NHS England Evidence Review:

Prolonged release fampridine for the treatment of adults with multiple sclerosis (MS) and associated walking impairment (as defined by Expanded Disability Status Score 4 to 7.5)

NHS England URN: 2341

NHS England Evidence Review

Prolonged release fampridine for the treatment of adults with multiple sclerosis (MS) and associated walking impairment (as defined by Expanded Disability Status Score 4 to 7.5)

Completed: March 2024

Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of prolonged release (PR) fampridine compared to standard care alone or standard care and placebo in the treatment of multiple sclerosis (MS) and acquired walking impairment.

People with MS can have recurrent episodes/relapses, leading to disability, or may experience progression without relapses and accrue disability slowly over years. In recent years, there has been a significant increase in the effective treatments to reduce the number of relapses people experience, thus reducing associated disability, however none of these treatments are curative. Progression of MS results in increased level of disability and most patients will eventually experience some degree of functional impairment and impaired mobility.

The population covered by this review is people with MS-associated walking impairment as defined by an Expanded Disability Status Scale (EDSS) score of 4 to 7.5.

Current management strategies for MS-related walking impairment are physical.

PR fampridine is a selective potassium channel blocker which helps nerve impulses travel more effectively down damaged nerves thus leading to improved speed and stamina when walking. It is a twice daily oral treatment. The license for PR fampridine is for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4 to 7).

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from PR fampridine more than others, the treatment duration and doses, frequency and route of administration of PR fampridine that were used, what definition of treatment responder was used, and what standard care practices for walking impairment were used for patients receiving PR fampridine and those receiving standard care in the included studies.

Copyright © NHS England 2024

2. Executive summary of the review

This review examined the clinical effectiveness, safety and cost-effectiveness of prolonged release (PR) fampridine compared to standard care alone or standard care and placebo in adults with multiple sclerosis (MS) and walking impairment (as defined by Expanded Disability Status Score [EDSS] 4 to 7.5). The searches for evidence published since 01 January 2009 were conducted on 24 November 2023 and identified 115 references. The titles and abstracts were screened, and 78 full text papers were obtained and assessed for relevance.

Ten papers were identified for inclusion: one paper was a *post hoc* integrated analysis of two randomised controlled trials (RCTs: ENHANCE and MOBILE), four papers related to three individual RCTs (the ENHANCE and MOBILE RCTs and one additional RCT not included in the *post hoc* integrated analysis), three papers were prospective case series, and two were cost-effectiveness studies. The *post hoc* integrated analysis included 765 adults with walking impairment and relapsing-remitting or progressive MS and compared PR fampridine versus placebo. The ENHANCE and MOBILE RCTs included in the *post hoc* integrated analysis were also included in this review because they reported additional outcome findings that were not presented in the *post hoc* integrated analysis. Where outcomes were reported in higher level evidence (for example, the *post hoc* integrated analysis of two RCTs) these outcomes were not also reported from studies of lower level evidence (for example, the individual RCTs). One paper was a *post hoc* analysis of the MOBILE RCT. One additional RCT compared slow release (SR) fampridine versus placebo, but the study only included adults with MS and walking impairment who had responded to previous treatment with SR fampridine in an open label explorative trial. The individual RCT sample sizes ranged from 37 to 636 patients. Outcomes were assessed at four weeks in one RCT and up to 24 weeks after treatment initiation in the ENHANCE and MOBILE RCTs.

As no randomised evidence was identified for the important outcome activities of daily living (ADLs), three prospective case series were included in this review to provide evidence for this outcome. The three prospective case series provided non-comparative evidence in adults with MS and walking impairment who were treated with fampridine (sample sizes between 30 and 89 patients). Follow-up assessments in the three case series were at two weeks, and one, three and six months. As higher level evidence from comparative studies was identified for the other outcomes listed in the PICO document, only findings relating to ADLs from these case series are presented in this evidence review.

The included papers for clinical effectiveness were published between 2016 and 2022. One individual study each was conducted in Brazil, China, Southern Denmark or Sweden, and the ENHANCE and MOBILE RCTs (reported in three papers) were conducted in multiple countries (including Belgium, Canada, Italy, The Netherlands, Sweden and the UK in MOBILE and not specified in ENHANCE).

Two papers assessed the cost-effectiveness of PR fampridine for the treatment of walking impairment in adults with MS. The studies were published in 2021 and 2022. One study was conducted from a Swedish perspective and the other from a Chinese perspective.

Fampridine is described differently across varying countries; the papers included in this review report on fampridine, PR fampridine or SR fampridine. For the purposes of this review, the terms referred to in the individual papers are used when referring to an individual paper, and PR fampridine is used when referring to a group of studies or when summarising the results for an outcome.

Copyright © NHS England 2024

In terms of clinical effectiveness:

- **Walking ability (critical):**
  - *PR fampridine vs placebo*

    One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and three individual RCTs (including ENHANCE and MOBILE) provided very low to moderate certainty evidence relating to walking ability. The MOBILE RCT provided moderate certainty evidence that a statistically significant greater proportion of patients with MS and walking impairment showed improvements in walking ability after treatment with PR fampridine compared to placebo at two weeks follow-up, measured using the patient global impression of change (PGIC):[1] 46% versus 26%, respectively. One RCT (not included in the *post hoc* integrated analysis) provided very low certainty evidence that statistically significant improvements were shown in patients receiving PR fampridine compared to placebo, reflected in reductions in the timed 25 foot walk (T25FW):[2] -13.6% versus 4.7%, respectively and six spot step test (SSST:[3] -11.4% versus 3.8%, respectively) at four weeks follow-up. The improvement in T25FW from baseline to four weeks follow-up in patients treated with PR fampridine was below the MCID which is estimated to be 20%.The *post hoc* integrated analysis provided moderate certainty evidence that PR fampridine showed statistically significant improvements in walking ability (measured using multiple sclerosis walking scale-12 (MSWS-12) score[4]): improvement in least square mean [LSM] from baseline to 24 weeks of −3.70 points [95% CI: −5.61 to −1.79]. The *post hoc* integrated analysis also reported that a statistically significant greater proportion of patients with MS and walking impairment who were treated with PR fampridine achieved a minimally clinically important difference (MCID) in mean improvement in MSWS-12 score of ≥8 points compared to placebo over 24 weeks (44.3% versus 33.0%, respectively). The individual ENHANCE RCT provided moderate certainty evidence that a statistically significant greater proportion of patients with MS and walking impairment treated with PR fampridine versus placebo achieved a mean improvement of ≥10 points in MSWS-12 score at 24 weeks follow-up (38% versus 27%, respectively), while the MOBILE RCT reported no statistically significant differences between treatment groups at that threshold. Furthermore, the individual ENHANCE and MOBILE RCTs provided low certainty evidence that within two weeks of stopping PR fampridine treatment [2-week post-dosing follow-up visit after 24 weeks of treatment], the effects of PR fampridine on the MSWS-12 dissipated.
- **Physical impact of MS (critical):**
  - *PR fampridine vs placebo*

    One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and the individual MOBILE RCT provided low to moderate certainty evidence on the physical impact of MS. The *post hoc* integrated analysis provided moderate certainty evidence that PR fampridine showed statistically significant greater improvements from baseline compared to placebo in walking ability (measured using timed up and go (TUG)

[1] The PGIC is a global assessment of the patient's impression of how the study drug affected their overall walking during the preceding seven days. The PGIC was scored on a seven-point scale (from 1 = very much worse to 7 = very much improved).
[2] The T25FW is a test that objectively measures functional capacity of the lower extremities in patients using a timed 25 foot walk.
[3] The SSST assesses functional capacity of the lower extremities in terms of walking speed, but also co-ordination and balance by kicking blocks out of five circles on the floor.
[4] The MSWS-12 score includes 12 questions that ask about different aspects of walking: ability and speed of walk; ability to run; ability to climb and descend stairs; balance and smoothness of gait; and support, effort, and concentration required. Patients rate limitations of their mobility due to MS on a Likert 5-point scale (from 1 = not at all to 5 = extremely). Total score ranges from 1 to 60 and is transformed to a scale of 0–100. A higher MSWS-12 score represents poorer walking ability.

Copyright © NHS England 2024

speed[5]): LSM difference in percentage change from baseline: 4.40 [95% CI: 0.97 to 7.83], the proportion of patients achieving MCID of ≥15% improvement in TUG speed (44.1% versus 34.5%, respectively), and in the physical impact of MS (measured using the multiple sclerosis impact scale-29 physical subscale (MSIS-29 PHYS) score[6]): LSM difference in percentage change from baseline: −3.18 [95% CI: −4.84 to −1.52] over 24 weeks of treatment. The individual MOBILE RCT provided low certainty evidence that within two weeks of stopping PR fampridine treatment [2-week post-dosing follow-up visit after 24 weeks of treatment], the effects of PR fampridine on the TUG speed dissipated.

