NHS England

Clinical Commissioning Policy Proposition:

Fampridine for multiple sclerosis (adults)

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Clinical Commissioning Policy Proposition: Fampridine for multiple sclerosis (adults)

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Plain Language Summary

The policy proposition aims to confirm NHS England's commissioning approach to fampridine for patients with multiple sclerosis.

Multiple sclerosis (MS) affects the nerves in the brain and the spinal cord. These nerves have a protective layer, called myelin, which is damaged in MS. This causes a range of symptoms, such as problems with vision, balance and muscle movement. Approximately 100,000 people in the UK have MS, with most people diagnosed between ages 20-40.

Fampridine is a drug which aims to improve walking in adults with MS. It is licensed in the UK to treat adults with MS who have a walking disability.

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of fampridine for patients with MS.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission fampridine.

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 fampridine for multiple sclerosis 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. The proposed intervention and clinical indication

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.

3. Definitions

Multiple sclerosis (MS): a neurological condition which 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.

Fampridine (brand name Fampyra; also called 4-aminopyridine and dalfampridine): a drug licensed to improve walking ability for specific patients with multiple sclerosis.

Expanded Disability Status Scale (EDSS): a method of measuring disability in multiple sclerosis, where a higher number refers to more severe disability. A score between 4 and 7 indicates some impairment to walking.

4. Aim and objectives

This policy proposition aims to define NHS England's commissioning position on fampridine as part of the treatment pathway for adult patients with multiple sclerosis.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with multiple sclerosis.

5. Epidemiology and needs assessment

Prevalence rates vary around the UK. Based on a study by McKenzie et al, the MS Trust estimated in 2012 that there are 107,000 people with MS in the UK, and that this number is growing around 2.4% annually due to increased life expectancy. It is estimated that the prevalence of MS in England is around 165 per 100,000. (MS Trust)

In the UK, 57% of patients with MS have an Expanded Disability Status Scale (EDSS) score of 4-7 (Fampyra Tracking Study, Market Research study for Biogen) and it is estimated that 66% of these patients have walking impairment (London New Drugs Group, 2011).

6. Evidence base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of fampridine for adults with multiple sclerosis.

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 famipridine 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 ≥ 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 MSW-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.

7. Documents which have informed this policy proposition

NHS Commissioning Board Clinical Commissioning Policy Statement: Fampridine for Multiple Sclerosis (NHSCB/D04/PS/d)
London New Drugs Group APC/DTC Briefing Document - Fampridine (August 2011)
NICE Guideline CG186: 'Multiple sclerosis: management of multiple sclerosis in primary and secondary care' (October 2014)

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)