NHS England

Evidence Review:

Amifampridine phosphate for the treatment of Lambert-Easton Myasthenic Syndrome

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Contents

1. Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is a rare disorder caused by a problem with the transmission of nerve signals to the muscles. The immune system mistakenly attacks the nerve endings, which causes an insufficient release of a chemical neuro transmitter called acetylcholine resulting in impaired nerve signal transmission. This weakens the nerve impulses from the nerves to the muscles and prevents the muscles contracting properly. Thus LEMS results in muscle weakness and sometimes dryness of the mouth, constipation and impotence.

In about 50% of people with LEMS, the disease is triggered by an underlying lung cancer. These people usually develop the disease in middle age or later. There is no obvious trigger in the other 50% of patients with LEMS who do not have cancer, and this form of the disease may start at any age.

If there is no cancer, LEMS does not shorten life but may have a considerable impact on quality of life. People with small cell lung cancer will have a shorter life expectancy because of the aggressive nature of the cancer. They can develop complications such as difficulty breathing, difficulty swallowing and pneumonia.

Amifampridine increases the release of acetylcholine from nerve cells. It is an inhibitor of voltage-dependent potassium channels and prolongs the depolarisation of the pre-synaptic cell membrane, allowing for enhanced calcium influx into the neuron which facilitates the release of acetylcholine, thereby improving neuromuscular transmission.

Amifampridine is the international non-proprietary name (INN) for 3,4-diaminopyridine (3,4-DAP). There are no licensed preparations of amifampridine available in the UK. Amifampridine phosphate (Firdapse®) (3,4-DAP phosphate) is the phosphate salt of amifampridine and is a stable formulation that does not require refrigeration. Amifampridine phosphate is the only treatment licensed for the symptomatic treatment of patients with Lambert-Eaton myasthenic syndrome (LEMS). Amifampridine phosphate (Firdapse®) was designated an orphan medicine by the European Medicines Agency in 2002, and was awarded a marketing authorisation under exceptional circumstances in 2009.

2. Summary of results

Amifampridine is the international non-proprietary name (INN) for 3,4 -diaminopyridine (3,4-DAP). There are no licensed preparations of amifampridine available in the UK. Amifampridine phosphate (Firdapse®) (3,4-DAP phosphate) is the phosphate salt of amifampridine and is a stable formulation that does not require refrigeration. Amifampridine phosphate is the only treatment licensed for the symptomatic treatment of patients with Lambert-Eaton myasthenic syndrome (LEMS).

The evidence review sought to answer the following questions:
1) Is amifampridine phosphate clinically effective in adult patients with confirmed Lambert-Eaton myasthenic syndrome (LEMS)?
2) Is amifampridine phosphate cost effective in adult patients with confirmed Lambert-Eaton Myasthenic Syndrome?

The clinical evidence supporting the use of amifampridine phosphate in LEMS originates from studies of unlicensed amifampridine. The evidence is consistent in demonstrating some improvement in muscle strength from treatment with amifampridine without clear demonstration of actual clinical benefit to the patients.

1) Is amifampridine phosphate clinically effective in adult patients with confirmed Lambert-Eaton myasthenic syndrome?

The literature search could not identify any studies of the clinical efficacy of amifampridine phosphate. This evidence review was therefore limited to the use of amifampridine base in LEMS.

There are only a few high quality studies of amifampridine in LEMS. The most recent Cochrane Review of amifampridine (3, 4-DAP) in patients with Lambert-Eaton myasthenic syndrome (Keogh et al., 2011) is a well-conducted systematic review and meta-analysis that summarises best available current evidence. This includes the four RCTs reporting on the efficacy of 3, 4-DAP treatment in LEMS (McEvoy, 1989; Oh, 2009; Sanders, 2000;

Wirtz, 2009). This review was graded as "limited but moderate to high quality evidence at low risk of bias" by the authors. The 4 RCTs demonstrate the efficacy of 3, 4-DAP in LEMS, with all reporting improvement in muscle strength score or myometric limb measurements. Meta-analysis of the efficacy endpoints showed 1) Quantitative Myasthenia Gravis (QMG) muscle score improvement of 2.44 points (mean) with a 95% confidence interval ranging from 3.6 to 1.22; and 2) Compound Muscle Action Potential (CMAP) amplitude improvement of 1.36 mV (mean) with a 95% confidence interval ranging from 0.99 to 1.72.