- **Health-related quality of life (HRQoL) (critical):**
  - *PR fampridine vs placebo*

    One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and one *post hoc* analysis of the MOBILE RCT provided low to moderate certainty evidence relating to HRQoL. The *post hoc* integrated analysis provided moderate certainty evidence of greater improvements from baseline to 24 weeks in patients with MS and walking impairment treated with PR fampridine versus placebo on the 3-level version of the EuroQol 5-dimensions (EQ-5D-3L)[7] utility index (LSM difference: 0.020 [95% CI: −0.001 to 0.041]) and EQ-5D visual analogue scale (VAS) score[8] (LSM difference: 0.9 [95% CI: −1.0 to 2.8]), but the findings were not statistically significant. The *post hoc* analysis of the MOBILE RCT provided low certainty evidence that a greater proportion of patients with MS and walking impairment treated with PR fampridine versus placebo showed mean improvements in six of nine subscale scores that reflected the psychological impact of MS (measured using multiple sclerosis impact scale psychological (MSIS-29 PSYCH) subscale scores[9] at 4, 12 and 24 weeks follow-up. No statistical measures were reported, but there was a statistically significant difference favouring PR fampridine for one item *"worries related to your MS"* at 12 and 24 weeks follow-up. A greater proportion of patients treated with placebo versus PR fampridine showed mean improvements in the remaining three MSIS-29 PSYCH items over 12 and 24 weeks, but the difference was not statistically significant.

- **Limb mobility/dexterity (important):**
  - *PR fampridine vs placebo*

    One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and three individual RCTs provided very low to moderate certainty evidence relating to limb mobility/dexterity in patients with MS and walking impairment. The *post hoc* integrated analysis provided moderate certainty evidence that there were statistically significant improvements from baseline in LSM percentage change in static and dynamic balance (measured using the Berg balance scale [BBS])[10] after treatment with PR fampridine versus placebo at 24 weeks (LSM difference: 0.62 [95% CI: 0.09 to 1.14]). The MOBILE

[5] TUG speed is an objective measure of dynamic balance and mobility. TUG measures the speed of individuals to move from a seated position to stand up, walk 3 m, turn, walk 3 m. In ENHANCE, TUG (feet/second) was performed at the same time (± 3 h) and with the same footwear and walking aids (if required) during each visit to avoid variation.
[6] The MSIS-29 PHYS score is a self-reported measure of the physical impact of MS. The MSIS-29 PHYS score is calculated by summing the 20 items and transforming the score to a scale of 0 (no impact of MS) to 100 (extreme impact of MS).
[7] The EQ-5D-3L comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results into a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.
[8] The EQ VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state.'
[9] The MSIS-29 PSYCH score is a self-reported measure of the psychological impact of MS. For each visit, MSIS-29 PSYCH score were calculated by totalling the nine individual items and transforming the score to a scale with a range of 0 (no impact of MS) to 100 (extreme impact of MS).
[10] The BBS score measures static and dynamic balance. Each task is scored from 0 (unable to perform) to 4 (able to perform independently). A higher BBS score represents better balance; recommended to predict multiple falls once a fall has occurred.

Copyright © NHS England 2024

RCT provided low certainty evidence that within two weeks of stopping PR fampridine treatment [2-week post-dosing follow-up visit after 24 weeks of treatment], the effects of PR fampridine on the BBS score dissipated. The ENHANCE RCT provided moderate certainty evidence that there was no statistically significant difference in LSM percentage change from baseline in hand dexterity (measured using ABILHAND scores)[11] at 24 weeks after treatment with PR fampridine versus placebo (LSM difference: 0.74 [95% CI: −0.38 to 1.86]). The second individual RCT (not included in the *post hoc* integrated analysis) provided very low certainty evidence that there was a statistically significant reduction in the time taken to complete the five times sit to stand (5-STS)[12] in patients with MS and walking impairment treated with SR fampridine (-7.6%) versus placebo (1.6%), but there was no statistically significant difference in nine-hole peg test (9-HPT) scores[13] between treatment groups (-1.0% versus 4.1%, respectively). The same individual RCT reported that, with the exception of rate of force development in the weakest leg for hip flexion, statistically significant improvements in composite scores for maximal concentric and isometric muscle strength were shown for all other measures in the weakest leg (but not in the strongest leg) at four weeks follow-up, favouring SR fampridine versus placebo.

- **Activities of daily living (ADL) (important):**
  - *PR fampridine vs placebo*

    No evidence was identified for this outcome.
  - *PR fampridine vs no comparator*

    Three prospective case series provided very low certainty evidence relating to ADLs, measured using the expanded disability status scale (EDSS).[14] One case series reported that EDSS *"remained stable"* compared to baseline in patients with MS and walking impairment after two weeks (EDSS 5.8) and three (EDSS 5.8) and six months (EDSS 5.7) treatment with PR fampridine. A second case series reported that there were no statistically significant differences in pre- and post-treatment EDSS scores in patients with MS and walking impairment. A third case series reported a statistically significant improvement in the mean EDSS score from baseline (6.1 [±SD 0.9]) to six months (5.6 [±SD 0.1]) in patients with MS and walking impairment who responded to PR fampridine. The same case series reported that improvements in EDSS resulted in 9.1% of all patients (treatment responders and non-responders) with MS and walking impairment reducing the number of supports needed for walking after six months of treatment with PR fampridine. Statistical measures were not reported.
- **Proportion of treatment responders (important):**
  - *PR fampridine vs placebo*

    One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs provided moderate certainty evidence that a statistically significant greater proportion of patients with MS and walking impairment responded to treatment (defined as mean MSWS-12 score improvement of ≥8 points from baseline) with PR fampridine compared to placebo at 24 weeks follow-up (44.3% versus 33.0%, respectively).

[11] ABILHAND measures manual ability to manage daily activities among chronic stroke patients. Patients estimate the ease or difficulty of performing each upper limb activity using a 3-level response scale: impossible (0), difficult (1), and easy (2). A higher ABILHAND score represents better manual ability.
[12] The 5-STS assesses functional capacity of the lower extremities in terms of time taken to stand up and sit down on a chair five times.
[13] The 9-HPT measures finger dexterity in terms of the time taken to place nine pegs into a square board with holes for the pegs.
[14] The EDSS score is a rating scale that assesses the degree of neurological disability taking into account eight functional systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and other) in MS patients. The scale ranges from 0 (normal) to 10 (death due to MS). EDSS values between 4.0 and 7.0 reflect a growing negative impact on the walking ability.

Copyright © NHS England 2024

In terms of safety:

- **Complications of PR fampridine therapy**
  - *PR fampridine vs placebo*
    The individual ENHANCE and MOBILE RCTs provided low certainty evidence that the proportion of patients with MS and walking impairment experiencing any type of adverse event was similar between patients treated with PR fampridine versus placebo at 24 weeks follow-up. For example, the proportions of patients experiencing any adverse event (AE) were 66% for PR fampridine versus 60% for placebo; for any treatment-related AE the proportions were 18% for PR fampridine versus 13% for placebo; and for any serious AE the proportion was 3% in both groups. Reasons for the similar proportions of patients experiencing AEs were not provided in the two RCTs. No statistical measures were reported.

In terms of cost-effectiveness:

- Two studies considered the cost-effectiveness of PR fampridine plus best supportive care (BSC) compared to BSC alone in adults with MS and walking impairment (EDSS 4 to 7).
  One study (Acosta et al 2021) considered the cost-effectiveness of PR fampridine plus BSC versus BSC alone for the treatment of adults with MS and walking impairment from a Swedish societal perspective. The base case analysis showed that PR fampridine plus BSC is cost-effective with an incremental quality-adjusted life years (QALY) gain of 0.12, incremental cost of 6,982 kronor (€685 and $816), and an incremental cost-effectiveness ratio (ICER) of 57,109 kronor per QALY gained (€5,607 and $6,675 per QALY gained) compared to BSC alone over a 20 year time horizon. Assuming a willingness-to-pay (WTP) threshold of 500,000 kronor per QALY gained (€49,088 and $58,445 per QALY gained), there was a 96.76% probability of cost-effectiveness at a price of 1,402.85 kronor per pack (i.e. 56 tablets).
  One study (Zhao et al 2022) considered the cost-effectiveness of PR fampridine plus BSC versus BSC alone in Chinese adults with MS and walking impairment. Over a 10 year time horizon, PR fampridine plus BSC resulted in an incremental QALY gain of 0.15 and lower total costs of -17,329 Chinese Yuan from the healthcare perspective, which dominated BSC alone with an ICER of -113,488 Chinese Yuan/QALY. From the societal perspective, PR fampridine plus BSC resulted in reduced total costs of -36,465 Chinse Yuan and dominated BSC alone with an ICER of -238,806 Chinese Yuan/QALY. Probabilistic sensitivity analysis found that at a WTP threshold of 80,976 Chinese Yuan/QALY, the probability of PR fampridine plus BSC being cost-effective was 100% in patients with MS and walking disability.

