



Evidence Review:

Fampridine for multiple sclerosis (adults)

NHS England

**Evidence Review:
Fampridine for multiple sclerosis (adults)**

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1. Introduction

Multiple sclerosis (MS) affects nerves in the brain and spinal cord, causing a wide range of symptoms including problems with muscle movement, balance and vision. Each nerve fibre in the brain and spinal cord is surrounded by a layer of protein called myelin, which protects the nerve and helps electrical signals from the brain travel to the rest of the body. In MS, the myelin becomes damaged.

It is estimated that there are currently around 100,000 people with MS in the UK. MS is most commonly diagnosed in people aged 20-40, although it can happen at any age. MS is three times as common in women as men, and more common in white people than black or Asian people.

Fampridine is a voltage-dependent, neuronal fast potassium-channel blocker. In people with MS, the myelin sheath around the nerves deteriorates, exposing potassium channels and causing slowing or stopping of nerve impulses and subsequent periods of muscle weakness, spasticity and physical fatigue. Fampridine targets the axonal block associated with this demyelination.

Fampridine is licensed in the UK to treat patients with MS who have a walking disability (i.e. EDSS score between 4 and 7). It is available as prolonged-release tablets (10 mg) in Europe.

NICE has published guidance on the use of fampridine within the document 'Multiple sclerosis: management of multiple sclerosis in primary and secondary care (CG186)', recommending "Do not use fampridine to treat lack of mobility in people with MS because it is not a cost effective treatment."

This policy proposition reviews and will replace the NHS Clinical Commissioning Policy Statement (NHSCB/D04/PS/c) as a full commissioning policy.

2. Summary of results

This evidence review was undertaken to answer the question if fampridine is clinically and cost effective in patients with multiple sclerosis (secondary progressive MS or relapsing-remitting MS or primary progressive MS or progressive-relapsing MS) compared to placebo and existing treatments.

Clinical effectiveness

For the purposes of this review clinical effectiveness was defined as improvement in walking as measured by timed walking test (T25WT), Multiple Sclerosis Walking Scale (MSWS-12) which is a patient-reported functional outcome measure assessing patients' perceptions of the impact of MS on their walking ability, LEMMT (lower extremity manual muscle test), quality of life, activities of daily living, ability to work and side effects.

The most recent comprehensive systematic literature review for fampridine was done as part of NICE guidance on Multiple Sclerosis in adults published in October 2014. This evidence review was based on eight randomised control trials (RCTs). Much of the evidence was graded low or very low as blinding was unclearly reported by most studies, and four demonstrated incomplete outcome reporting. (NICE Clinical Guideline 186, Appendix G).

This review was undertaken to systematically identify any further key evidence for fampridine in Multiple Sclerosis since the NICE review. Five RCTs from the NICE reviews were included to help establish the background for the current review. Review of more current literature identified three recent publications (2013-2015) relevant to the research questions which may not have been available at the time of NICE review. These include one systematic review (Jansen et al 2014) and one pooled data analysis (Hobart et al, 2013) and one post-hoc secondary analysis for health utility gains (Limone et al, 2013) based on data from Goodman et al (2010). None of these studies were of better quality than those included in the NICE review. All of the randomised studies were placebo controlled and there was no direct comparison with existing treatments. Majority of evidence was from industry-sponsored or affiliated studies.

Goodman et al (2008) concluded that that a subgroup of patients, when treated with fampridine, experiences a clinically relevant improvement in walking ability, which is sustained for at least 14 weeks. It is not clear the extent

to which this conclusion is statistically valid, or clinically significant. Goodman et al (2009) in a study with 301 patients recruited across 39 centres concluded that fampridine improved walking ability in some people with multiple sclerosis. This improvement was associated with a reduction of patients' reported ambulatory disability, and is a clinically meaningful therapeutic benefit. However, the statistical effect size of the walking speed changes (i.e. how many people would need to be given fampridine to get this response in the total MS population) was not stated. Goodman et al (2010), a randomised study of 239 patients across 39 centres concluded that fampridine extended-release tablets produce clinically meaningful improvement in walking ability in a subset of people with MS, with the effect maintained between doses. It was difficult to draw any conclusions on the subgroups that may derive most benefit. Rossini et al conclude there is no difference between changes in fatigue scores, EDSS and cognitive functions between fampridine and placebo. Van Diemen et al (1992) concluded that patients with temperature-sensitive symptoms and patients characterized by having a longer duration of the disease and being in a progressive phase of the disease were likely to show clear clinical benefit.