The authors also note that the improvement produced by 3, 4-DAP treatment of LEMS may not be regarded as clinically significant based on the accepted QMG improvement to actual clinical benefit cut off being pegged at >2.6 points (Barohn et al., 1998). The key limitations remain the small trial sizes and the relatively short time periods of the trials reviewed. A further review of the use of aminopyridines in neuromuscular disorders (Sedehizadeh et al., 2012), also focussed on the four trials covered in the Cochrane review, reaching similar conclusions.

Amifampridine is contraindicated in patients who have epilepsy, uncontrolled asthma or congenital QT syndromes. Given very few studies on safety of amifampridine in LEMS, a large case series (n=669) report on the use of amifampridine at the French treatment centre was included in this review although majority of patients multiple sclerosis and only three had LEMS (Flet et al., 2010). At a mean treatment dose of 30 mg daily (which is lower than what is usually prescribed for LEMS), 16% of all patients discontinued treatment due to an adverse drug reaction out of which 8% could be directly linked to amifampridine. Most side effects were mild to moderate with paraesthesias as the most common complaint. 6 patients had serious adverse events including seizures, cardiovascular and hepatic disorders. These findings indicate that amifampridine is generally well tolerated but should be prescribed after thorough investigation for seizure history and with provisions of continued monitoring of liver and cardiac function during treatment especially for patients on high dosage. Sedehizadeh et al., 2012 recommend that the daily dose of the drug should not exceed 80 mg/day on the basis of the finding that 3 patients on dosage > 100mg/ day developed seizures.

In conclusion, the current evidence is consistent in demonstrating some improvement in muscle strength from treatment with amifampridine but ambiguous on the actual clinical impact of this improvement. Amifampridine is generally well tolerated at lower doses with adverse effects generally correlated with daily prescribed dose.

2) Is amifampridine phosphate cost effective in adult patients with confirmed Lambert-Eaton Myasthenic Syndrome?

No studies reporting on the cost-effectiveness of amifampridine phosphate were identified in the literature search.

The Cochrane Review (Keogh et al., 2011) provided a brief commentary on the cost-benefit of 3, 4-DAP (base) versus 3, 4-DAP (phosphate). Using an average dose of 40mg daily, an average price for 3,4-DAP base of £1/tablet and an average price for 3,4-DAP phosphate of £2,017/100 tablets, the authors estimated a yearly cost per person of £730 for the base versus £29,448 for the phosphate formulation. This was not a cost-effectiveness analysis, but rather a commentary on the increased pricing associated with the phosphate formulation.

Future research on use of amifampridine phosphate in LEMS should focus on trials with larger numbers of patients and measure actual clinical benefit to patients and compare it with other treatments including cholinesterase inhibitors, cancer chemotherapeutic agents, immunomodulation and immunosuppression.

3. Research questions

Is amifampridine phosphate clinically effective in adult patients with confirmed Lambert-Eaton myasthenic syndrome?

