Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

amifampridine 10mg tablet, as phosphate (Firdapse®) SMC No.(660/10)

BioMarin UK Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

amifampridine phosphate (Firdapse®) is not recommended for use within NHS Scotland.

Indication under review: Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

There are no clinical data for amifampridine phosphate and efficacy has been extrapolated from studies of amifampridine base (3,4-diaminopyridine), to which amifampridine phosphate has been accepted to be bioequivalent by the European Medicines Agency. In randomised controlled studies in patients with LEMS, 3,4-diaminopyridine treatment was associated with greater improvement in muscle strength and neuromuscular transmission than placebo.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition, the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

Dosing Information

Amifampridine phosphate should be taken orally in divided doses, three or four times a day. The recommended starting dose is 15mg a day, which can be increased in 5mg increments every four to five days, to a maximum of 60mg per day. No single dose should exceed 20mg. Tablets should be taken with food.

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

Product availability date

April 2010. Designated orphan medicine for use in the European Union for the treatment of LEMS in 2002.

Summary of evidence on comparative efficacy

Lambert-Eaton myasthenic syndrome (LEMS) is a rare auto-immune neurological condition with an estimated prevalence of one per 100,000 in the European Union. Antibodies against voltage-gated calcium channels in the neuron result in a reduction in acetylcholine release at the neuromuscular junction. This results in ascending muscle weakness that starts predominantly in the legs. The condition is also associated with dysfunction of the autonomic nervous system. In rare cases, the syndrome has been life threatening when associated with weakness of the respiratory muscles. In approximately half of patients, LEMS is a paraneoplastic disease and it is predominantly associated with small cell lung cancer. Amifampridine phosphate is an inhibitor of voltage-dependent potassium channels that 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. It was designated an orphan medicine by the European Medicines Agency (EMA) in 2002, and was awarded a marketing authorisation under exceptional circumstances in 2009.[1]

Amifampridine phosphate is a phosphate salt of 3,4-diaminopyridine (3,4-DAP). No randomised controlled studies have been performed to determine its efficacy and safety. However, amifampridine phosphate (Firdapse®) was shown to be bioequivalent with the 3,4-DAP base formulation and the Committee for Human Medicinal Products of the EMA concluded that the efficacy and safety data from published studies with 3,4-DAP in the treatment of LEMS could be extrapolated to Firdapse®.

Two pivotal studies are relevant to this submission. The first was a randomised, double-blind, placebo-controlled study of cross-over design, conducted in 12 patients admitted to a single site in the United States of America. Patients with electro-physiologically confirmed LEMS with stable or progressive weakness scoring at least 20/100 in the strength dimension of the Neurologic Disability Score (in which the weakness of 25 muscle groups on each side of the

body are assessed, scored and summed, 0=no weakness, and 4=no movement) were recruited. Patients taking immunosuppressive agents were required to have been taking stable doses for the preceding 5 months. Acetyl-cholinesterase inhibitors were discontinued at least 4 days before entry into the study. Participants entered into a pre-randomisation, 8-day open-label dose-finding phase in which the dose of 3,4-DAP was titrated to either the maximum tolerated dose or 25mg four times daily. Thereafter, patients were randomly assigned to placebo or 3,4-DAP at the dose determined in the preceding open-label phase for 3 days, after which patients crossed-over to receive the alternative treatment for 3 days.[2]

No primary outcome was stated but outcome measures reported were neurologic disability scores, isometric-strength tests and electrophysiologic studies. There was a significant improvement in neurologic disability scores associated with 3,4-DAP treatment compared with placebo, a decrease from a baseline score of 40 to 22 and 35, respectively ($p<0.05$). Treatment with 3,4-DAP was associated with greater improvements in isometric strength in both upper and lower extremities compared with placebo ($p<0.005$), as well as improvements in compound muscle action potential amplitudes (3,4-DAP almost doubled the baseline resting amplitude). In terms of autonomic symptoms, subjectively all six patients with dry mouth noted improvement and two of three patients reported resolution of their erectile dysfunction when taking 3,4-DAP. All patients continued with 3,4-DAP post-study and four patients also received pyridostigmine after 3 months. Neurologic testing was repeated every 3 months. Resting compound-muscle action potential amplitudes were maintained over 15 months of follow-up reported.[2]

