HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

2 June 2010

FIRDAPSE 10 mg, tablets
B/100 (CIP code: 3471556)

Applicant: BIOMARIN EUROPE LTD

amifampridine
ATC code: N07XX05

List I
Medicine for hospital prescription only. For prescription by specialists in oncology, neurology or internal medicine only. Medicine requiring special monitoring during treatment.

Orphan designation granted (18 December 2002)

Date of Marketing Authorisation (centralised) under "exceptional circumstances"[1]: 23 December 2009

Reason for request: Inclusion on the list of drugs reimbursed by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

[1] A Marketing Authorisation was granted for this medicine "under exceptional circumstances". This means that because the disease is rare, it has not been possible to obtain complete information about the medicine. Every year, the European Medicines Agency (EMA) will reassess any new information that may have become available, and the Summary of Product Characteristics (SPC) will be updated if necessary.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
amifampridine

1.2. Background
Amifampridine blocks voltage-dependent potassium channels, thereby prolonging pre-synaptic cell membrane depolarisation. Prolonging the action potential enhances the transport of calcium into the nerve ending. The resulting increase in intra-cellular calcium concentrations facilitates exocytosis of acetylcholine-containing vesicles, which in turn enhances neuromuscular transmission.

1.3. Indication
“Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.”

1.4. Dosage
“FIRDAPSE should be given in divided doses, three or four times a day. The recommended starting dose is 15 mg a day, which can be increased in 5 mg increments every 4 to 5 days, to a maximum of 60 mg per day. No single dose should exceed 20 mg.”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

N	:	Nervous system
N07	:	Other nervous system drugs
N07	:	Other nervous system drugs
N07XX	:	Other nervous system drugs
N07XX05	:	Amifampridine

2.2. Medicinal products in the same therapeutic category

Comparator drugs

None

2.3. Medicinal products with the same therapeutic aim

None

3. ANALYSIS OF AVAILABLE DATA

FIRDAPSE (amifampridine) has the same active ingredient as diaminopyridine phosphate (3,4 DAP-base) which has been manufactured by AGEPS as a preparation for hospital use since 1996. 3,4 DAP-base has been used since 1977 to treat Lambert-Eaton myasthenic syndrome (LEMS). Since 2006, it has been used under "*ATU nominative", the* French compassionate use in different indications including LEMS.
The dossier is based on two pivotal studies by McEvoy *et al.,* 1989, and Sanders *et al*., 2000, carried out using the preparation for hospital use. Three other studies are available only in the form of conference poster abstracts (Murray *et al.,* 1984, Wirtz *et al.,* 2002, Sanders *et al.,* 1993). They will not therefore be analysed in this document.
In published data there is a randomised placebo-controlled trial published in 2009 (study by Oh *et al.*).

3.1. Efficacy

Study by McEvoy *et al.,* 1989[2]
Placebo-controlled randomised crossover study in 12 patients with LEMS.

The aims of the study were not clearly defined.
The efficacy endpoints used were the Neurological Disability Score (NDS) (measuring muscle strength and reflexes on both right and left sides), isometric strength and electrophysiological findings.
Electrophysiological findings were measured by electromyography and nerve conduction studies of the upper and lower extremities, using repeated 2 Hz stimulation of the cubital, median, musculocutaneous, sciatic and tibial nerves both at rest and after exercise. Compound muscle action potentials (CMAP) were used for subsequent repeated stimulations on D3, D5, D12 and D15.
Isometric muscle strength was tested on D1, D3, D5, D9, D12 and D15. The tests included measurement of strength generated by bilateral bending of the elbows and wrists, extension of the knees and dorsiflexion of the hip. NDS scores were measured at the same intervals.
Autonomic nervous system functions were also measured. These consisted of a sweat production test (quantitative sudomotor axon reflex test), salivation test, tilt table test and Valsalva manoeuvre corrected for age. Electroencephalograms and electrocardiograms were obtained at inclusion and on D3, D5, D8 and D15.