Is amifampridine phosphate cost effective in adult patients with confirmed Lambert-Eaton myasthenic syndrome?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Level	Study design and intervention			Outcomes					Reference	Other		
Level of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
0	Other	54	3-4 DAP oral (or intravenous equivalent) <n 100 mg per day	Clinical effectiveness of the intervention	Ref Keoghet al 2011	-	Safety	The only significant adverse events noted were seizures in 3 patients treated with 3,4-DAP outside the confines of these 4 trials, usually at a daily dose of 100 mg, and therefore it has been recommended that the daily oral dose of 3,4-DAP should not exceed 80 mg. No cardiacabnormalities were encountered in the trials at these doses of 3,4-DAP.	Sedehizadeh, Saam; Keogh, Michael; Maddison, Paul. The use of aminopyridines in neurological disorders. Clin Neuropharmacol 2012;35(4):191-200.	-	-	Population: LEMS patients, ages not provided. Comments: This review repeats the findings from Cochrane review by Keough et al 2011.

1+	Systematic Review + Meta-analysis	Four controlled trials of 3,4-diaminopyridine compared with placebo in a total of 54 participants with Lambert-Eaton myasthenic syndrome were eligible	3,4-DAP	Clinical effectiveness of the intervention	Improvement in the score on a muscle strength scale, (the QMG score) or when not available, limb muscle strength measured by myometry.	A meta-analysis of the primary endpoint showed Quantitative Myasthenia Gravis (QMG) muscle score assessed between three and eight days was likely to improve by a mean of 2.44 points (95% confidence interval 3.6 to 1.22). (All trials reported a significant improvement in either muscle strength score, or myometric limb measurement following treatment. However, a meta-analysis of the results was not possible because of marked differences between these trials regarding primary outcome measures. The authors were, however, able to compare the overall treatment effect by looking at the change in QMG score from baseline with either 3,4-DAP treatment, or placebo treatment from two trials (Oh et la 2009; Sanderset al 2000). A generalised inverse variance analysis of these two trials showed that QMG scores decreased i.e. improved.) The reveiwers however note that the QMG score as a surrogate for clinical effect in trials (as extablished by Barohn et al 1998)is currently pegged at a treatment producing more than 2.6 units of change in QMG score to be of clinical significance. It therefore remains inconclusive as to whether the improvement produced by 3,4-DAP treatment of LEMS is clinically significant .	Improvement in the amplitude of the resting CMAP(Compound Muscle ActionPotential) (mean of all muscles tested)	Meta-analysis of the secondary endpoint CMAP amplitude also showed a mean improvement of 1.36 mV (95% confidence interval 0.99 to 1.72) over the same period.	Keogh M, Sedehizadeh S, Maddison P.. Treatment for Lambert-Eaton myasthenic syndrome.. Cochrane Database Syst Rev. 2011;(2):CD003279..	The authors noted that there are insufficient data at present to quantify this effect. The authors also note the increased costs associated with the 3,4-DAP phosphate product versus the 3,4-DAP base product in the following statements, "Currently, the cost of one hundred 10 mg tablets in the UK is £2,017, and therefore using a 40 mg per day average dose would result in a yearly expenditure of £29,448 per patient (UKMi Pharmacists 2010). The increased cost of amifampridine may provide significant cost pressures for organisations." In total 42 patients received 3,4-DAP. Serious side effects were extremely rare. One patient had a generalised seizure using high dose 3,4-DAP (McEvoy et al). Minor side effects of limb or perioral paraesthesia occurred in 19 participants, with insomnia and headache occurring in 5.	Four trials of 3,4-diaminopyridine reported significant improvement in the primary outcome, muscle strength score, or myometric limb measurement for between hours and a week following treatment, and significant improvement in resting compound muscle action potential (CMAP) amplitude following 3,4-diaminopyridine, compared with placebo. The risk of bias was determined to be low, and quality of evidence moderate to high by the authors. There were "four randomised placebo-controlled trials of 3,4-DAP in people with LEMS (McEvoy 1989;Oh 2009; Sanders 2000; Wirtz 2009). A cross-over trial of 12 participants conducted by McEvoy et al (McEvoy 1989) showed a significant improvement in isometric muscle strength and a parallel increase in resting CMAP amplitudes following 3,4-DAP treatment in all participants compared with placebo. Sanders et al (Sanders 2000) found a significant improvement in mean Quantitative Myasthenia Gravis (QMG) score and median CMAP amplitude in people with LEMS treated with 3,4-DAP compared with placebo. In a subsequent open-label phase of the trial, only one of 25 participants had no symptomatic improvement on 3,4-DAP. Wirtz et al (Wirtz 2009) in a cross-over trial of nine participants showed that isometric muscle testing and mean CMAP amplitude improved with 3,4-DAP treatment, and that pyridostigmine in isolation was no better than placebo, and failed to confer any additional benefit when used in conjunction with 3,4-DAP. A further cross-over trial of seven participants showed that CMAP amplitude, QMG score, subjective symptom score, muscle strength score and LEMS classification all improved with 3,4-DAP when compared to baseline and placebo (Oh 2009)."	Population: adults and children with a diagnosis of LEMS, with or without small-cell lung cancer. Comments: This is a well-conducted systematic review and meta-analysis of the RCTs supporting the efficacy of 3,4-DAP treatment in LEMS, with "limited but moderate to high quality evidence." The review does not include any studies on 3,4-DAP phosphate, however. 4 RCTs were found that demonstrate the efficacy of 3,4-DAP in LEMS in regard to improvement in muscle strength score and resting CMAP amplitude. The authors note that "there are insufficient data at present to quantify this treatment effect." The authors noted that they were unable to assess allocation concealment in 3 of the 4 trials. Other limitations are the small trial sizes inherent in studying a rare disease, the small number of trials conducted, and the relatively short time period of the trials reviewed. The authors do comment on the higher price of the newer 3,4-DAP phosphate product versus the 3,4-DAP base compounded product, and state "the increased cost of amifampridine [phosphate] may provide significant cost pressures for organisations."

