when only safety information was necessary for approval. Guanidine acts on the presynaptic junction and, thus, is an ideal drug for symptomatic treatment of LEMS. It was mostly studied in cases reports and has not been studied in randomized trials. Guanidine has been used in about 50 LEMS cases and clinical improvement was reported in most cases.<sup>29</sup> The most common side effects are gastrointestinal symptoms and distal paresthesia. The most serious, but rare, side reactions of guanidine are hematologic abnormalities and renal insufficiency, which seems to be dose related.<sup>23</sup> Because of these rare side reactions, guanidine is

precluded as a general use in LEMS. Combination therapy of low-dose of guanidine (less than 1 g a day) with a liberal dose of pyridostigmine was beneficial in nine LEMS cases with an improvement in muscle strength and CMAP amplitude without any undue serious side reactions.<sup>23</sup> This suggests that combination therapy of low-dose guanidine and pyridostigmine can be used as an alternative therapy for LEMS when 3,4-DAP is not readily available.

### Calcium Channel Agonist

Since LEMS is primarily due to the defect of pre-synaptic calcium channel, a calcium-channel agonist would be ideal for symptomatic treatment. So far, such medication is not available. Tarr et al. developed GV-58 (a modified (R)-roscovitine), a calcium channel agonist, and evaluated this in a passive transfer mouse model of LEMS. They found that weakened LEMS-model neuromuscular synapses are significantly strengthened following exposure to GV-58.<sup>30</sup> This suggests that this calcium channel agonist is potentially effective for symptomatic treatment in LEMS. This compound, however, needs clinical trial evaluation for efficacy and safety in humans.

### Immunotherapy in Lambert-Eaton Myasthenic Syndrome

Considering that LEMS is an autoimmune disorder, immunotherapy should be the main stay of treatment if symptomatic treatment fails. IV immunoglobulin (IVIG) is the only therapy in which a rigorous controlled study showed effectiveness. One randomized, double-blind, placebo-controlled study showed a significant improvement in myometric strength and a significant decline in serum VGCC antibody titers with IVIG compared with placebo in nine patients.<sup>31</sup> Various immunosuppressive therapies such as prednisolone, azathioprine, cyclosporin, or plasma exchange have shown efficacy in LEMS, but the proportions of patients showing improvements were limited and the effects were short-lived in plasma exchange.<sup>32–35</sup> In LEMS patients, corticosteroids can be used when required for the disease treatment; however, immunosuppressants should be avoided before the presence of a tumor is excluded.<sup>36</sup> Rituximab, an anti-CD 20 antibody, is a promising agent also for LEMS, but there are few reports of its use in this disease.<sup>33,37</sup>

### Tumor Treatment in Lambert-Eaton Myasthenic Syndrome

In patients with the paraneoplastic form of LEMS, it is critical that anti-tumor treatments are given to treat underlying malignancies.<sup>38</sup> Unlike other paraneoplastic syndromes, which are usually resistant to any therapy, LEMS is known to be consistently responsive to immunotherapy or anticancer therapy.<sup>32</sup> Clinical data suggest that the immune response associated with LEMS may suppress tumor activity, thus prolonging survival times of LEMS patients with cancer.<sup>39,40</sup> Chemotherapeutic agents, such as vincristine, doxorubicin, and cyclophosphamide, are effective against SCLC-associated LEMS, but the proportions of patients benefiting are small.<sup>32,35</sup> In a study of 16 patients with LEMS associated with small-cell carcinoma, 13 patients received specific tumor therapy and most also received pharmacologic and immunologic treatment for LEMS.<sup>32</sup> Seven of 11 patients surviving for more than 2 months after tumor therapy showed substantial neurologic improvement, but only one patient was in complete remission 7 years after the cancer therapy. In three of these 11 patients, improvement was only transient.