In terms of subgroups:

- **Walking ability by EDSS score ≤6.0 vs >6.0**
  - *PR fampridine vs placebo*
    One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs reported that there was no statistically significant difference between PR fampridine versus placebo in the proportion of patients with MS achieving mean MSWS-12 score improvement of ≥8 points over 24 weeks, by baseline EDSS score of ≤6.0 (47% versus 34%, respectively)

Copyright © NHS England 2024

versus baseline EDSS score of >6.0 (31% versus 26%). An improvement in the MSWS-12 score of ≥8 is considered to be the MCID.

- **Limb mobility/dexterity by EDSS score ≤6.0 vs 6.5 and 7.0**
  - *PR fampridine vs placebo*

    The individual ENHANCE RCT reported that there were *"small numerical improvements that were larger in the more disabled participants"* on the ABILHAND score in patients with MS and a baseline EDSS score of ≤6.0 versus 6.5 and 7.0 after treatment with PR fampridine versus placebo. The difference in LSM change from baseline for PR fampridine versus placebo was not statistically significant [although formal significance testing was not undertaken for subgroup analyses]: EDSS score ≤6.0: 0.10 (95% CI: −1.04 to 1.24) and EDSS score 6.5 and 7.0: 3.05 (95% CI: -0.09 to 6.19).

Please see the results table (section 5) in the review for further details of outcomes.

Limitations

Study populations included patients with different types of MS (primary progressive, progressive-relapsing, relapsing-remitting, and secondary progressive), and proportions for each type varied across and within the included studies. The included studies administered PR fampridine 10 mg twice daily, but treatment durations varied across the different studies. The included studies did not provide specific details on standard care practices for walking impairment in patients receiving PR fampridine and those receiving standard care alone. Treatment responders were defined differently across the included studies. One RCT only included adults with MS and walking impairment who had responded to previous treatment with SR fampridine in an open label explorative trial, which introduces very serious selection bias. Although the RCT population did not clearly match the PICO eligibility criteria in terms of population selected for inclusion, the RCT was included in this review but downgraded due to very serious indirectness. Responder analysis was conducted in patients with MS who met the criteria of a PR fampridine MSWS-12 responder compared to MSWS-12 non-responders and compared to patients receiving placebo, but this type of analysis should be interpreted with caution as it does not reveal the underlying factors involved in the reasons why some patients respond to treatment and others do not. Responders were identified after treatment had commenced; hence the definition of responders did not allow the responder group to be defined ahead of treatment.

As no comparative evidence was identified for the important outcome activities of daily living (ADLs), three prospective case series were included in this review to provide evidence for this outcome. The main limitation of the three prospective case series was the lack of a comparator group to enable a comparison in outcomes between patients who did and did not receive fampridine. Additional limitations for the three prospective case series included the small sample sizes, which limits the potential to generalise the findings to the wider population of interest, and the duration of follow-up, which was insufficient to draw conclusions on longer-term effectiveness and safety in patients with MS.

The certainty in the clinical effectiveness evidence was very low to moderate for one critical outcome (walking ability), and low to moderate for two critical outcomes (HRQoL and physical impact of MS). The certainty in the evidence was very low to moderate for one important outcome (limb mobility/dexterity), very low for one important outcome (ADLs), moderate for the important outcome, proportion of treatment responders, and low for safety. Factors reducing confidence in the outcomes reported include the very serious risk of bias in one RCT and two prospective case series (due to, for example, potential selection bias, unclear study methods and incomplete outcome reporting); very serious indirectness due to one RCT including only

Copyright © NHS England 2024

patients who had previously responded to treatment with SR fampridine; and the lack of a comparator in the three prospective case series. Further limitations include the small numbers of patients included in some of the studies, unclear study methods (or not following standard systematic review methods and procedures in the *post hoc* integrated analysis), potential selection bias, and the number of patients lost to follow-up or discontinuing treatment. All the studies included in this evidence review reported outcomes in terms of clinical relevance, but this was measured using different tests and thresholds and the duration of follow-up was insufficient to enable conclusions to be drawn on the longer-term effectiveness and safety in patients with MS and walking impairment.

Evidence for the cost-effectiveness of PR fampridine for the treatment of walking impairment in adults with MS was available from two studies (Acosta et al 2021, Zhao et al 2022). The cost-effectiveness studies varied in terms of the perspectives (whether from a Swedish or Chinese healthcare or societal perspective) and time horizons (whether for 10 years, 20 years, or over a lifetime). Both studies used an appropriate model to calculate costs and health outcomes and tested assumptions using one-way and probabilistic sensitivity analysis. The results are unlikely to be generalisable to current patients in England, as costs in the two studies are based on those in Sweden and China and the willingness-to-pay (WTP) thresholds used in the studies differ from those used by the National Institute of Health and Care Excellence (NICE) in England.

Conclusion

The very low to moderate certainty evidence from the four comparative clinical effectiveness studies included in this review suggest that, overall, PR fampridine in adults with MS and walking impairment improves self-perceived physical and psychological impacts of MS compared to placebo, although the differences between treatment groups were not always statistically significant. Both the ENHANCE and MOBILE RCTs indicated that PR fampridine was well tolerated, but when patients discontinued treatment with PR fampridine therapy after the trial duration, any improvements in outcome measures disappeared and patients approached pre-treatment levels within two weeks. Non-comparative evidence on the important outcome (ADLs) was provided by three prospective case series, which reported mixed findings. Although the increased sample size in the *post hoc* integrated analysis provided greater power in terms of evaluating treatment differences between PR fampridine and placebo, the limitations of some of the included studies reduce the confidence in the findings. Limitations include the very serious indirectness for one RCT due to the inclusion of only patients who had previously responded to treatment with SR fampridine, and the lack of a comparator in the three prospective case series. Further limitations include the small numbers of patients included in some of the studies and the serious or very serious risk of bias for all included studies associated with, for example, unclear study methods (or not following standard systematic review methods and procedures in the *post hoc* integrated analysis), potential selection bias, and the number of patients lost to follow-up or discontinuing treatment.

Evidence for the cost-effectiveness of PR fampridine for the treatment of walking impairment in adults with MS was available from two studies, conducted from a Swedish or Chinese healthcare or societal perspective. The results are unlikely to be generalisable to current patients in England, as costs in the two studies are based on those in Sweden and China and the willingness-to-pay (WTP) thresholds used in the studies differ from those used by the National Institute of Health and Care Excellence (NICE) in England.

Copyright © NHS England 2024

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people with MS associated walking impairment (EDSS 4 to 7.5), what is the clinical effectiveness of PR fampridine compared with standard care alone or standard care and placebo?
2. In people with MS associated walking impairment (EDSS 4 to 7.5), what is the safety of PR fampridine compared with standard care alone or standard care and placebo?
3. In people with MS associated walking impairment (EDSS 4 to 7.5), what is the cost-effectiveness of PR fampridine compared with standard care alone or standard care and placebo?
4. From the evidence selected, are there any subgroups of patients that may benefit from PR fampridine more than the wider population of interest?
5. From the evidence selected, what doses, frequency and route of administration of PR fampridine treatment were used and what was the duration of treatment?
6. From the evidence selected, what definition of treatment responder was used, how was responder status measured, and at what time point after initiating treatment was this assessed?
7. From the evidence selected what were the standard care practices for walking impairment for patients receiving PR fampridine and those receiving standard care alone?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 24th November 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

Copyright © NHS England 2024

4. Summary of included studies

Ten papers were identified for inclusion in this evidence review (Acosta et al 2021, Alvarez-Payero et al 2017, Fragoso et al 2016, Gasperini et al 2016, Hobart et al 2019, Hupperts et al 2016, Hupperts et al 2022, Jensen et al 2016, Marzal-Alfaro et al 2018, Zhao et al 2022). One paper was a *post hoc* integrated analysis (Hupperts et al 2022) which included two randomised controlled trials (RCTs) (Hobart et al 2019 [ENHANCE), Hupperts et al 2016 [MOBILE]). Three studies (four papers) were RCTs assessing the clinical effectiveness and safety of prolonged release (PR) fampridine in adults with multiple sclerosis (MS) and associated walking impairment (as defined by EDSS 4 to 7.5) (Gasperini et al 2016, Hobart et al 2019, Hupperts et al 2016, Jensen et al 2016). Two of these RCTs (ENHANCE and MOBILE) were included in the integrated analysis (Hupperts et al 2022) but were also included separately in this review because they presented additional relevant outcomes not reported in the integrated analysis. One paper (Gasperini et al 2016) was a *post hoc* analysis of the MOBILE RCT and provided additional outcome data not reported in the *post hoc* integrated analysis or individual MOBILE RCT. Three papers were case series which were included because they reported results for an outcome (activities of daily living [ADLs]) that was not reported by the RCTs (Alvarez-Payero et al 2017, Fragoso et al 2016, Marzal-Alfaro et al 2018), and two were cost-effectiveness studies (Acosta et al 2021, Zhao et al 2022).