Jansen et al (2014) published a systematic review of thirty five studies including 16 experimental studies (in vitro and animal) on the effect of 4-aminopyridine base as a symptomatic treatment of decreased walking capacity in patients with multiple sclerosis when administered as a short acting and an extended release compound (fampridine is currently registered with EMA as extended release form). The review concluded that experimental studies, though somewhat heterogeneous, provide strong evidence that fampridine improves impulse conduction through a demyelinated lesion. The two studies with non-clinical endpoints suggest fampridine improves impulse conduction in the visual and motor tracts. The review further concludes that clinical trials on fampridine show improvement in walking speed and muscle strength in the lower extremities measured by LEMMT which is in line with bio-physiological action identified in the experimental studies. Approximately 40% of patients respond to the drug and responders are easily identified within first two weeks of starting the treatment. The review also mentions that some studies suggest improvement in visual, oculomotor function, cognition, fatigue and spasticity. Fampridine was reported to be generally a safe drug and safer than its non-extended release form. In the absence of a meta-analysis, this literature review adds limited value to the NICE 2014 review as the body of evidence includes the same RCTs in addition to some small case series.

Hobart et al (2013) conducted a study specifically designed to consider the clinical utility of changes in the timed 25-Foot Walk (T25FW) measure. Data were pooled from two phase II/III studies (Goodman et al, 2009 & Goodman et al, 2010). These trials had reported that there was a greater change (improvement) from baseline in walking speed in the fampridine than the placebo group but no effect sizes were given. This analysis concluded that improvements in T25FW speed of $\geq 20\%$ are meaningful clinical impact for people with MS. This could help throw a new light on the evidence from the earlier RCTs where the actual effect size of the reported improvements was not clear. However, given the original studies which were the source of pooled data concerned the effects of fampridine on the population of adults with multiple sclerosis that responded to fampridine (responders) and not the population of adults with multiple sclerosis, further validation of this measure will be preferable before it is used as a predictor of clinically meaningful outcome in future MS clinical trials.

Limone et al (2013) undertook a post-hoc analysis on the data from Goodman et al (2009), to estimate the health utility benefits of the impact of fampridine on walking ability. In this study two mapping equations for MSWS-12 onto the Euroqol 5-Dimension (EQ-5D) health utility index were used, one derived in a North American registry and the other a United Kingdom registry as cross-validation/ sensitivity analysis. The study concluded that regardless of the mapping equation used, fampridine response was found to be associated with small-to-moderate health utility gains for patients with at least 20% improvement in walking speed on T25FW test (responders) compared to patients on placebo and those who responded less than $<20\%$ on T25FW (non-responders). This improvement in health utility was observed starting between week 2 (UK equation) or week 6 (North America equation) and maintained at weeks 10 and 12. The health utility gains were not evident after fampridine was discontinued at weeks 16 and 18. Those with $<20\%$ (non-clinically relevant) T25FW improvement did not show health utility gains compared to placebo at any visit. It should be noted that MSWS-12 was a secondary outcome measure in the original RCT. It is not clear if the study was sufficiently powered to detect a difference in outcome between fampridine and the placebo group. Furthermore, original randomisation and thus group comparability at baseline, was broken by the post-hoc selection of the responder sub-group from the fampridine group in this analysis. By virtue of being selected for their greater timed walk performance to fampridine, the possibility of correlations between greater T25FW and health utility may lead to a general overestimation of effect for fampridine.

In summary this review supports the conclusion from the NICE 2014 evidence review i.e. fampridine appears to be generally safe and although it improved some walking ability in MS patients, its effectiveness in terms of objectively measured walking speed, these were too small to be considered clinically important. Fampridine was generally safe and associated with mostly non-serious adverse events, such as nausea, dizziness and insomnia. The studies showed that the improvement in walking speed was limited to a subgroup of patients. Hence, the actual effect size and meaningful clinical impact in multiple sclerosis population and not just those with better response to fampridine, remains unknown.