### The Evidence Supporting Amifampridine (3,4-diaminopyridine) as a Treatment of Lambert-Eaton Myasthenic Syndrome

In LEMS, the most widely used treatment for symptom relief is 3,4-DAP, which was first suggested to improve muscle strength and autonomic function in a small case series of LEMS patients more than 30 years ago.<sup>41</sup> Amifampridine is not yet approved for LEMS in the US and currently is only available through expanded access or compassionate use programs, compounding pharmacies or in clinical trials. Amifampridine blocks voltage-gated potassium ion channels in membranes and facilitates synaptic transmission.<sup>42</sup> The blocking of potassium ion channels prolongs the depolarization of nerve action potentials, thereby increasing the open-time of VGCCs and consequently the influx of calcium ions into the nerve terminal. This increased calcium influx enhances the quantal release of acetylcholine, which is calcium-dependent.

Both 4-aminopyridine (4-AP) and 3,4-DAP have been used to treat LEMS but 4-aminopyridine has proved to be less effective and has a narrow toxic to therapeutic margin,<sup>43</sup> with many neurologic side effects reported, including seizures.<sup>22</sup> 3,4-DAP has been shown in animals to be more potent in improving neuromuscular transmission and less convulsant than 4-AP. In addition, it has an advantage over 4-AP because it crosses the blood–brain barrier less rapidly, resulting in fewer central nervous system side effect

Since the first use of 3,4-DAP in LEMS in 1982, the efficacy and safety of 3,4-DAP in LEMS treatment have been consistently well documented in repeated case reports and one open trial in more than 70 cases.<sup>29</sup> Moderate to marked functional improvement was seen in patients receiving 3,4-DAP at doses of 24–80 mg/day IV or 76 mg/day po in non-randomized trials (n=1–53).<sup>29,35,41,44–47</sup>

Three randomized, placebo-controlled trials (RCTs) (n=7–26) compared 3,4-DAP with placebo for treating LEMS over periods up to 8 weeks (see *Table 1*).<sup>21,24–26</sup> All three trials showed a significant improvement in muscle strength or quantitative MG (QMG) score, and CMAP amplitude in LEMS, providing definite evidences for effective symptomatic treatment for LEMS. In the trial of Oh et al., patients with LEMS were treated with 3,4-DAP or placebo for 3 to 8 days in a randomized, double-blind, crossover study design (n=7).<sup>48</sup> Their results showed significantly better CMAP, LEMS class, Medical Research Council (MRC) muscle strength, quantitative MG (QMG), and subjective symptom (SS) scores (p=0.0017–0.0246) (see *Figure 1*). Long-term open-label treatment for up to 1 year in four patients showed further improvements in QMG and MRC scores.

All the studies showed that 3,4-DAP was generally well tolerated with a favorable risk: benefit ratio. Few adverse effects were reported, and these were mild, transient, and dose-related, and included paresthesia, heat sensation, difficulty sleeping, light-headedness, and fatigue.<sup>49</sup> 3,4-DAP can, however, increase the risk for seizure, especially in patients on high daily doses (100 mg or more) and with brain metastases. An observational, retrospective cohort study included 669 patients who were treated at a multiple sclerosis (MS) clinic in France.<sup>50</sup> Treatment with 3,4-DAP resulted in less than 20 % of patients presenting with adverse drug reactions (ADRs) while using moderate doses of 3,4-DAP (either 20–30 mg daily for MS fatigue, or up to 80 mg daily for patients with LEMS) for periods of up to 51 months. The majority of ADRs were mild to moderate and transient or reversible at the end of treatment or after dose

**Table 1: Summary of Randomized, Placebo- or Active-controlled Trials with 3,4-diaminopyridine in the Treatment of Lambert-Eaton Myasthenic Syndrome**