Method:
The study was carried out in two phases:

- phase 1: for the first 8 days of treatment (open phase), patients received 3,4 DAP from day 2 to day 9. The oral dose was gradually increased up to the maximum tolerated dose for an individual, or a maximum of 25 mg four times a day.

- phase 2: patients then entered the double-blind crossover phase. They were randomised to receive 3,4 DAP and placebo in succession. At the end of the study, patients could continue treatment with 3,4 DAP during an open phase if they wished.

There is no detail about patient selection criteria.

Results:
Among the twelve patients were included, 8 were women and 4 men. They were aged between 34 and 75 years. Seven of these patients had cancer and five had autoimmune disorders. Ten of them had previously been treated with acetylcholinesterase inhibitors. Four

[2] McEvoy K, Windembank A, Daube J, Low P. 3,4 Diaminopyridine in the Treatment of Lambert-Eaton Myasthenic Syndrome. The New England Journal of Medicine. 1989; 321: 1567-71.

had been treated with prednisolone, four with guanidine, three with plasmapheresis and two with azathioprine.

All patients included completed both phases of the study.
Ten patients tolerated the maximum dose of 25 mg four times a day. One patient was maintained below 15 mg and another below 10 mg because of adverse effects.
NDS scores fell from a mean baseline of 40 to 22 under 3,4 DAP versus 40 to 35 under placebo ($p < 0.05$).
Muscle strength in the upper extremities increased from an average of 70% of normal at inclusion to 81% of normal ($p<0.005$ compared with placebo). Muscle strength in the lower extremities improved from 45 to 65% of normal ($p<0.001$ compared with placebo). There are no result for isometric strength in the placebo group.
Mean resting CMAP amplitude in the arm was 5.1±0.9 mV in the 3,4 DAP group and 2.8±0.6 mV in the placebo group. Mean resting CMAP amplitude in the leg was 3.2±0.7 mV in the 3,4 DAP group and 1.8±0.4 mV in the placebo group. Baseline values are not available for either group.
Increased foot sweating was observed in 10 of the 12 patients ($p<0.05$) but it was not different in the forearms.
There was no difference between the two groups for blood pressure or heart rate measured both during deep breathing and during a Valsalva manoeuvre.

Data for the open period are available for 3 months for all patients and for 9 months for 11 patients (1 patient had died from pre-existing cancer).
There was no significant reduction in treatment efficacy; mean resting CMAP amplitude at 9 months was 5.1±1.0 mV in the arm and 3.1±0.7 mV in the leg. Similar values were recorded at 15 months (5.5±1.2 mV in the arm and 3.2±0.8 mV in the leg).
After the initial 3-month period, four patients received pyridostigmine as well as 3,4 DAP. It is difficult to interpret these results because an additive effect of pyridostigmine global effect cannot be ruled out.

Study by Sanders D *et al.,* 2000[3].
Placebo-controlled randomised crossover study in 26 patients with LEMS.

Primary endpoint: quantitative myasthenia gravis (QMG) score, which is a composite endpoint to assess global change in muscle strength.
For each patient included in the study, mean QMG scores over two consecutive days before the start of the study were compared with the scores for D5 and D6 of treatment.

Secondary endpoint: changes in compound muscle action potential (CMAP) amplitude induced by nerve stimulation; the mean CMAP amplitude value obtained for two consecutive days before the start of the study was used as reference CMAP amplitude value, with the mean CMAP amplitude value obtained on D5 and D6 of treatment used as final value. The difference between these two values was calculated for each patient.
QMG score and nerve stimulation tests were performed at inclusion and repeated on D5 and D6 of treatment. An ECG, EEG and blood tests were repeated on D6.
Patients took one capsule of study treatment or placebo three times a day for six days.

Results:
All randomised patients (n=26) completed the study. There were 15 women and 11 men aged 41-68; 10 of these patients had cancer. Fourteen patients took placebo and twelve took 3,4 DAP.
The difference in QMG score compared with inclusion was in favour of 3,4 DAP, i.e. -2.0 versus 0.25, p=0.01.