Fampridine is described differently across varying countries; the papers included in this review report on fampridine, PR fampridine or SR fampridine. For the purposes of this review, the terms referred to in the individual papers are used when referring to an individual paper, and PR fampridine is used when referring to a group of studies or when summarising the results for an outcome.

Table 1 provides a summary of these included studies and full details are given in Appendix E Evidence table.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Acosta et al 2021 Cost-effectiveness study Sweden	Cost-effectiveness data based on four PR fampridine trials, with the modelled patient population consisting of adult MS patients with EDSS scores between 4 and 7[a]	**Intervention** PR fampridine 10 mg tablet twice daily plus BSC **Comparison** BSC alone BSC included all supportive care that could be used concomitantly to manage MS symptoms.	**Important Outcomes** • Cost-effectiveness: ICERs in terms of QALY gain from PR fampridine plus BSC versus BSC alone
Alvarez-Payero et al 2017 Case series Spain	• Total sample size: N=55 • Adults with MS and evidence of affected gait, and an EDSS score of 4 to 7 • Fampridine: N=55 • Control: None • No relevant subgroups reported	**Intervention** Fampridine 10 mg twice daily **Comparison** No comparator	Follow-up at six months **Important Outcomes** • Activities of daily living ○ Mean (±SD) EDSS score from baseline in treatment responders[b]
Fragoso et al 2016 Case series Brazil	• Total sample size: N=89 • Adults with MS and receiving fampridine for gait disorders • Fampridine: N=89 • Control: None	**Intervention** Fampridine 10 mg twice daily **Comparison** No comparator	Follow-up at one month **Important Outcomes** • Activities of daily living ○ Mean (±SD) improvement of disability

Copyright © NHS England 2024

Study	Population	Intervention and comparison	Outcomes reported
	• No relevant subgroups reported		assessed by EDSS score from baseline
Gasperini et al 2016 *Post hoc* analysis of Phase II double-blind RCT (MOBILE) Canada and Europe	• Total sample size: N=132 • See Hupperts et al (2016) • PR fampridine: n=68 • Placebo: n=64 • No relevant subgroups reported	**Intervention** PR fampridine 10 mg tablets twice daily **Comparison** Placebo twice daily See Hupperts et al (2016) for concomitant treatment	Follow-up at week 24 **Critical Outcomes** • HRQoL ○ % difference in mean reduction in MSIS-29 PSYCH[c] subscale score from baseline
Hobart et al 2019 Phase III double-blind RCT (ENHANCE) Multicentre (92 centres in 11 countries)	• Total sample size: N=636 • Adults with a diagnosis of MS (any subtype), an EDSS score of 4 to 7, and investigator-assessed walking impairment • PR fampridine: n=317 (mITT: n=315) • Placebo: n=319 (mITT: n=318) • See Hupperts et al (2022) for subgroup outcomes	**Intervention** PR fampridine 10 mg twice daily **Comparison** Matching placebo Concomitant medication (e.g. baclofen, methylprednisolone) and non-drug therapy (e.g. physiotherapy, rehabilitation) were permitted in both treatment arms	Follow-up at 24 weeks, unless otherwise stated **Critical outcome** • Walking ability ○ Proportion of patients with improvement of ≥10 points in MSWS-12 from baseline ○ MSWS-12 score at 26 weeks [i.e. two week post-dosing follow-up visit after 24 weeks of fampridine treatment] • Physical impact of MS ○ See Hupperts et al (2022) • HRQoL ○ See Hupperts et al (2022) **Important Outcomes** • Limb mobility/dexterity ○ LSM (95% CI) change from baseline in ABILHAND score[d] • Safety ○ Any AE ○ Any serious AE ○ Treatment-emergent AEs ○ Serious treatment-emergent AEs ○ AEs leading to treatment discontinuation
Hupperts et al 2016 Phase II double-blind RCT (MOBILE) Belgium, Canada, Italy, The Netherlands, Sweden and the UK (24 centres)	• Total sample size: N=132 • Adults with a diagnosis of MS (any subtype), an EDSS score of 4 to 7, and investigator-assessed walking impairment • PR fampridine: n=68 • Placebo: n=64 • See Hupperts et al (2022) for subgroup outcomes	**Intervention** PR fampridine 10 mg tablets every 12 hours **Comparison** Matching placebo every 12 hours Most stable concomitant therapies for treatment of MS were permitted.	Follow-up at 24 weeks, unless otherwise stated **Critical outcome** • Walking ability ○ Number of patients reporting improvements on PGIC[e] at two weeks follow-up (*post hoc* analysis) ○ Mean MSWS-12 score improvement of ≥1 to ≥7, ≥9 and ≥10 points from baseline

Copyright © NHS England 2024

Study	Population	Intervention and comparison	Outcomes reported
			○ MSWS-12 score at 26 weeks [i.e. two week post-dosing follow-up visit after 24 weeks of fampridine treatment] • Physical impact of MS ○ TUG speed[f] at 26 weeks [i.e. two week post-dosing follow-up visit after 24 weeks of fampridine treatment] ○ See Hupperts et al (2022) • HRQoL ○ See Hupperts et al (2022) **Important Outcomes** • Limb mobility/dexterity ○ BBS score[i] at 26 weeks [i.e. two week post-dosing follow-up visit after 24 weeks of fampridine treatment] ○ See also Hupperts et al (2022) • Safety ○ AEs ○ Serious AEs
Hupperts et al 2022 *Post hoc* integrated data from two double-blind RCTs (ENHANCE and MOBILE) Multicentre 92 centres in 11 countries (1 RCT), 24 centres in 6 countries (1 RCT)	• Total sample size: N=765 • Two RCTs comparing PR fampridine vs placebo in adults aged 18 to 70 years with an EDSS score of 4.0 to 7.0; diagnosis of PPMS, SPMS, PRMS or RRMS of ⩾3 months' duration • PR fampridine: n=383 • Placebo: n=382 • Subgroup analyses of MSWS-12 scores in patients with lower EDSS score (≤6) vs greater EDSS score (6.5 and 7)	**Intervention** PR fampridine 10 mg tablets every 12 hours **Comparison** Matching placebo every 12 hours In the pooled MOBILE and ENHANCE studies, concomitant disease-modifying treatments included alemtuzumab, fingolimod, dimethyl fumarate, glatiramer acetate, interferon beta-1a, interferon beta-1b, atalizumab, and teriflunomide.	Follow-up at 24 weeks, unless otherwise stated **Critical outcome** • Walking ability ○ LSM change (95% CI) from baseline in MSWS-12 score ○ Proportion of patients with mean improvement in MSWS-12 score ≥8[f] • Physical impact of MS ○ LSM change (95% CI) from baseline in TUG speed ○ Proportion of patients with mean improvement in TUG speed of ≥15%[g] ○ LSM change (95% CI) from baseline in MSIS-29 PHYS score[h] • HRQoL ○ LSM change (95% CI) from baseline in EQ-5D-3L utility index score ○ LSM change (95% CI) from baseline in EQ-5D VAS **Important Outcomes** • Limb mobility/dexterity ○ LSM change (95% CI) from baseline in BBS score[i]

Copyright © NHS England 2024

Study	Population	Intervention and comparison	Outcomes reported

			• Proportion of treatment responders
			  ○ % patients with a clinically meaningful improvement in MSWS-12 (≥8 points) from baseline
			• Safety
			  ○ See Hobart et al (2019) and Hupperts et al (2016)

Jensen et al 2016
Double-blind RCT
Southern Denmark
	• Total sample size: N=37
	• Adults aged 18 to 60 years meeting the McDonald criteria for MS; EDSS between 4 and 7 with a pyramidal functional subscore ≥2, and fulfil the responder criterion
	• SR fampridine: n=17
	• Placebo: n=20
	• No relevant subgroups reported
		Intervention
		SR fampridine 10 mg twice daily
		Comparison
		Placebo twice daily
		The authors did not state whether use of concomitant treatments [other than those stated in the exclusion criteria] were permitted.
			Follow-up at four weeks
			Critical outcome
			• Walking ability
			  ○ Mean change (±SD) from baseline in T25FW[j]
			  ○ Mean change (±SD) from baseline in SSST[k]
			Important Outcomes
			• Limb mobility/dexterity
			  ○ Mean change (±SD) from baseline in 5-STS[l]
			  ○ Mean change (±SD) from baseline in 9-HPT[m]
			  ○ Mean change (±SD) from baseline in composite scores for muscle strength