Study and Reference	Design	Treatments and Numbers of Patients	Endpoints	Results
Oh et al. 2009 <sup>48</sup>	Randomized, double-blind, crossover drug trial (randomized phase: 308 days, follow-up 3–4 months)	3,4-DAP (30 mg titrated to maximum 80 mg/day, oral) or placebo (n=7)	SS score, LEMS classification, muscle strength score, QMG score RNS test and SFEMG (to determine CMAP)	Significant improvements with DAP for SS score, LEMS classification, muscle strength score, QMG, and CMAP (p=0.0112–0.0246). Not all patients preferred DAP. AEs: paresthesias; difficulty sleeping in 1 patient and high blood pressure. 50 % sustained improvement during follow-up
Wirtz et al. 2009 <sup>21</sup>	Randomized, double-blind, double dummy, crossover (open label in follow-up) single dose only	4 treatment groups (n=9): 3,4-DAP 10 mg, pyridostigmine 2 x 1 mg, 3,4-DAP + pyridostigmine, placebo	Isometric muscle strength, CMAP amplitude	Differences from placebo seen with 3,4-DAP and combination but not with pyridostigmine. Combination therapy did not have supra-additive effect. AEs: Peri-oral and lingual paresthesias; upper arm pain (study drug injection site)
McEvoy et al. 1989 <sup>24</sup>	Open-label phase to determine 3,4-DAP dose (8 days) for randomized, double-blind crossover phase (3 days) (Open label in follow-up, ≥3 months)	3,4-DAP titrated to 10 mg/day or as tolerated or placebo (and 3,4-DAP ± pyridostigmine oral in follow-up (n=12)	NDS, isometric muscle strength, CMAP amplitude. Autonomic function	Significant improvements with 3,4-DAP compared with baseline and placebo NDS, isometric muscle strength and CMAP amplitude (p<0.001 to <0.05) in crossover phase. In open-label phase, NDS decreased with increasing 3,4-DAP doses. AEs: Paresthesias, epigastric distress, sleeping problems rhinorrhoea. 1 seizure during follow-up
Sanders et al. 2000 <sup>26</sup>	Randomized, parallel group study (6 days) with open label follow-up	3,4-DAP (n=12) or placebo (n=14) (n=25 in follow-up)	QMG score, CMAP amplitude	Symptomatic improvement in QMG and CMAP (p=0.01 and p<0.001). 96 % of patients had a ≥2-point increase in QMG score—usually in combination with pyridostigmine. AEs: Peri-oral and digital paresthesias

AEs = adverse events; CMAP = compound muscle action potential; 3,4-DAP = 3,4-diaminopyridine; NDS = Neurologic Disability Score; QMG = quantitative myasthenia gravis score; RNS = repetitive nerve stimulation test; SFEMG = single-fiber electromyography; SS = subjective symptom.

\*Murray et al. studied a double-blind comparison between a single dose of 20 mg 3,4-DAP and 120 mg pyridostigmine in six patients. Improvement was more marked with 3,4-DAP in five by both clinical and electrophysiologic criteria. This is not included in this table because the result was only available in abstract format.<sup>66</sup>

adjustment. Most did not require discontinuation. The most commonly observed ADRs were paresthesias. There was one case of epileptic seizure, one of hepatotoxicity, and one of heart palpitations thought ‘possibly’ to be linked to 3,4-DAP. The overall incidence of certain side effects of 3,4-DAP is unknown due to limited clinical experience. Because of this, treated patients must be monitored regularly including laboratory testing and an electrocardiogram (ECG) is recommended if there is evidence of cardiac arrhythmias prior to the initiation of treatment. A Cochrane review<sup>61</sup> analyzed the results of four of these RCTs in a total of 54 patients with LEMS and concluded that there is limited to moderate high-quality evidence showing that 3,4-DAP for up to 8 weeks or IVIG improved muscle strength scores and CMAP in LEMS. In 2009, Oh et al. concluded that 3,4-DAP is the first-line treatment option for patients with LEMS.<sup>48</sup> They further stated that there is no scientific justification for denying the general use of 3,4-DAP in the US and strongly advocate FDA approval of DAP for general use in the treatment of LEMS in the US. The present data suggest that 3,4-DAP is effective in relieving symptoms in most patients with LEMS with 20–60 mg a day and the maximum daily dose should be less than 80 mg a day.