[3] Sanders D, Massey J, Sanders L, Edwards L. A Randomised trial of 3,4-diaminopyridine in Lambert-Eaton Myasthenic Syndrome. Neurology 2000;54:603-607.

Table 1: Results for QMG score

QMG (points)	Placebo n=14	DAP n=12	p
Inclusion	12.3 (9.0 - 13.5)	8.5 (7.3 - 17.0)	0.62
End of treatment	13.0 (9.0 - 13.5)	6.5 (5.0 - 14.3)	0.14
difference	0.25 (-1.0 - 1.0)	-2.0 (-3.0 - 0.0)	0.01

Median CMAP amplitude increased by 1.30 mV in patients treated with 3,4 DAP compared with a median decrease of 0.1 mV in patients in the placebo group (p<0.001).

Table 2: Results for CMAP score

MAP (mV)	Placebo n=14	DAP n=12	p
Inclusion	1.3 (0.8 - 2.2)	1.5 (0.6 - 2.6)	0.79
End of treatment	1.3 (1.1 - 2.9)	3.4 (1.5 - 5.1)	0.05
difference	-0.1 (-0.1 - 0.1)	1.3 (0.5 - 2.5)	< 0.001

Open follow-up phase data:
During this phase, patients received pyridostigmine in addition to 3,4 DAP. It is difficult to interpret these results because an additive effect of pyridostigmine global effect cannot be ruled out.

Study by Oh *et al.*, 2009[4]
Placebo-controlled randomised crossover study in 8 patients with LEMS.
The aims of the study were not clearly defined.
The efficacy endpoints described below were studied.
Neurological status was assessed using a subjective symptom score and three objective scores.
The subjective symptoms score (SS score) used descriptive general terms (severe = 3; moderate = 2; mild = 1; none = 0) in the following three areas: general fatiguability, difficulty walking and mouth dryness.
The objective scores were LEMS classification, MRC (Medical Research Council) score and QMG score. For the LEMS classification, as pelvic girdle weakness is uniformly observed in LEMS, disease severity was based on the following MRC pelvic girdle muscle strength score: 0 (asymptomatic) = 5 ; I (mild) = 4 ; II (moderate) = 3 ; III (severe) = 0-2. For the MRC score, muscle strength was tested in 22 muscles (so the total MRC with normal muscle strength was 110).

Duration of treatment with 3,4 DAP or placebo was initially eight days, subsequently reduced to three days to reduce study duration.
Three tablets of 3,4 DAP (30 mg) were taken on D1. The dose was increased up to a maximum of 75 mg/day for three days for the 3-day duration and up to 80 mg/day for the 8-day duration.

Results:
Eight patients with LEMS (7 men and 1 woman) were recruited over a 12 year period, between 1996 and 2008.
All patients had proximal leg weakness and reduced or absent reflexes at the time of diagnosis.
Three patients had concomitant small cell lung cancer. Voltage-dependent calcium channel antibodies (VDCC Ab) were found in four of the six patients tested.

[4] Oh SJ *et al*. 3,4-Diaminopyridine is more effective than placebo in a randomized, double-blind, cross-over drug study in LEMS. Muscle Nerve 2009 ;40(5):795-800