Marzal-Alfaro et al 2018 Prospective case series Spain	• Total sample size: N=30 • Patients with diagnosed MS, EDSS >4 and <7, absence of seizure disorder antecedents and normal renal function (creatinine clearance >80 mL/min) • Fampridine: N=30 • Control: None • No relevant subgroups reported	**Intervention** Fampridine 10 mg twice daily **Comparison** No comparator	Follow-up at six months **Important Outcomes** • Activities of daily living ○ Mean change in EDSS score from baseline
Zhao et al 2022 Cost-effectiveness study China	Cost-effectiveness data based on a cohort of Chinese adult MS patients with walking disability (EDSS scores 4 to 7) and four PR fampridine trials	**Intervention** PR fampridine 10 mg plus BSC **Comparison** BSC alone BSC consisted of other supportive medication, examinations and laboratory tests, hospitalisation, rehabilitation, neurologist visits and other outpatient visits	**Important Outcomes** • Cost-effectiveness: ICERs in terms of QALY gain from PR fampridine plus BSC versus BSC alone

Abbreviations
AE: adverse event; BBS: Berg balance scale; BSC: best supportive care; CI: confidence interval; EDSS: expanded disability status score; HRQoL: health-related quality of life; EQ-5D-3L: EuroQol five dimension three-level version; EQ-5D VAS: EuroQol five dimension visual analogue scale; 9-HPT: 9 hole peg test; ICER: incremental cost effectiveness ratio; LSM: least squares mean; mITT: modified intention-to-treat; MS: multiple sclerosis; MSIS-29 PHYS: multiple sclerosis impact scale physical impact subscale; MSIS-29 PSYCH: multiple sclerosis impact scale psychological impact subscale; MSWS-12: 12-item multiple sclerosis walking scale; PGIC: patient global impression of change; PPMS: primary progressive multiple sclerosis; PR: prolonged release; PRMS: progressive-relapsing multiple sclerosis; QALY: quality adjusted life years; RCT: randomised controlled trial; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis; SR: slow release; SSST: six spot step test; 5-STS: 5 times sit to stand; TUG: timed up and go test; T25FW: timed 25-foot walk test.

Copyright © NHS England 2024

Study	Population	Intervention and comparison	Outcomes reported

a. Response was defined as increased gait speed (≥20%) using the T25FW test and decreased MSWS-12 score (≥4 points).
b. The EDSS score is a rating scale that assesses the degree of neurological disability taking account of eight functional systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and other) in MS patients. The scale ranges from 0 (normal) to 10 (death due to MS). EDSS values between 4.0 and 7.0 reflect a growing negative impact on the walking ability.
c. The MSIS-29 PSYCH score is a self-reported measure of the psychological impact of MS. For each visit, MSIS-29 PSYCH score were calculated by totalling the nine individual items and transforming the score to a scale with a range of 0 (no impact of MS) to 100 (extreme impact of MS).
d. ABILHAND measures manual ability to manage daily activities among chronic stroke patients. Patients estimate the ease or difficulty of performing each upper limb activity using a 3-level response scale: impossible (0), difficult (1), and easy (2). A higher ABILHAND score represents better manual ability.
e. The PGIC is a global assessment of the patient's impression of how the study drug affected their overall walking during the preceding seven days. The PGIC was scored on a seven-point scale (from 1 = very much worse to 7 = very much improved).
f. The MSWS-12 score includes 12 questions that ask about different aspects of walking: ability and speed of walk; ability to run; ability to climb and descend stairs; balance and smoothness of gait; and support, effort, and concentration required. Patients rate limitations of their mobility due to MS on a Likert 5-point scale (from 1 = not at all to 5 = extremely). Total score ranges from 1 to 60 and is transformed to a scale of 0–100. A higher MSWS-12 score represents poorer walking ability.
g. TUG speed is an objective measure of dynamic balance and mobility. TUG measures the speed of individuals to move from a seated position to stand up, walk 3 m, turn, walk 3 m. In ENHANCE, TUG (feet/second) was performed at the same time (± 3 h) and with the same footwear and walking aids (if required) during each visit to avoid variation.
h. The MSIS-29 PHYS score is a self-reported measure of the physical impact of MS. The MSIS-29 PHYS score is calculated by summing the 20 items and transforming the score to a scale of 0 (no impact of MS) to 100 (extreme impact of MS).
i. The BBS score measures static and dynamic balance. Each task is scored from 0 (unable to perform) to 4 (able to perform independently). A higher BBS score represents better balance; recommended to predict multiple falls once a fall has occurred.
j. The T25FW is a test that objectively measures functional capacity of the lower extremities in patients using a timed 25 foot walk.
k. The SSST assesses functional capacity of the lower extremities in terms of walking speed, but also co-ordination and balance by kicking blocks out of five circles on the floor.
l. The 5-STS assesses functional capacity of the lower extremities in terms of time taken to stand up and sit down on a chair five times.
m. The 9-HPT measures finger dexterity in terms of the time taken to place nine pegs into a square board with holes for the pegs.

Copyright © NHS England 2024

5. Results

In people with MS associated walking impairment (EDSS 4 to 7.5), what is the clinical effectiveness and safety of PR fampridine compared with standard care alone or standard care and placebo?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Walking ability **Certainty of evidence:** Very low to Moderate	This outcome is important to patients because walking impairment reduces independence and negatively impacts health-related quality of life, productivity, and daily activities. One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and three individual RCTs provided evidence relating to walking ability in patients with MS and walking impairment. The MOBILE RCT reported walking ability outcomes as defined by proportion of patients reporting improvements on PGIC at a follow-up duration of two weeks. One individual RCT (which was not included in the *post hoc* integrated analysis) compared walking ability (defined as mean change in T25FW and SSST) in patients with MS and walking impairment after four weeks of treatment with SR fampridine versus placebo. The *post hoc* integrated analysis and the individual ENHANCE and MOBILE RCTs assessed MSWS-12 scores at different thresholds in patients with MS and walking impairment after treatment with PR fampridine versus placebo. The follow-up duration was 24 weeks, with a two week post-dosing follow-up (i.e. at 26 weeks) in the two individual ENHANCE and MOBILE RCTs. PGIC[15] *PR fampridine vs placebo* **At two weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) conducted a *post hoc* analysis, which indicated that in patients with MS and walking impairment a greater number of patients treated with PR fampridine versus placebo showed improvements in PGIC at two weeks follow-up: n=31 (46%) versus n=16 (26%), respectively. The difference between treatment groups was *statistically significant* (p=0.023). **(MODERATE)** T25FW[16] *SR fampridine vs placebo* **At four weeks follow-up** • One RCT (Jensen et al 2016; n=37) reported greater reductions in the T25FW in patients with MS and walking impairment treated with SR fampridine (−13.6% [±SD 18.3]) compared to placebo (4.7% [±SD 24.1]). The difference between treatment groups was *statistically significant* (p=0.02). **(VERY LOW)** SSST[17] *SR fampridine vs placebo* **At four weeks follow-up** • One RCT (Jensen et al 2016; n=37) reported greater reductions in the SSST in patients with MS and walking impairment treated with SR fampridine (−11.4% [±SD 17.7]) compared to placebo (3.8% [±SD 19.6]). The difference between treatment groups was *statistically significant* (p=0.005). **(VERY LOW)**

[15] The PGIC is a global assessment of the patient's impression of how the study drug affected their overall walking during the preceding seven days. The PGIC was scored on a seven-point scale (from 1 = very much worse to 7 = very much improved).
[16] The T25FW is a test that objectively measures functional capacity in the lower extremities in patients using a timed 25 foot walk.
[17] The SSST assesses functional capacity of the lower extremities in terms of walking speed, but also co-ordination and balance by kicking blocks out of five circles on the floor.

Copyright © NHS England 2024

Outcome	Evidence statement
	MSWS-12 score[18] *PR fampridine vs placebo* **At 24 weeks follow-up** • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022; n=765) reported that PR fampridine was associated with an improvement in LSM of −3.70 points (95% CI: −5.61 to −1.79) in MSWS-12 score versus placebo over 24 weeks in patients with MS and walking impairment. The difference was *statistically significant* (p<0.001). **(MODERATE)** MSWS-12 score (mean improvement of ≥1 point) *PR fampridine vs placebo* **At 24 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥1 point in MSWS-12 score (64.7% versus 54.7%, respectively). The difference was *not statistically significant* (p=NS). **(MODERATE)** MSWS-12 score (mean improvement of ≥2 points) *PR fampridine vs placebo* **At 24 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥2 points in MSWS-12 score (61.8% versus 51.6%, respectively). The difference was *not statistically significant* (p=NS). **(MODERATE)** MSWS-12 score (mean improvement of ≥3 points) *PR fampridine vs placebo* **At 24 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥3 points in MSWS-12 score (61.8% versus 50.0%, respectively). The difference was *not statistically significant* (p=NS). **(MODERATE)** MSWS-12 score (mean improvement of ≥4 points) *PR fampridine vs placebo* **At 24 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥4 points in MSWS-12 score (61.8% versus 46.9%, respectively). The difference was *not statistically significant* (p=NS). **(MODERATE)** MSWS-12 score (mean improvement of ≥5 points) *PR fampridine vs placebo* **At 24 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥5 points in MSWS-12 score (54.4% versus 40.6%, respectively). The difference was *not statistically significant* (p=NS). **(MODERATE)**

[18] The MSWS-12 score includes 12 questions that ask about different aspects of walking: ability and speed of walk; ability to run; ability to climb and descend stairs; balance and smoothness of gait; and support, effort, and concentration required. Patients rate limitations of their mobility due to MS on a Likert 5-point scale (from 1 = not at all to 5 = extremely). Total score ranges from 1 to 60 and is transformed to a scale of 0–100. A higher MSWS-12 score represents poorer walking ability.