Some studies have compared 3,4-DAP with other treatments. An example was a study comparing IV 3,4-DAP with IV pyridostigmine in the treatment of LEMS that showed muscle strength and CMAP were significantly improved with 3,4-DAP, but not with pyridostigmine. Furthermore, combining the treatments produced no advantage over 3,4-DAP alone.<sup>21</sup> Gastrointestinal cramps and diarrhea may occur when 3,4-DAP is taken with the cholinesterase inhibitor pyridostigmine and can be minimized by reducing the dose of the latter.<sup>2</sup> Pyridostigmine shows poor efficacy when used alone in LEMS, but can be used to increase the efficacy and reduce the required dose of 3,4-DAP.<sup>52</sup>

## Recent and Ongoing Studies on Amifampridine in Lambert-Eaton Myasthenic Syndrome

Since the above studies were completed, an additional phase III trial and a phase II trial have been initiated to further investigate the efficacy and safety of 3,4-DAP in small populations of LEMS patients (see Table 2). The studies are ongoing and results are awaited with interest. A further phase I double-blind study on 59 healthy volunteers is the first formal investigation of the cardiac safety of the amifampridine phosphate (known as a thorough QT or TQT study). This trial is completed and preliminary results indicate that the treatment at and above normal dose levels has no effect on heart rate or cardiac depolarization (Biomarin, unpublished data), which was the prespecified primary endpoint. None of the study subjects developed new clinically relevant electrocardiographic or morphologic changes and there was no prolongation of QT interval.

A further trial on long-term treatment of congenital LEMS with 3,4-DAP over 1 to 10 years is in progress. In addition, several expanded access studies of 3,4-DAP in LEMS are in progress at individual treatment centers in the US.

## Registration Status of Amifampridine (3,4-diaminopyridine) Phosphate and Amifampridine for the Treatment of Lambert Eaton Myasthenic Syndrome

As a result of a review of available efficacy and safety data, amifampridine phosphate (Firdapse™) was recommended as a first-line symptomatic treatment of LEMS by the European Federation of Neurologic Societies.<sup>49</sup> This salt species of 3,4-DAP has been shown to have superior stability

**Table 2: Ongoing Clinical Trials of 3,4-diaminopyridine Phosphate and 3,4-diaminopyridine Base in Lambert-Eaton Myasthenic Syndrome**

Study Title and Identifier	Design and Estimated Recruitment	Treatments and Planned Numbers of Patients	Endpoints
Phase III, placebo-controlled, randomized discontinuation Evaluating Efficacy and Safety of Amifampridine Phosphate in Patients With Lambert-Eaton Myasthenic Syndrome (LEMS). NCT01377922/LMS-002	Randomized, double-blind placebo-controlled trial 30 patients	4-part study: 1. Open label run-in; 2. Patients randomized to continue 3,4- DAP phosphate or titrate to placebo; 3. 3,4-DAP or placebo for 7 days; 4. Open-label extension (all receiving 3,4-DAP)	Primary: QMG score; secondary: T25FW test; tertiary CMAP amplitude, CGI-I score, CGI-S score, and SGI score. Safety assessments :AEs, vital signs, laboratory tests (chemistry, hematology, urinalysis) and physical exam
Phase II inpatient double-blind placebo-controlled withdrawal study of 3,4-DAP base in subjects with known LEMS. (DAPPER) NCT01511978	Randomized, placebo-controlled trial 30 patients	Patients start on 3,4-DAP base, 3–4 times daily then randomized to continue or titrate down to placebo and followed for 7 days	Primary: TUG Test, Secondary: Self-assessment of LEMS-related weakness
Open-label trial Of 3,4-DAP in LEMS and congenital myasthenic syndromes. NCT00872950	Long-term, open-label single-group study 25 patients	Patients to receive 3,4-DAP over 1–10 year timeframe	Increase in strength and autonomic symptoms