Cost effectiveness

The original cost–utility analysis undertaken for the NICE guidance on Multiple Sclerosis(2014) found that fampridine was not cost effective compared to placebo for treating mobility problems in people with MS who have had been categorised as responders to fampridine treatment following a four week trial. QALYs were estimated by mapping MSWS-12 data from the clinical review to EQ-5D utility (health-related quality of life). Fampridine costed £160,884 per QALY gained compared to placebo. In addition it was noted that fampridine would likely to be even less cost effective taking into consideration the need to establish the subgroup that responds to treatment as that would mean including additional costs for the initial assessment and treatment for up to four weeks without additional patient benefits. Currently the manufacturer covers the drug costs of this trial but there will still likely be costs in terms of healthcare professional time. No further cost effectiveness studies including those on specific subgroups were identified in the current review.

3. Research questions

1) Is fampridine clinically effective in patients with multiple sclerosis (secondary progressive MS or relapsing-remitting MS or primary progressive MS or progressive-relapsing MS) compared to:

- placebo?
- existing treatments?

2) Is fampridine cost effective in patients with multiple sclerosis (secondary progressive MS or relapsing-remitting MS or primary progressive MS or progressive-relapsing MS) compared to:

- placebo?
- existing treatments?

3) Is there a subgroup in whom it is cost effective?

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.

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Appendix One

Grade	Study design and			Population		Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Population characteristics	Subgroup	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
1-	RCT	206	fampridine (10, 15, or 20 mg twice daily)	Aged 18-70; MS defined by McDonald's criteria. Needed to be able to do 2 trials of the T25FW in between 8-60 secs	na	Clinical effectiveness of the intervention	percent change in walking speed based on the timed 25-foot walk	no significant differences between any of the 4 groups, though all actively treated groups had larger numerical improvements than the placebo group	Lower extremity manual muscle test (LEMMT)	Significant differences between placebo and 10mg (p=0.018) and 15mg (p=0.003), but not with 20mg (p>0.05).	Goodman, A. D.; Brown, T. R.; Cohen, J. A.; Krupp, L. B.; Schapiro, R.; Schwid, S. R.; Cohen, R.; Marinucci, L. N.; Blight, A. R.; Fampridine MS-F202 Study Group. Dose comparison trial of sustained-release fampridine in multiple sclerosis. Neurology 2008;71(15):1134-1141.	na	na	The study concluded that that a subgroup of patients, when treated with fampridine, experienced a clinically relevant improvement in walking ability, which is sustained for at least 14 weeks. It is not clear the extent to which this conclusion is statistically valid, or clinically significant. Equally it is not clear whether this is a study with significant biases.