Copyright © NHS England 2024

Outcome	Evidence statement
	MSWS-12 score (mean improvement of ≥6 points) *PR fampridine vs placebo* **At 24 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥6 points in MSWS-12 score (51.5% versus 35.9%, respectively). The difference was *not statistically significant* (p=NS). **(MODERATE)** MSWS-12 score (mean improvement of ≥7 points) *PR fampridine vs placebo* **At 24 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥7 points in MSWS-12 score (50.0% versus 31.3%, respectively). The difference was *statistically significant* (p<0.0275). **(MODERATE)** MSWS-12 score (MCID for mean improvement of ≥8 points)[19,20] *PR fampridine vs placebo* **At 24 weeks follow-up** • One *post hoc* integrated analysis of ENHANCE and MOBILE RCTs (Hupperts et al 2022; n=765) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥8 points in MSWS-12 score (44.3% versus 33.0%, respectively): OR 1.68 (95% CI: 1.23 to 2.29). The difference was *statistically significant* (p<0.001). **(MODERATE)** MSWS-12 score (mean improvement of ≥9 points) *PR fampridine vs placebo* **At 24 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥9 points in MSWS-12 score (48.5% versus 26.6%). The difference was *statistically significant* (p<0.0088). **(MODERATE)** MSWS-12 score (mean improvement of ≥10 points) *PR fampridine vs placebo* **At 24 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥10 points in MSWS-12 score (41.2% versus 26.6%). The difference was *not statistically significant* (p=NS). **(MODERATE)** • The ENHANCE RCT (Hobart et al 2019; n=633) reported a greater proportion of patients with MS and walking impairment receiving PR fampridine versus placebo who met the threshold of improvement of ≥10 points in MSWS-12 score (38% versus 27%). The difference was *statistically significant* (p=0.003). **(MODERATE)** MSWS-12 score

[19] The proportion of patients with MS with a mean improvement in MSWS-12 score exceeding the predetermined threshold (⩾8 points) from baseline over 24 weeks (i.e. people with MS who met the definition of PR-fampridine responders for this analysis), analysed using a logistic regression model with treatment group as the classification variable and study, baseline MSWS-12 score, baseline TUG speed, age, and screening EDSS score as covariates.

[20] Findings on the MSWS-12 score for mean improvement of ≥8 points are also reported for the important outcome 'proportion of treatment responders' as this was how treatment responders were defined in the two RCTs and *post hoc* integrated analysis of the two RCTs.

Copyright © NHS England 2024

Outcome	Evidence statement
	PR fampridine vs placebo **At 26 weeks follow-up (i.e. two weeks follow-up visit after 24 week treatment period)** • The MOBILE RCT (Hupperts et al 2016; n=132) reported that *"after treatment discontinuation at week 24, improvements declined and approached zero by the week 26 follow-up visit in the PR-fampridine group"*. No further details were provided and statistical measures were not reported. **(LOW)** • The ENHANCE RCT (Hobart et al 2019; n=633) reported that *"within 2 weeks of stopping PR-fampridine treatment, the effects of PR-fampridine on the MSWS-12 dissipated"*. No further details were provided and statistical measures were not reported. **(LOW)** **One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and three individual RCTs (including ENHANCE and MOBILE) provided very low to moderate certainty evidence relating to walking ability. The MOBILE RCT provided moderate certainty evidence that a statistically significant greater number of patients with MS and walking impairment showed improvements in walking ability after treatment with PR fampridine compared to placebo at two weeks follow-up, measured using the PGIC. One RCT (not included in the *post hoc* integrated analysis) provided very low certainty evidence that statistically significant improvements were shown in patients receiving PR fampridine compared to placebo, reflected in reductions in the T25FW and SSST at four weeks follow-up. The improvement in T25FW from baseline to four weeks follow-up in patients treated with PR fampridine was below the MCID which is estimated to be 20%.The *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs provided moderate certainty evidence that PR fampridine was associated with an improvement in walking ability (measured by MSWS-12 score) and that a greater proportion of patients treated with PR fampridine achieved the MCID for mean improvement in MSWS-12 score of ≥8 points compared to placebo over 24 weeks in patients with MS and walking impairment. The differences were *statistically significant*. The ENHANCE RCT provided moderate certainty evidence that a *statistically significant* greater proportion of patients with MS and walking impairment treated with PR fampridine versus placebo achieved a mean improvement of ≥10 points in MSWS-12 score at 24 weeks follow-up, while the MOBILE RCT reported that there were *no statistically significant* differences between treatment groups at this threshold. The individual ENHANCE and MOBILE RCTs provided low certainty evidence that at 26 weeks follow-up (two weeks after stopping PR fampridine) any improvements shown on the MSWS-12 during 24 weeks of PR fampridine treatment had dissipated.**
Physical impact of MS **Certainty of evidence:** Low to Moderate	This outcome is important to patients as it measures functional mobility, and links to enablement, independence and active participation. One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs provided evidence relating to physical impact of MS (measured using the TUG speed and MSIS-29 PHYS score, which assesses the physical impact of MS on patients) in patients with MS and walking impairment. This analysis compared PR fampridine versus placebo from baseline up to 24 weeks. The individual MOBILE RCT provided evidence relating to TUG speed in patients with MS and walking impairment at 26 weeks follow-up (i.e. two weeks after stopping treatment with PR fampridine). TUG speed[21] *PR fampridine vs placebo* **At 24 weeks follow-up** • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022; n=765) reported greater LSM improvements from baseline in percentage change in TUG speed after 24 weeks of treatment with

[21] TUG speed is an objective measure of dynamic balance and mobility. TUG measures the speed of individuals to move from a seated position to stand up, walk 3 m, turn, walk 3 m. In ENHANCE, TUG (feet/second) was performed at the same time (± 3 h) and with the same footwear and walking aids (if required) during each visit to avoid variation.

Copyright © NHS England 2024

Outcome	Evidence statement
	PR fampridine versus placebo in patients with MS and walking impairment: LSM difference: 4.40 (95% CI: 0.97 to 7.83). The difference between treatment groups was *statistically significant* (p=0.012). **(MODERATE)** **At 26 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported that *"after treatment discontinuation at week 24, improvements declined and approached zero by the week 26 follow-up visit in the PR-fampridine group"*. No further details were provided and statistical measures were not reported. **(LOW)** <u>TUG speed (MCID ≥15% improvement in TUG speed [metres/second])</u> *PR fampridine vs placebo* **At 24 weeks follow-up** • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022; n=765) reported that a greater proportion of PR fampridine treated patients with MS and walking impairment achieved a ⩾15% mean improvement in TUG speed versus placebo treated patients (44.1% versus 34.5%, respectively) over 24 weeks of treatment: OR 1.54 (95% CI: 1.13 to 2.11). The difference between treatment groups was *statistically significant* (p=0.007). **(MODERATE)** <u>MSIS-29 PHYS score (physical impact of MS in patients)[22]</u> *PR fampridine vs placebo* **At 24 weeks follow-up** • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022; n=765) reported that over 24 weeks of treatment, patients with MS and walking impairment treated with PR fampridine had significantly greater LSM improvements in MSIS-29 PHYS score compared to placebo: LSM difference: −3.18 (95% CI: −4.84 to −1.52). The difference between treatment groups was *statistically significant* (p<0.001). **(MODERATE)** **One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs provided moderate certainty evidence that over 24 weeks of treatment PR fampridine showed *statistically significant* improvements compared to placebo in walking ability (measured by TUG speed), the proportion of patients achieving ≥15% improvement in TUG speed (≥15% improvement from baseline is considered to reflect the MCID for this outcome), and in the physical impact of MS (measured by MSIS-29 PHYS score). The MOBILE RCT provided low certainty evidence that at 26 weeks follow-up (two weeks after stopping PR fampridine) any improvements shown in TUG speed during 24 weeks of PR fampridine treatment had dissipated, but no further details were reported and statistical measures were not presented.**
HRQoL **Certainty of evidence:** Low to Moderate	This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and one *post hoc* analysis of the MOBILE RCT provided evidence relating to HRQoL in patients with MS and walking impairment. The *post hoc* integrated analysis compared HRQoL (measured using the EQ-5D-3L utility index score and EQ-5D VAS) after treatment with PR fampridine versus placebo up to 24 weeks. The *post hoc* analysis of the MOBILE RCT compared HRQoL (measured using the MSIS-29 PSYCH score, which assess the psychological impact of MS on patients) from baseline to 4, 12 and 24 weeks after treatment with PR fampridine versus placebo. <u>EQ-5D-3L utility index score</u>

[22] The MSIS-29 PHYS score is a self-reported measure of the physical impact of MS. The MSIS-29 PHYS score is calculated by summing the 20 items and transforming the score to a scale of 0 (no impact of MS) to 100 (extreme impact of MS).