AEs = adverse events; CMAP = compound muscle action potential; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; 3,4-DAP = 3,4-diaminopyridine; LEMS = Lambert-Eaton myasthenic syndrome; QMG = Quantitative Myasthenia Gravis; SGI = Subject Global Impression; T25FW = Timed 25-Foot Walking; TUG = Triple Timed Up & Go. Source: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

compared with the base,<sup>53</sup> and an oral formulation containing amifampridine phosphate, equivalent to 10 mg base, was developed. Although the safety and efficacy of amifampridine phosphate has not been directly compared with 3,4-DAP base in a RCT, it has been shown to be essentially bioequivalent with the base preparation,<sup>54</sup> and has been produced with vigorous quality control and pharmacovigilance standards as required by regulators. It should be noted, however, that in the US, amifampridine (3,4-DAP) is predominantly administered to patients with LEMS under treatment Investigational New Drugs (INDs) and expanded access (also referred to as 'compassionate use') programs. Availability of amifampridine in the US is generally limited to treatment centers where physicians are willing to accept regulatory restrictions, take responsibility for oversight, monitoring, recordkeeping, and ensure human subject protections applicable to clinical trials are in place. Physicians must also accept any potential liability related to the use of amifampridine.

Amifampridine phosphate was granted orphan medicinal product status in Europe and was approved for use in this indication by the European Medicines Agency in March 2011. In the US, it was granted orphan drug designation by the FDA in November 2009 and, more recently, the drug was granted Breakthrough Therapy designation in August 2013. This status can permit a fast-track New Drug Application (NDA) process.<sup>55</sup> The NDA filing will be supported by a substantial package of safety and efficacy data derived from 54 preclinical and six clinical trials. From these data, labeling will be approved providing adequate directions for use, along with information on the risks and benefits of the product's use. It is envisaged that amifampridine phosphate may be available for use in LEMS in the US within 2–3 years.

In December 1990, FDA granted orphan drug designation to 3,4-DAP. However, the sponsor of that application has yet to submit an NDA for approval. While the sponsor has been providing the drug free of charge to patients under treatment and expanded access protocols for many years, such provision in the absence of NDA approval circumvents important public health requirements and limits access of patients to the drug. Treating specialists are frequently unwilling to accept the malpractice risks associated with prescribing an unapproved product or unwilling to take

on the responsibilities associated with gaining access to an investigational drug required by the FDA. Patients may themselves be unwilling or unable to travel to physicians with INDs in place to be able to gain access.

### Compounding by Local Pharmacies—A Serious Concern in 3,4-diaminopyridine Prescribing

Compounded drug products are produced by the *ad hoc* preparation of drug doses tailored to the needs of individual patients as performed in many independent community pharmacies.<sup>56</sup> The practice is controversial because it involves producing a drug formulation for which safety and efficacy have not been demonstrated. Compounding requires high staff competency to ensure consistent quality, but pharmacies are not usually equipped to comply with Good Manufacturing Practice (GMP) standards, which requires drug products to have an active ingredient range limit of 95–105 % of the declared label content.<sup>57</sup> Compounded medications may vary significantly in dosage and absorption characteristics, with no independent check of quality or variation. This results in uncertainty of the doses supplied and raises concerns for patient therapy.<sup>58</sup>

Compounding factors have arisen with numerous different drugs. This is illustrated in a survey of compounded drug products, including female hormones, local anesthetics, and inhalation drugs, by the FDA that found 33 % of products failed testing criteria, either due to sub- or super-potency or lack of uniformity of individual dosage units. Potency ranged from 67.5 % to 268.4 % of the amount of drug declared on the product labeling.<sup>56,59–61</sup> The seriousness of the problem is illustrated by accidental overdoses of 4-AP due to pharmacy errors that resulted in life-threatening seizures or status epilepticus in patients with MS or other conditions.<sup>60,61</sup> Conversely, compounding that provides an insufficient dose can result in low efficacy and even treatment failure.