The second pivotal study was a single-centre, randomised, double-blind, placebo-controlled parallel group study with an open-label extension phase. Adults with confirmed LEMS (predominant weakness in proximal limb muscles and electrophysiological signs of the syndrome), with a quantitative myasthenia gravis (QMG) score ≥5 were eligible for inclusion. QMG is an assessment of the function of the muscle groups involved in myasthenia gravis and LEMS, with scores ranging from 0 (no disability) to 39 (most severe functional disability). Patients were randomly allocated to receive 3,4-DAP 20mg three times daily for 6 days (n=12) or placebo (n=14). Thereafter, following a 24-hour washout, all patients were given open-label 3,4-DAP at a dose of 10mg or 20mg three times daily, which was then titrated to response, and after that, a titrated dose of pyridostigmine was added.[3]

The primary outcome measure was the difference between the groups in the change in QMG score from baseline to day 6. Treatment with 3,4-DAP was associated with a median change in QMG score of -2.0 (interquartile range: -3.0 to 0.0) compared with a change in QMG score of 0.25 (interquartile range: -1.0 to 1.0) with placebo, a statistically, but not clinically, significant treatment difference of -2.25 ($p=0.01$). For secondary outcomes, there was a significantly greater improvement in median summed compound muscle action potential amplitude in patients treated with 3,4-DAP (1.3mV [an increase from baseline of 64%]) compared with placebo (-0.1mV [a decrease from baseline of 3.2%]), $p<0.001$, and patient-completed symptom questionnaires found significant differences between the groups in favour of 3,4-DAP treatment. During the open-label phase of the study, 25 patients took open-label 3,4-DAP, and only one failed to have symptomatic improvement. The majority of patients (n=22/25) experienced at least a two point improvement in QMG score. Concomitant pyridostigmine may have contributed to the results observed in the open-label phase.[3]

There is no evidence concerning the effect of treatment on quality of life.

Summary of evidence on comparative safety

No comparative safety data are available. The most commonly reported adverse reactions in the published literature are paraesthesiae and gastrointestinal disorders.

Amifampridine is associated with a dose-dependent increased risk of epileptic seizures. The carcinogenicity of amifampridine has not been determined, therefore, in patients with the non-paraneoplastic form of LEMS, the risks and benefits of using amifampridine should be assessed prior to commencing treatment. Electrocardiogram (ECG) monitoring is recommended annually.

Summary of clinical effectiveness issues

Amifampridine phosphate is a phosphate salt of 3,4-DAP. It was designated an orphan drug by the EMA in 2002 and is the first medicine to be licensed in the UK for the symptomatic treatment of LEMS. The marketing authorisation was awarded under 'exceptional circumstances' with clinical data for 3,4-DAP extrapolated to the phosphate salt. A bioequivalence study analysing the pharmacokinetics of 3,4-DAP and amifampridine phosphate demonstrated that the area under the curve was similar, but the maximum concentration was higher, and time to maximum concentration shorter for the phosphate salt, so the EMA accepted extrapolation of the clinical data but with a reduced maximum daily dose.

Clinical experts consulted by SMC have advised that unlicensed formulations of 3,4-DAP and off-label pyridostigmine are used as treatment options for patients with LEMS in NHS Scotland.

A Cochrane Systematic Review has been conducted of randomised or quasi-randomised studies of adults and children with LEMS. Four small studies, including the two pivotal studies, comprising 54 patients, were identified in which 3,4-DAP was compared with placebo. While there was a limited number of randomised controlled studies, the evidence was graded moderate to high quality and it demonstrated that 3,4-DAP improved muscle strength scores and compound muscle action potential amplitudes in patients with LEMS. Quantification of treatment effect was not possible due to insufficient data. Meta-analysis of two studies (pooled number of patients=40), one of which was the second pivotal study, resulted in a mean change in QMG score assessed between 3 and 8 days of -2.44 (95% confidence interval [CI]: -1.22 to -3.60) compared with placebo. The secondary endpoint of the systematic review was improvement in mean compound muscle action potential amplitude, and four studies with a total of 94 patients were included. The mean change in mean compound muscle action potential amplitude was significantly greater than placebo (1.36mV [95% CI: 0.99 to 1.72mV]).[4]