Table 3: Comparison of changes under placebo and 3,4 DAP

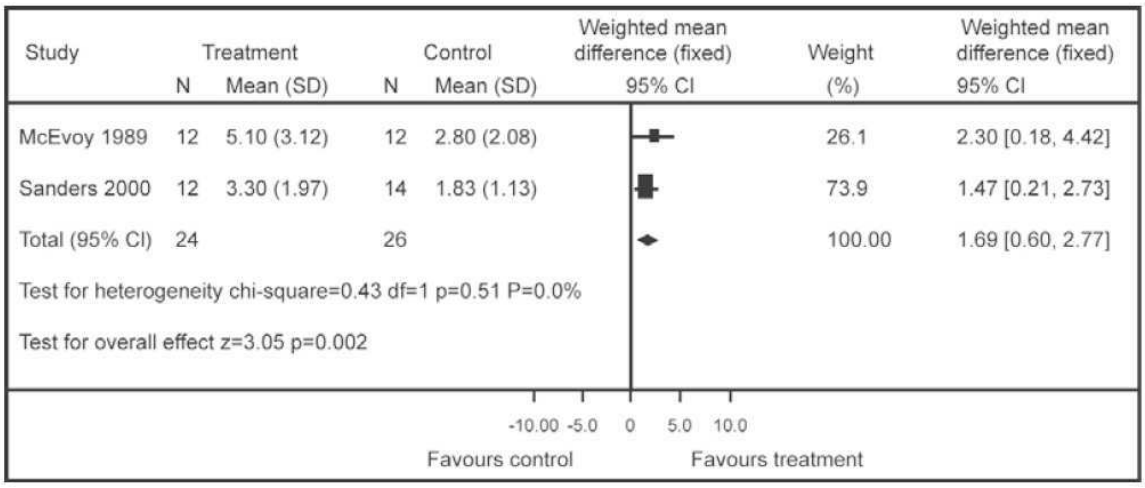
	Change Placebo(*N* = 7)	Change 3,4 DAP (N= 13)	p
SS score	0.50 ± 0.84	-0.69 ± 0.86	0.011
LEMS classification	0.33 ± 0.52	-0.85 ± 0.69	0.001
MRC score	-0.12 ± 0.50	1.23 ± 1.00	0.006
QMG score	0.40 ± 1.14 (n=6)	-2.36 ± 2.25 (n=11)	0.022
CMAP	-0.90 ± 1.78 (n=6)	1.79 ± 2.05 (n=11)	0.024

Subjective score improved in only three patients under 3,4 DAP.
MRC score improved in six patients, four of whom achieved a score of 110, i.e. normal. The difference in mean MRC score between 3,4 DAP and placebo was 2.8 points. Three patients had an improvement >3 points.
QMG score improved in four patients with 3,4 DAP. Three patients had an improvement of more than 3 points with 3,4 DAP, and none with placebo.

Other data:
Both pivotal studies (McEvoy and Sanders) were included in a Cochrane review of treatment for LEMS published in 2005[5]. As the primary endpoints were different in the two studies, a meta-analysis had to be performed on CMAP, a secondary endpoint in both studies.
Global weighted mean difference in CMAP values was 1.69 mV 95% CI [0.60 - 2.77] in favour of treatment with 3,4 DAP.

[5] Maddison P *et al*. Treatment for Lambert-Eaton myasthenic syndrome. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD003279.

Table 4: Global weighted mean difference in CMAP values, Cochrane Review



3.2. Adverse effects

As 3,4 DAP has been used for many years in the form of magistral and hospital preparations, and since 2006 under the nominative temporary use authorization in France in a number of indications, safety data for 3,4 DAP have been collected for a larger population compared with the population for the indication.
The most common adverse effect reported is paraesthesia. Some patients have reported transient vertigo, dizziness or fatigue after taking 3,4 DAP. Convulsions are the most common serious adverse effect.
In view of the very small number of data, it is not possible to establish frequencies for each of the adverse effects in this indication.