2-	Cohort	669 (Multiple scelrosis patients wit a small subset (n=3) of LEMS.)	3,4-diaminopyridine (20–30 mg daily or up to 80 mg daily for patients with LEMS).	Safety of the intervention	Adverse drug reactions (ADRs)	164 ADRs from 122 patients (18.2%). 67.1 % were assigned as 'unlikely', 25 as 'possible', and 7.9 as 'probable' to be linked to 3,4-DAP treatment. 6 were serious adverse events (2 epileptic seizures or aggravation , 1 left-sided paraesthesias , 2 serious cardiovascular disorders, 1 drug-induced hepatitis). The most commonly observed ADRs were paraesthesias (36%). Majority of were short-term and reversible and did not cause treatment discontinuation. This was followed by gastrointestinal, cardiovascular and psychiatric ADRs.	-	-	Flet L, Polard E, Guillard O et al. . 3,4-Diaminopyridine safety in clinical practice: an observational, retrospective cohort study. . Journal of Neurology 2010;257:937-46 2010;.	-	The authors note that the ADR rates were lower in this case series compared to published dose. This is likely because most patients were started on lower dose which was progressively caliberated. They conclude that These findings underline the need for continued monitoring during treatment with 3,4-DAP. Liver enzymes should be monitored and an ECG done before and during treatment with aminopyridines. In conclusion, 3,4-DAP is contraindicated in patients with a medical history of seizure, and a risk–benefit analysis should be carefully evaluated for each patient.	Population: Average age 46.3 +/- 10.7 years when 3,4 DAP was started.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	To include 3,4-Diaminopyridine
Updated search terms - Population	Lambert Eaton Syndrome LEMS Eaton-Lambert Syndrome Lambert-Eaton Syndrome Myasthenic Syndrome
Updated search terms - Intervention	Amifampridine INN-Amifampridine Firdapse Zenas 3,4-Diaminopyridine 3,4-Pyridinediamine Diamino-3,4-pyridine 3,4-DAP 3,4-Diaminopyridine(DAP) DAP
Updated search terms - Comparator	None
Updated search terms - Outcome	None

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	Title/Abstract Published date <5 yrs, <10 yrs RCTs, SRs, MAs English language
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	None