Copyright © NHS England 2024

Outcome	Evidence statement
	PR fampridine vs placebo **At 24 weeks follow-up** • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022; n=765) reported improvements on the EQ-5D-3L utility index score from baseline over 24 weeks in patients with MS and walking impairment after treatment with PR fampridine versus placebo: LSM difference 0.020 (95% CI: −0.001 to 0.041). The difference between treatment groups was *not statistically significant*. **(MODERATE)** EQ-5D VAS *PR fampridine vs placebo* **At 24 weeks follow-up** • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022; n=765) reported improvements on the EQ-5D VAS score from baseline over 24 weeks in patients with MS and walking impairment after treatment with PR fampridine versus placebo: LSM difference 0.9 (95% CI: −1.0 to 2.8). The difference between treatment groups was *not statistically significant*. **(MODERATE)** MSIS-29 PSYCH score (psychological impact of MS on patients)[23] *PR fampridine vs placebo* **At four weeks follow-up** • One *post hoc* analysis of the MOBILE RCT (Gasperini et al 2016; n=132) reported that a greater proportion of patients with MS and walking impairment treated with PR fampridine versus placebo showed mean improvements in MSIS-29 PSYCH subscale scores at four weeks follow-up, with a difference in scores of 42%. Statistical measures were not reported. **(LOW)** **At 12 weeks follow-up** • One *post hoc* analysis of the MOBILE RCT (Gasperini et al 2016; n=132) reported that a greater proportion of patients with MS and walking impairment treated with PR fampridine versus placebo showed mean improvements in MSIS-29 PSYCH subscale scores at 12 weeks follow-up, with a difference in scores of 57%. Statistical measures were not reported. **(LOW)** • One *post hoc* analysis of the MOBILE RCT (Gasperini et al 2016; n=132) reported that a greater proportion of patients with MS and walking impairment treated with PR fampridine versus placebo showed mean improvements in six of the nine PSYCH items. The difference was *statistically significant* for one item *"worries related to your MS"* at 12 weeks follow-up (p=0.044). A greater proportion of patients treated with placebo versus PR fampridine showed mean improvements in the remaining three PSYCH items at 12 weeks, but the difference was *not statistically significant*. **(LOW)** **At 24 weeks follow-up** • One *post hoc* analysis of the MOBILE RCT (Gasperini et al 2016; n=132) reported that a greater proportion of patients with MS and walking impairment treated with PR fampridine versus placebo showed mean improvements in MSIS-29 PSYCH subscale scores at 24 weeks follow-up, with a difference in scores of 148%. Statistical measures were not reported. **(LOW)** • One *post hoc* analysis of the MOBILE RCT (Gasperini et al 2016; n=132) reported that a greater proportion of patients with MS and walking impairment treated with PR fampridine versus placebo showed mean improvements in six of the nine PSYCH items. The difference was *statistically significant* for one item *"worries related to your MS"* at 24 weeks follow-up (p=0.006). A greater proportion of patients treated with placebo versus PR fampridine showed mean improvements in the remaining three PSYCH items at 24 weeks, but the difference was *not statistically significant*. **(LOW)** **One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and one *post hoc* analysis of the MOBILE RCT provided low to moderate certainty**

[23] For each visit, MSIS-29 PSYCH scores were calculated by totalling the nine individual items and transforming to a scale with a range of 0 (no impact of MS) to 100 (extreme impact of MS).

Copyright © NHS England 2024

Outcome	Evidence statement
	evidence relating to HRQoL. The *post hoc* integrated analysis reported improvements from baseline over 24 weeks in patients with MS and walking impairment treated with PR fampridine versus placebo on the EQ-5D-3L utility index and EQ-5D-VAS scores, but findings were *not statistically significant*. The *post hoc* analysis of the MOBILE RCT reported that a greater proportion of patients with MS and walking impairment treated with PR fampridine versus placebo showed mean improvements in the psychological impact of MS (measured by MSIS-29 PSYCH subscale scores) at 4, 12 and 24 weeks follow-up. No statistical measures were reported, but there was a *statistically significant* difference favouring PR fampridine for one item *"worries related to your MS"* at 12 and 24 weeks follow-up.
Important outcomes	
Limb mobility/dexterity **Certainty of evidence:** Very low to Moderate	This outcome is important to patients because a reduction in upper and lower limb mobility and dexterity, which is associated with MS, reduces independence and negatively impacts health-related quality of life, productivity, and daily activities. One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and three individual RCTs provided evidence relating to limb mobility/dexterity in patients with MS and walking impairment. The *post hoc* integrated analysis compared BBS scores after treatment with PR fampridine versus placebo at 24 weeks. The MOBILE RCT provided evidence relating to BBS in patients with MS and walking impairment at 26 weeks follow-up (i.e. two weeks after stopping treatment with PR fampridine). The ENHANCE RCT compared ABILHAND scores at 24 weeks after treatment with PR fampridine versus placebo. The second RCT (not included in the *post hoc* integrated analysis) compared 5-STS and 9-HPT scores, and composite scores for maximal concentric and isometric muscle strength at four weeks follow-up. 5-STS (for functional capacity)[24] *SR fampridine vs placebo* **At four weeks follow-up** • One RCT (Jensen et al 2016; n=37) reported a *statistically significant* (p=0.006) reduction in the time taken to complete the 5-STS in patients with MS and walking impairment in the SR fampridine group compared to placebo group: −7.6% (±SD 37.1) versus 1.6% (±SD 13.7), respectively. **(VERY LOW)** 9-HPT (for hand dexterity)[25] *SR fampridine vs placebo* **At four weeks follow-up** • One RCT (Jensen et al 2016; n=37) reported *no statistically significant* difference (p=0.1) in time taken to complete the 9-HPT in patients with MS and walking impairment in the SR fampridine group compared to placebo group: −1.0% (±SD 8.4) versus 4.1% (±SD 12.0), respectively. **(VERY LOW)** Composite scores for maximal concentric and isometric muscle strength – weakest leg (MVC [Nm]) *SR fampridine vs placebo* **At four weeks follow-up**

[24] The 5-STS assesses functional capacity of the lower extremities in terms of time taken to stand up and sit down on a chair five times.
[25] The 9-HPT measures finger dexterity in terms of the time taken to place nine pegs into a square board with holes for the pegs.

Copyright © NHS England 2024

Outcome	Evidence statement
	• One RCT (Jensen et al 2016; n=37) reported greater improvements in muscle strength of knee extension in patients with MS and walking impairment treated with SR fampridine compared to placebo: 11.6% (±SD 24.1) versus -0.8% (±SD 11.3), respectively. The difference between treatment groups was *statistically significant* (p=0.03). **(VERY LOW)** • One RCT (Jensen et al 2016; n=37) reported greater improvements in muscle strength of knee flexion in patients with MS and walking impairment treated with SR fampridine compared to placebo: 11.2% (±SD 29.5) versus -4.8% (±SD 12.9), respectively. The difference between treatment groups was *statistically significant* (p=0.03). **(VERY LOW)** • One RCT (Jensen et al 2016; n=37) reported greater improvements in muscle strength of hip flexion in patients with MS and walking impairment treated with SR fampridine compared to placebo: 14.3% (±SD 14.9) versus -1.3% (±SD 20.5), respectively. The difference between treatment groups was *statistically significant* (p=0.05). **(VERY LOW)** Composite scores for maximal concentric and isometric rate of force development – weakest leg (Nm/s) *SR fampridine vs placebo* **At four weeks follow-up** • One RCT (Jensen et al 2016; n=37) reported greater improvements in rate of force development of knee extension in patients with MS and walking impairment treated with SR fampridine compared to placebo: 23.3% (±SD 32.2) versus -2.2% (±SD 30.3), respectively. The difference between treatment groups was *statistically significant* (p=0.002). **(VERY LOW)** • One RCT (Jensen et al 2016; n=37) reported greater improvements in rate of force development of knee flexion in patients with MS and walking impairment treated with SR fampridine compared to placebo: 34.7% (±SD 43.0) versus -6.7% (±SD 32.2), respectively. The difference between treatment groups was *statistically significant* (p<0.001). **(VERY LOW)** • One RCT (Jensen et al 2016; n=37) reported *no statistically significant difference* (p=0.09) in change in rate of force development of hip flexion in patients with MS and walking impairment treated with SR fampridine compared to placebo: 12.4% (±SD 51.2) versus -8.4% (±SD 54.4), respectively. **(VERY LOW)** Composite scores for maximal concentric and isometric muscle strength – strongest leg (MVC [Nm]) *SR fampridine vs placebo* **At four weeks follow-up** • One RCT (Jensen et al 2016; n=37) reported *no statistically significant difference* (p=0.06) in change in muscle strength of knee extension in patients with MS and walking impairment treated with SR fampridine versus placebo: 8.3% (±SD 13.4) versus 1.5% (±SD 6.3), respectively. **(VERY LOW)** • One RCT (Jensen et al 2016; n=37) reported *no statistically significant difference* (p=0.08) in change in muscle strength of knee flexion in patients with MS and walking impairment treated with SR fampridine versus placebo: 13.7% (±SD 16.5) versus 4.1% (±SD 19.6), respectively. **(VERY LOW)** • One RCT (Jensen et al 2016; n=37) reported *no statistically significant difference* (p=0.9) in change in muscle strength of hip flexion in patients with