Outcome measures used in the studies to determine improvements in muscle strength included QMG, neurologic dysfunction score, and isometric strength tests and in neuromuscular transmission (e.g. compound muscle action potentials). The Cochrane systematic review considered QMG to be the preferred measure of muscle strength and recommended it as a primary outcome in future studies of treatment in LEMS, and that change in compound muscle action potential amplitude was an appropriate objective secondary outcome measure. Across all studies presented, effects were consistently in favour of 3,4-DAP compared with placebo; however, a meta-analysis of QMG outcome data from two studies found that the treatment effect (-2.44) was smaller than the minimal clinically significant difference (-2.6 points). The pivotal study in which QMG was the primary endpoint (3,4-DAP treatment effect = -2.25 points)

was powered to detect a difference of 2 points only and was therefore not designed to detect the minimal clinically significant difference.

The sample sizes in the studies are small but in the context of this orphan indication are considered reasonable. While the Cochrane systematic review judged the evidence to be of moderate to high quality, notable limitations of the evidence from the first pivotal study included: no defined objective so it was unclear what were the primary and secondary outcomes; blinding may have been compromised since patients were given open-label 3,4-DAP prior to randomisation; and ten of the twelve patients took a dose of 25mg four times daily, which is greater than the maximum licensed daily dose of amifampridine phosphate (60mg).

There are no active comparator data; however, the recent Cochrane review identified only one other randomised study of treatment in patients with LEMS using an alternative therapy, intravenous immunoglobulin, and this was placebo-controlled. European clinical guidelines recommend 3,4-DAP as a first-line symptomatic treatment of LEMS.

The marketing authorisation given to amifampridine phosphate assures the availability to the market of a product with established stability and quality.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing amifampridine phosphate with palliative care for patients with LEMS. A one year time horizon was used. While it is recognised that the unlicensed 3,4-DAP is currently used as a treatment in NHS Scotland, it was not SMC policy at the time the submission was made to permit the use of an unlicensed medicine as a comparator therefore the choice of comparator was appropriate.

Limited clinical evidence for amifampridine phosphate has been used in the economic model. Instead, the key benefit of treatment was in terms of quality of life; the model assumes that there is no increase in overall survival. The base case analysis presented by the company assumed that 100% of patients would respond to amifampridine and show improvements in quality of life accordingly.

Given limited information on quality of life in LEMS patients, quality of life estimates in the model were based on patients with multiple sclerosis. The submitting company asserted that the quality of life score for a patient with LEMS is equivalent to a patient with an expanded disability status score (EDSS) of 8 without treatment. However, with treatment the patient's quality of life is expected to improve to an EDSS score of 7. The gain in utility score with treatment was estimated at 0.346 as patients move from EDSS 8 to EDSS 7.

A complex patient access scheme (PAS) was proposed by the submitting company. The PAS was not accepted by the Patient Access Scheme Assessment Group (PASAG) therefore the cost-effectiveness estimates based on the PAS were not considered by SMC as part of the economic case.

The base case cost per quality adjusted life year (QALY) was estimated at £92,267 based on incremental QALYs of 0.36 and incremental costs of £33,124, without the PAS.

There were a number of key limitations with this base case analysis. For example, the analysis assumed 100% effectiveness of amifampridine and SMC clinical experts questioned the face validity of the health states used to proxy quality of life. In addition, the use of a one year time horizon was an issue as SMC clinical experts suggested that treatment is likely to be continued beyond a year in some patients.

Revised analysis using lower levels of effectiveness for amifampridine are shown in the table below. Non-responders were assumed to discontinue treatment at 3 months. The company asserted that a discontinuation rate of 12% might be expected. These analyses used a 1-year time horizon.