The quality of compounded drug formulations is an important public health concern. Its use requires local, hospital, or other pharmacies to prepare tablets or capsules from the amifampridine base compound.<sup>53</sup> These are used either orally or in the preparation of solutions for IV administration. Raust et al. demonstrated that 3,4-DAP is much less stable under stress conditions than its phosphate salt, with 27 % of the

base form degraded compared with only 0.1 % of the salt form.<sup>53</sup> Since the base compound is potentially unstable (stable for up to 12 months under refrigeration) and there are potential compounding errors in preparation, these matters have implications for the efficacy and safety of the product. The potential instability necessitates the shipping and storage of 3,4-DAP tablets under refrigerated conditions whereas manufactured tablets of the phosphate salt can be shipped and stored at room temperature. Furthermore, compounded forms of 3,4-DAP do not have appropriate safety monitoring and pharmacovigilance systems in place to capture, analyze, and report efficacy and safety data.

The 3,4-DAP content of tablet or capsule samples prepared in nine different pharmacies was assessed in a recent study. The pharmacies were located in the US (4), Germany (2), Italy (1), the Netherlands (1), and the UK (1) and the doses claimed to contain 5, 10, 20, or 50 mg of active drug.<sup>62</sup> Ten samples of each preparation were analyzed. The variability in dosage form weight ranged from 0.81 % relative standard deviation (RSD) to 4.82 % RSD. Among the 90 samples tested, the 3,4-DAP content varied from 22.2 % to 125.2 % of the declared label content and none complied with the GMP standard range of 95–105 % of declared content. There was considerable variation of 3,4-DAP within the content of samples from the same pharmacies. All 10 of the samples from one pharmacy had active drug content well below the stated label content (35.0–57.1 %). There was no evidence of significant levels of degradation products in any of the samples. The variability in compounded 3,4-DAP samples appeared to be mostly the result of heterogeneity of the formulated material.

Similar findings were observed in another recent study of the active content variability of compounded 3,4-DAP in solid oral dosage forms, which evaluated 10 units each of 21 samples obtained from pharmacies in Belgium (2), Germany (17), Italy (1), and Spain (1), within the stated shelf life.<sup>63</sup> The variability in dosage form weight ranged from 1.16 % RSD to 5.48 % RSD. Among the 210 units tested, 3,4-DAP content ranged from 53.5–128.5 %. No dosage form achieved the GMP standard range of declared content for all 10 units tested. All samples of one dosage form contained at least 10 % below the declared content (mean  $\pm$  SD 69.8 $\pm$ 5.6 %), and all samples of another dosage form contained at least 10 % above the declared content (121.8 $\pm$ 5.3 %). The most variable dosage form averaged 85.9 % of declared content but ranged from 53.5 % to 118.1 %. There was no evidence of a significant presence of degradation products or related substances in 15 dosage forms. Four dosage forms contained total impurities/degradation peaks that amounted to  $\leq$ 0.20 % 3,4-DAP equivalent. Two dosage forms contained higher levels of potential impurities/degradation peaks (0.43 % and 1.14 % 3,4-DAP equivalent).<sup>63</sup>

The data from these studies indicate that compounded formulations of 3,4-DAP can vary widely and that patients may be exposed to unnecessary risks. There is a need for pharmaceutical grade oral dosage forms of amifampridine to ensure consistent efficacy and patient safety.<sup>64</sup>

## The US Food and Drug Administration and Compounding of Amifampridine<sup>65</sup>

The FDA Modernization Act of 1997 created an exemption to ensure continued availability of compounded drug products, allowing patients access to individualized therapies not available commercially. The FDA, after consulting with the United States Pharmacopeia (USP) and

the Pharmacy Compounding Advisory Committee, used the following four criteria for inclusion in the compounding list: (1) The chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists.