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1-	RCT	301 (229 in fampridine group and 72 in placebo group).	Fampridine tablets 10mg twice daily	18-70 years, with clinically defined MS. Able to complete 2 trials of the T25FW in an average time of 8-45secs	ns	Clinical effectiveness of the intervention	Response to treatment – considered achieved if at least 3 of the 4 walking speed tests during the 14 week Rx period were faster than any of the 4 speed tests measured before treatment or 1 at 2 weeks post treatment	78/224 (35%) in the fampridine group were considered responders, versus 6/72 (8%) in the placebo group	Changes in walking speed	Greater improvement in fampridine group (p=0.0004), but no effect sizes stated	Goodman, Andrew D.; Brown, Theodore R.; Krupp, Lauren B.; Schapiro, Randall T.; Schwid, Steven R.; Cohen, Ron; Marinucci, Lawrence N.; Blight, Andrew R.; Fampridine MS-F203 Investigators. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet 2009;373(9665):732-738.	na	na	This study concludes that Fampridine improved walking ability in some people with multiple sclerosis. This improvement was associated with a reduction of patients' reported ambulatory disability, and is a clinically meaningful therapeutic benefit. It is worth noting that the effect size of walking speed is not stated, and the objective difference in the primary outcome seems of uncertain clinical significance. There may be unresolved questions with regard to the bias inherent in the funders role in data collection and analysis. Finally this was a small study with 301 patients recruited across 39 centres. Given the declared conflicts this study may be considered to have a high potential for bias.
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1-	RCT	239 randomised (120 in fampridine group and 119 in placebo group)	Fampridine tablets 10mg twice daily (every 12 hours) [termed dalfampridine in this study but it is the same drug].	18-70 years, with clinically defined MS. Able to complete 2 trials of the T25FW in an average time of 8-45secs	na	Clinical effectiveness of the intervention	Response to treatment – considered achieved if at least 3 of the 4 walking speed tests during the 14 week Rx period were faster than any of the 4 speed tests measured before treatment or 1 at 2 weeks post treatment	51/119 (42.9%) in the Fampridine group were judged to have met the primary outcome versus 11/118 (9.3%) in the placebo group.	Walking speed – T25FW	The average improvement from baseline in walking speed was assessed as 13.99% (17.8) in the fampridine group vs 7.67% (17.8) in the placebo group. P value 0.007 (Only % change and p values provided by the paper). However SD values (assuming same value for each group) were calculated from the effect size and the p value.	Goodman, Andrew D.; Brown, Theodore R.; Edwards, Keith R.; Krupp, Lauren B.; Schapiro, Randall T.; Cohen, Ron; Marinucci, Lawrence N.; Blight, Andrew R.; MSF204 Investigators. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. Ann. Neurol. 2010;68(4):494-502.	na	na	This study concludes that fampridine extended-release tablets produce clinically meaningful improvement in walking ability in a subset of people with MS, with the effect maintained between doses. This was a study that recruited 239 patients across 39 centres. It was commercially sponsored and placebo controlled. Given the declared conflicts this may be considered a study with high potential for bias.
1-	RCT	54 randomised. 5 dropped out during the first 6 months, all in the placebo to 4 AP arm (thus they were having placebo at the time).	8mg 4-Aminopyridine (4- AP) administered 4x per day for 6 months with oral capsules. No wash out period before placebo stage.	Patients with both primary and secondary clinically definite MS and stable neurological deficits for at least 2 months.	na	Clinical effectiveness of the intervention	Expanded Disability Status Scale (EDSS) – a 10 point scale measuring function, and, in particular, mobility	Change in EDSS (higher worse) in the fampridine group was -0.05 (0.5), and - 0.05(0.37) in the placebo group. note that paired data (i.e. the difference in the change) was not presented	none	na	Rossini, P. M.; Pasqualetti, P.; Pozzilli, C.; Grasso, M. G.; Millefiorini, E.; Graceffa, A.; Carlesimo, G. A.; Zibellini, G.; Caltagirone, C.. Fatigue in progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled, crossover trial of oral 4-aminopyridine. Mult. Scler. 2001;7(6):354-358.	na	na	The study concludes there is no difference between changes in fatigue scores, EDSS and cognitive functions between 4-AP and placebo.