	Cost per QALY without PAS
90% effectiveness (10% discontinuation rate)	£98,393
80% effectiveness (20% discontinuation rate)	£101,717
50% effectiveness (50% discontinuation rate)	£119,667

Sensitivity analysis to show the impact of smaller utility gains associated with successful treatment was also provided around these estimates. This showed that the results were very sensitive to changes in utility gains. For example, at an 80% level of effectiveness but a utility gain of 0.2, the cost per QALY ratios increased to £175,971 without the PAS.

A further weakness with the analysis was failure to consider pyridostigmine as a relevant comparator: SMC clinical experts have indicated that this is a treatment option.

SMC considered the likely range of cost-effectiveness ratios for amifampridine in this setting and the remaining uncertainties in the economic case. The committee considered the benefits of amifampridine in the context of the SMC's orphan and other decision modifiers. SMC agreed that although the criterion for the emergence of a licensed alternative treatment where an unlicensed therapy is standard clinical practice in NHS Scotland was met the committee was unable to accept amifampridine due to the high cost per QALY with the additional upwards uncertainty.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The European Federation for Neurological Societies (EFNS) published updated "Guidelines for treatment of autoimmune neuromuscular transmission disorders" in 2010. Based on evidence from small randomised controlled studies indicating improved muscle strength scores and compound muscle action potential amplitudes in patients with LEMS, summarised in a recent

Cochrane Review, the guideline recommends the use of 3,4-DAP first-line. Therapeutic effects may be increased when used in combination with pyridostigmine. In cases in which symptomatic improvement is insufficient, immunosuppression should be employed using a combination of corticosteroid and azathioprine. Evidence describing the use of ciclosporin or mycophenolate is limited to case series reports. In 50% of patients LEMS is a paraneoplastic disease and treatment of the underlying tumour is essential to its management. In associated guidance, published in 2006, "Management of paraneoplastic neurological disorders: report of an EFNS task force", the EFNS recommended that intravenous immunoglobulin be considered in patients not responding adequately to 3,4-DAP and pyridostigmine.

Additional information: comparators

There are no other licensed medicines for the treatment of LEMS. Unlicensed formulations of amifampridine base (3,4-DAP) are used as well as off-label use of pyridostigmine, intravenous immunoglobulin, and immunosuppressant agents (e.g. corticosteroids, azathioprine, ciclosporin, mycophenolate).

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Amifampridine phosphate	**15mg to 60mg orally daily in three to four divided doses**	**9,910 to 39,640**
Human normal immunoglobulin *	1g/kg/day for two days[≠]	5,320 per two-day course.
Pyridostigmine*	300mg to 1,200mg orally in divided doses. [Δ]	413 to 1,652

Medicines used for symptomatic treatment of Lambert-Eaton myasthenic syndrome. Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 30 April 2012, except for human immunoglobulin, taken from MIMS February 2012.

* Use outwith product marketing authorisation.

[≠] Dose as per study cited in Cochrane systematic review although details of the formulation used are not known. Dose is based on 70kg body weight.

[Δ] Dose as per the treatment of myasthenia gravis in adults.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 13 in year 1 and 16 in year 5. Based on an estimated uptake of 75% in year 1 (9 patients) rising to 90% in year 5 (13 patients), the impact on the medicines budget was estimated at £270K in year 1 and £400K in year 5 without the PAS.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission.

1) European Medicines Agency. Assessment report for Zenas: Procedure No.: EMEA/H/C/001032. http://www.emea.europa.eu (accessed 09 April 2012)

2) McEvoy KM, Windebank AJ, Daube JR & Low PA. 3,4-diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. N Engl J Med 1989; 321: 1567-71.

3) Sanders DB, Massey JM, Sanders LL, & Edwards LJ. A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. Neurology 2000; 54: 603-7

4) Keogh M, Sedehizadeh S & Maddison P. Treatment for Lambert-Eaton myasthenic syndrome. Cochrane Database of Systematic Reviews 2011 Issue 2, Art. No.: CD003279.

This assessment is based on data submitted by the applicant company up to and including 15 June 2012.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.