In their 1999 notice, the FDA noted the following about 3,4-DAP as a candidate for the compounding list:<sup>65</sup>

3,4-Diaminopyridine. The drug substance 3,4-Diaminopyridine (DAP), which is well characterized chemically, is a potassium channel blocker that may enhance the release of acetylcholine from nerve terminals. DAP has been used in the treatment of several neuromuscular disorders, including Lambert-Eaton myasthenic syndrome, MG, amyotrophic lateral sclerosis, and MS. At doses reported in the literature, DAP appears to be well tolerated and its toxicity appears to be dose related. There have been reports of seizures with its use, however, and DAP is contraindicated in patients with epilepsy. The FDA would like more information about the historical use, safety, and effectiveness of DAP before deciding whether to propose it for inclusion on the bulk drugs list. The Pharmacy Compounding Advisory Committee similarly expressed a desire for more information about DAP before making a recommendation about its status to the agency. FDA is soliciting public input on these and any other issues that are relevant to the agency's consideration of this substance for the bulk drugs list.

Subsequently, at its May 6–7, 1999 meeting, the Pharmacy Compounding Advisory Committee voted 7 to 4 against inclusion of 3,4-DAP on the bulk drugs list, largely based on the safety concerns and the commitment of Jacobus Pharmaceuticals to make the drug available under compassionate-use INDs, while pursuing FDA approval. Therefore, the individual or firm that compounds a drug product containing 3,4-DAP may be subject to a warning letter, seizure of product, injunction, and/or criminal prosecution for violations of the Food, Drug, and Cosmetic Act.

## Conclusions and Future Developments

LEMS is a rare but seriously disabling neuromuscular disease for which effective therapy is critical. Amifampridine (3,4-DAP) has proved to be an effective treatment of LEMS in a series of randomized studies. The tolerability has been found to be acceptable and the risk: benefit ratio was favorable. However, the variability of 3,4-DAP found in compounded preparations from different pharmacies and the associated safety risks suggest that compounding can be problematic and that approved products available as accurately measured doses would be a more effective, safe, and reliable alternative. The phosphate salt of amifampridine appears to be as effective as the base in relieving the symptoms of LEMS and has a comparable tolerability profile. Using manufactured doses of amifampridine phosphate assures efficacy and safety by supplying reliable and consistent doses that are prepared using validated processes in compliance with current GMPs, ensuring quality and purity and thus avoiding the problems associated with compounding of 3,4-DAP at local pharmacies. It also does not require shipping and storage under refrigerated conditions.

Most adverse effects associated with amifampridine are dose-dependent, and the drug may have a narrow therapeutic window. Possible improvement

in terms of side-effects and LEMS symptoms might be obtained by slow-release tablets, or a combination of amifampridine with other agents. All studies on 3,4-DAP in LEMS conducted to date have included limited patient populations. Two controlled clinical trials involving larger numbers of patients are ongoing and intended by their sponsors to support FDA approval for general use of amifampridine or its phosphate salt for the symptomatic treatment of LEMS.

The recently released cardiac safety results in volunteers and earlier safety data support the use of amifampridine phosphate over extended durations in LEMS patients and minimize cardiac safety concerns. In

addition, the Breakthrough Therapy designation indicates that the FDA recognizes the urgent need for an approved medication for LEMS in the US and that the potential benefit of amifampridine in LEMS is supported by positive clinical efficacy and safety evidence. Within a few years, therefore, a greater proportion of patients with this disabling condition may have access to a treatment with demonstrated safety and efficacy. Data from the numerous nonclinical and more than six clinical studies evaluating the safety and efficacy of amifampridine administered as the phosphate salt will lead to proper labeling that will provide physicians adequate directions for use and to appropriately instruct both physicians and patients on its risks and benefits. ■

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