3.3. Conclusion

FIRDAPSE (amifampridine) has the same active ingredient as diaminopyridine phosphate (3,4 DAP-base) which has been manufactured by AGEPS as a preparation for hospital use since 1996.
Demonstration of the efficacy of 3,4 DAP in Lambert-Eaton myasthenia gravis (LEMS) is based on two comparative studies against placebo (studies by McEvoy *et al.,* 1989 and Sanders *et al.,* 2000) carried out with the hospital form and considered by the EMA to be the pivotal studies. However, these studies are old and their design was poor.
Evaluation of the efficacy of 3,4 DAP is based on tests to measure muscle weakness and motor deficit, notably the compound muscle action potential (CMAP), quantitative acute myasthenia gravis score (QMG), the Neurological Disability Score (NDS) (measuring muscle strength and reflexes on both right and left sides).
In the McEvoy study with a small population (n=12), 3,4-DAP base was superior to placebo for upper and lower limb muscle strength. In the Sanders study (n=26) the difference in change in quantitative acute myasthenia gravis score (QMG) compared with baseline (-2.0 vs 0.25, p=0.01) and change in median compound muscle action potential (CMAP) amplitude were in favour of 3,4 DAP (+1.30 mV vs - 0.1 mV, p<0.001).
The two pivotal studies were pooled in the Cochrane review based on compound muscle action potential (CMAP), their common secondary endpoint. Global weighted mean difference in CMAP was 1.69 mV 95% CI [0.60 - 2.77] in favour of treatment with 3,4 DAP.
The Committee regrets the absence of quality of life data in the studies available.

With regard to safety, paraesthesia was the most commonly reported adverse effect. Transient vertigo, dizziness or fatigue were observed in some patients after taking 3,4 DAP. Convulsions were the most common serious adverse effect.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Lambert-Eaton myasthenic syndrome is a rare neurological disorder. It includes a muscle weakness predominantly affecting the lower limbs and the trunk. It is characterised by progression to motor incapacity and may be life-threatening if the respiratory muscles are involved;
This medicinal product is used as symptomatic therapy;
The efficacy/adverse effects ratio is moderate;

Public health benefit:

Lambert-Eaton myasthenic syndrome (LEMS) in adults is a serious and incapacitating disorder that may be life-threatening, but is a minor burden on public health because it is rare (orphan disease).

As improvement in the management of orphan diseases is an established GTNDO priority (GTNDO = French national rare diseases plan), management of the disorder is a public health need.

In view of the limited clinical data available and the absence of quality of life data, it is not possible to quantify the anticipated impact of the medicinal product FIRDAPSE in terms of morbidity and quality of life.

It is not certain that the medicinal product FIRDAPSE will provide a response to the established public health need.

Consequently, and in view of the small size of the population concerned, no public health benefit is anticipated from placing the medicinal product FIRDAPSE on the market in this indication.

The drug is intended to be used as first-line therapy.
There are no validated alternative medicinal products in this indication.

The actual benefit provided by FIRDAPSE is moderate.

4.2. Improvement in actual benefit (IAB):

Despite the poor quality of study design but considering not only the absence of any validated alternative therapies but also the effects observed compared with current management, the Transparency Committee provides a minor (level IV) improvement in actual benefit to FIRDAPSE in the symptomatic treatment of Lambert-Eaton myasthenic syndrome.

4.3. Therapeutic use

Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) involves substances that prolong the duration of membrane depolarisation of the synaptic nerve ending.
In 2006, the European Federation of Neurological Societies (EFNS) recommended 3,4 DAP as first-line symptomatic therapy for LEMS.
Guanidine is no longer widely used because of its potential risks (nephrotoxicity, hepatotoxicity, myelotoxicity and cardiotoxicity). However, other substances (e.g. pyridostigmine) are used off-label. In the most severe cases, plasmapheresis or intravenous injection of immunoglobulins may obtain rapid results but they only offer temporary improvement in symptoms. The aetiological management of LEMS consists of treating any underlying cancer. LEMS that is not associated with cancer is often associated with other autoimmune disorders, and is treated with immunosuppressants.

4.4. Target population

The prevalence of Lambert-Eaton myasthenic syndrome in Europe is between 1/100 000[6] and 1/400 000[7] depending on publication, i.e. an estimated population In France of 160-640 patients.
Experts estimate that there are no more than 300 patients in France with LEMS.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in these two extensions of indication.

1.1.1. Packaging:
The packaging is appropriate for the prescription conditions.

1.1.2. Reimbursement level: 100%

[6] Orphanet, http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=43393, viewed 5 February 2010
[7] Verschuuren JJ *et al.* Available treatment options for the management of Lambert-Eaton myasthenic syndrome. Expert Opin Pharmacother. 2006 Jul;7(10):1323-36.