



Clinical Commissioning Policy Proposition: Amifampridine phosphate for the treatment of Lambert-Easton Myasthenic Syndrome

Reference: NHS England D04X01/01

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**Clinical Commissioning Policy Proposition:
Amifampridine phosphate for the treatment of Lambert-Easton
Myasthenic Syndrome**

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Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

This policy proposition describes NHS England's commissioning approach for the use of amifampridine phosphate for patients with Lambert-Eaton myasthenic syndrome.

Lambert-Eaton myasthenic syndrome (LEMS) is a rare disorder caused by a problem with how the patient's nerves send signals to their muscles. LEMS occurs because the immune system mistakenly attacks the nerve endings. This weakens the nerve signals from the nerves to the muscles and prevents the muscles contracting (tightening) properly. It 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, usually the type associated with smoking. 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.

Amifampridine increases the release of a chemical which aids nerve signal transmission. Amifampridine phosphate (Firdapse®) is the only treatment licensed for the symptomatic treatment of patients with Lambert-Eaton myasthenic syndrome in the UK.

NHS England has reviewed the available evidence and concluded that there is not sufficient evidence to routinely commission amifampridine phosphate (Firdapse®) for patients with Lambert-Eaton myasthenic syndrome.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission amifampridine phosphate (Firdapse®) for patients with Lambert-Eaton myasthenic syndrome.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether amifampridine phosphate for Lambert-Eaton myasthenic syndrome will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. Proposed Intervention and Clinical Indication

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.

3. Definitions

Lambert-Eaton myasthenic syndrome (LEMS) is a chronic progressive debilitating condition of presynaptic neuromuscular transmission. It is caused by insufficient release of a chemical neurotransmitter called acetylcholine from the synaptic vesicles resulting in impaired nerve signal transmission.

Amifampridine (3,4-DAP) increases the release of acetylcholine from nerve cells. It inhibits the 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 phosphate (Firdapse®) is the phosphate salt of amifampridine.

4. Aim and Objectives

This policy proposition aims to define NHS England's commissioning position on amifampridine phosphate (Firdapse®) as part of the treatment pathway for adult patients with Lambert-Eaton myasthenic syndrome.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with Lambert-Eaton myasthenic syndrome.

5. Epidemiology and Needs Assessment

Lambert-Eaton myasthenic syndrome (LEMS) is a rare condition with prevalence estimated at 5 per 2 million. It is therefore estimated that there are 150 patients with LEMS in the UK [1].

LEMS is strongly associated with cancer, especially small-cell lung cancer (SCLC). It is estimated that about 3% of patients with SCLC have LEMS, and 40 to 60% of patients with LEMS have SCLC; 5% have other cancers. Where LEMS occurs in the absence of cancer it is often associated with an autoimmune disorder [1].

In 75- 95% of cases the patient's immune system attacks their nerve endings. The aetiology can be traced to auto-antibodies that are directed against voltage gated calcium channels [1].

6. Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of amifampridine phosphate (Firdapse®) for the treatment of Lambert-Eaton myasthenic syndrome.

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.

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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.

7. Documents That Have Informed This Policy Proposition

[1] Clinical Commissioning Policy Statement: Amifampridine (Firdapse) for Lambert Easton Myasthenic Syndrome (LEMS). Published date: April 2013. Reference : NHSCB/D04/PS/a

8. Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).