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1-	RCT	70. 1 patient withdrew before taking medication.	4-AP for 12 weeks. Starting dose at 10-15 mg/day in 2-3 divided doses, which was elevated with 5-15mg/day at weeks 2 and 6 respectively, and weeks 14 and 18 up to a maximum dose of 0.5mg/kg of body weight	Patients age 23-68 years (mean: 41.6); duration of disease 2 months-25 years (mean: 86 months); EDSS mean: 5; chronic progressive form in 74.3%, the rest relapsing remitting; 67% temperature sensitive	na	Clinical effectiveness of the intervention	EDSS – dichotomous and continuous.	EDSS significant improvement (drop outs not included in denominator as that would require imputation) was seen in 10/61 of patients taking active drug and 0/61 when the patients were placebo treated	Subjective response of patients.	18/61 when treated with intervention said they considered they'd had a subjective response compared with 1/61 when placebo treated	van Diemen, H. A.; Polman, C. H.; van Dongen, T. M.; van Loenen, A. C.; Nauta, J. J.; Taphoorn, M. J.; van Walbeek, H. K.; Koetsier, J. C.. The effect of 4-aminopyridine on clinical signs in multiple sclerosis: a randomized, placebo-controlled, double-blind, cross-over study. Ann. Neurol. 1992;32(2):123-130.	na	na	The study concludes that especially patients with temperature-sensitive symptoms and patients characterized by having a longer duration of the disease and being in a progressive phase of the disease were likely to show clear clinical benefit.
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3	Systematic	ns	misc	na	na	Clinical effectiveness of the intervention	walking speed	the review concludes that phase III trials demonstrate approximately 25% increase in walking speed in roughly 40% of treated patients	muscle strength in lower extremities	the review concludes that phase III trials demonstrate improved muscle strength in the lower extremities	Jensen, Henrik Boye; Ravnborg, Mads; Dalgas, Ulrik; Stenager, Egon. 4-Aminopyridine for symptomatic treatment of multiple sclerosis: a systematic review. Ther Adv Neurol Disord 2014;7(2):97-113.	na	na	This was a systematic review, with no meta analysis of the data. As such there is heterogeneity of patients, treatment protocols and outcome measures recorded. The study concludes that in vitro studies provide strong, though somewhat heterogeneous evidence of the mechanisms of action of 4-AP, which provides explanation of the effects and to some extent the side effects of the drug; and that clinical studies provide strong evidence for the effects and side effects of the drug in patients with MS The study ends with a statement that there is a considerable consistency between the results in experimental and clinical studies. Experimental studies provide evidence for the mechanisms of 4-AP that can be translated into clinical studies providing evidence of the effect of 4-AP
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3	Other	na	fampridine (10, 15, or 20 mg twice daily)	Aged 18-70; MS defined by McDonald's criteria. Needed to be able to do 2 trials of the T25FW in between 8-60 secs	na	other	health utility scores - MSWS-12 then mapped to EQ-5D	Using the USA-derived equation, dalfampridine-ER 20%-responders demonstrated improvement in health utility vs. placebo; starting at week 6 (mean difference in ES = 0.44, p = 0.002) and maintained at weeks 10 (ES = 0.41, p = 0.01) and 14 (ES = 0.71, p < 0.001). These improvements were no longer evident after dalfampridine-ER was discontinued (p > 0.05 at weeks 16 and 18)	na	na	Limone, Brendan L.; Sidovar, Matthew F.; Coleman, Craig I.. Estimation of the effect of dalfampridine-ER on health utility by mapping the MSWS-12 to the EQ-5D in multiple sclerosis patients. Health Qual Life Outcomes 2013;11(0):105.	na	na	The study concludes that regardless of the mapping equation used, results suggest dalfampridine-ER response is associated with a noteworthy - "small-to-moderate, but clinically-relevant improvement" - in health utility starting six weeks after initiation of double-blind treatment improvement in health utility in MS patients. The authors state the post hoc nature of the study tends to increase the possibility of type two error as the analysis was not prospectively defined. Furthermore the authors note that an inadequate sample size may also increase the uncertainty in the results. The data was taken from a post hoc secondary analysis of Goodman (2009). The clinical significance of the utility gain is uncertain and not stated. The potentially biased nature of Goodman 2009 should be considered in the interpretation of this result.
1-	Other	533	fampridine 10mg TD	MS duration c14 years, detailed sample characteristics set out in table 1	na	Clinical effectiveness of the intervention	Timed 25-Foot Walk (T25FW)	T25FW speed variability was small (within- and between-visit averages = 7.2%-8.7% and 14.4%-16.3%)	na	na	Hobart, Jeremy; Blight, Andrew R.; Goodman, Andrew; Lynn, Frances; Putzki, Norman. Timed 25-foot walk: direct evidence that improving 20% or greater is clinically meaningful in MS. Neurology 2013;80(16):1509-1517.	na	na	This study was specifically designed to consider the clinical utility of changes in the timed 25-Foot Walk (T25FW) measure. Data were pooled from two phase II studies (Goodman 2009 & Goodman 2010). The study reports that it provides direct evidence that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. The potentially biased nature of the studies that provided the data for this analysis should be considered.

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Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	n/a
Updated search terms - Population	multiple sclerosis OR ms
Updated search terms - Intervention	fampridine OR fampyra OR ampyra OR 4-aminopyridine
Updated search terms - Comparator	n/a
Updated search terms - Outcome	n/a
Inclusion criteria	General inclusion criteria
	<p>In order of decreasing priority, articles will be selected based on the following criteria.</p> <ol style="list-style-type: none"> 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) <p>>>>> If studies included reaches 30, inclusion stops here</p> <ol style="list-style-type: none"> 3.All relevant case control and cohort studies, that qualify after exclusion criteria <p>>>>> If studies included reaches 30, inclusion stops here</p> <ol style="list-style-type: none"> 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria <p>>>>> If studies included reaches 30, inclusion stops here</p>
	Specific inclusion criteria
	RCTs NICE assessment English

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Exclusion criteria	General exclusion criteria
	Studies with the following characteristics will be excluded:
	<ol style="list-style-type: none"> 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)
	Specific exclusion criteria
	n/a