Copyright © NHS England 2024

Outcome	Evidence statement
	MS and walking impairment treated with SR fampridine compared to placebo: 10.9% (±SD 28.2) versus 8.3% (±SD 16.4), respectively. **(VERY LOW)** Composite scores for maximal concentric and isometric rate of force development – weakest leg (Nm/s) *SR fampridine vs placebo* **At four weeks follow-up** • One RCT (Jensen et al 2016; n=37) reported *no statistically significant difference* (p=0.2) in change in rate of force development of knee extension in patients with MS and walking impairment treated with SR fampridine versus placebo: 13.3% (±SD 32.3) versus 14.6% (±SD 36.4), respectively. **(VERY LOW)** • One RCT (Jensen et al 2016; n=37) reported *no statistically significant difference* (p=0.1) in change in rate of force development of knee flexion in patients with MS and walking impairment treated with SR fampridine versus placebo: 41.2% (±SD 63.5) versus 18.6% (±SD 56.1), respectively. **(VERY LOW)** • One RCT (Jensen et al 2016; n=37) reported *no statistically significant difference* (p=0.3) in change in rate of force development of hip flexion in patients with MS and walking impairment treated with SR fampridine compared to placebo: 33.4% (±SD 93.9) versus 1.6% (±SD 8.8), respectively. **(VERY LOW)** ABILHAND score[26] *PR fampridine vs placebo* **At 24 weeks follow-up** • The ENHANCE RCT (Hobart et al 2019; n=627) reported improvements in manual ability (measured using ABILHAND scores) in patients with MS and walking impairment treated with PR fampridine versus placebo, but the difference was *not statistically significant*: difference in LSM change 0.74 (95% CI: −0.38 to 1.86); p=0.197. **(MODERATE)** BBS score[27] *PR fampridine vs placebo* **At 24 weeks follow-up** • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022; n=765) reported improvements in static and dynamic balance (measured using BBS) in patients with MS and walking impairment treated with PR fampridine versus placebo. The difference was *statistically significant*: difference in LSM change 0.62 (95% CI: 0.09 to 1.14); p=0.021. **(MODERATE)** **At 26 weeks follow-up** • The MOBILE RCT (Hupperts et al 2016; n=132) reported that *"after treatment discontinuation at week 24, improvements declined and approached zero by*

[26] ABILHAND measures manual ability to manage daily activities among chronic stroke patients. Patients estimate the ease or difficulty of performing each upper limb activity using a 3-level response scale: impossible (0), difficult (1), and easy (2). A higher ABILHAND score represents better manual ability.
[27] The BBS score measures static and dynamic balance. Each task is scored from 0 (unable to perform) to 4 (able to perform independently). A higher BBS score represents better balance; recommended to predict multiple falls once a fall has occurred.

Copyright © NHS England 2024

Outcome	Evidence statement
	the week 26 follow-up visit in the PR-fampridine group". No further details were provided and statistical measures were not reported. **(LOW)** **One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and two individual RCTs provided very low to moderate certainty evidence relating to limb mobility/dexterity in patients with MS and walking impairment. The *post hoc* integrated analysis provided moderate certainty evidence that there was a *statistically significant* difference in tests of balance (as measured by BBS scores) after treatment with PR fampridine versus placebo at 24 weeks. The MOBILE RCT provided low certainty evidence that at 26 weeks follow-up (two weeks after stopping PR fampridine) any improvements shown in the BBS score during 24 weeks of PR fampridine treatment had dissipated, but no further details were reported and statistical measures were not presented. The ENHANCE RCT provided moderate certainty evidence that there was *no statistically significant* difference in hand dexterity (measured by ABILHAND scores) at 24 weeks after treatment with PR fampridine versus placebo. The second RCT (not included in the *post hoc* integrated analysis) provided very low certainty evidence that there was a *statistically significant* reduction in the time taken to complete the 5-STS in patients with MS and walking impairment treated with SR fampridine versus placebo, but there was *no statistically significant* difference in 9-HPT scores between treatment groups. The same RCT reported that, with the exception of rate of force development in the weakest leg for hip flexion, *statistically significant* improvements in composite scores for maximal concentric and isometric muscle strength and rate of force development were shown for all other measures in the weakest leg (but not in the strongest leg) at four weeks follow-up, favouring SR fampridine versus placebo.**
ADL **Certainty of evidence:** Very low	This outcome is important to patients because it reflects daily functioning and how well people can engage in education, employment and recreational activities. Three prospective case series provided non-comparative evidence on ADLs in patients with MS and walking impairment. ADLs were measured using the EDSS at two weeks, and one, three or six months follow-up. *PR fampridine vs placebo* No evidence was identified for this outcome. EDSS score[28] *PR fampridine vs no comparator* **At two weeks follow-up** • One prospective case series (Marzal-Alfaro et al 2018; n=27) reported that the mean EDSS score remained the same compared to baseline in patients with MS and walking impairment after two weeks of treatment with PR fampridine: EDSS 5.8 at both timepoints. No statistical measures were reported. **(VERY LOW)** **At one month follow-up** • One prospective case series (Fragoso et al 2016; n=NR[29]) reported that improvements in the mean EDSS score from baseline were observed in 14 (17.5%) patients with MS and walking impairment after one month of treatment with PR fampridine. The difference between pre- and post-treatment scores was *not statistically significant* (p=0.29). **(VERY LOW)** **At three months follow-up** • One prospective case series (Marzal-Alfaro et al 2018; n=26) reported that the mean EDSS score remained the same compared to baseline in patients with MS and walking impairment after three months of treatment with PR fampridine: EDSS 5.8 at both timepoints. No statistical measures were reported. **(VERY LOW)**

[28] The EDSS score is a rating scale that assesses the degree of neurological disability taking into account eight functional systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and other) in MS patients. The scale ranges from 0 (normal) to 10 (death due to MS). EDSS values between 4.0 and 7.0 reflect a growing negative impact on the walking ability.

[29] The number of patients assessed by EDSS was not reported; although 89 patients were included in the study, the observed improvements in 14 (17.5%) patients suggests that not all patients were assessed.

Copyright © NHS England 2024

Outcome	Evidence statement
	At six months follow-up • One prospective case series (Marzal-Alfaro et al 2018; n=18) reported that the mean EDSS score *"remained stable"* compared to baseline in patients with MS and walking impairment after six months of treatment with PR fampridine: EDSS 5.8 at baseline versus 5.7 at six months. No statistical measures were reported. **(VERY LOW)** • One prospective case series (Alvarez-Payero et al 2017; n=25) reported an improvement from baseline in the mean EDSS score in treatment responder patients with MS and walking impairment after six months of treatment with PR fampridine: 6.1 (±SD 0.9) versus 5.6 (±SD 0.1), respectively. The difference between pre- and post-treatment scores was *statistically significant* (p<0.05). **(VERY LOW)** • One prospective case series (Alvarez-Payero et al 2017; n=30) reported that improvements in EDSS resulted in 9.1% of all patients (treatment responders and non-responders) with MS and walking impairment reducing the number of supports needed for walking after six months of treatment with PR fampridine. Statistical measures were not reported. **(VERY LOW)** **Three prospective case series provided very low certainty evidence relating to ADLs, measured using the EDSS. One case series reported that EDSS *"remained stable"* compared to baseline in patients with MS and walking impairment after two weeks and three and six months treatment with PR fampridine. The second case series reported *no statistically significant* differences between pre- and post-treatment EDSS scores in patients with MS and walking impairment after one month of treatment with PR fampridine. The third case series reported a *statistically significant* improvement from baseline in the mean EDSS score in treatment responder patients with MS and walking impairment after six months of treatment with PR fampridine. The same case series reported that improvements in EDSS resulted in 9.1% of all patients (treatment responders and non-responders) with MS and walking impairment reducing the number of supports needed for walking after six months of treatment with PR fampridine. Statistical measures were not reported for this result.**
Proportion of treatment responders **Certainty of evidence:** Moderate	This outcome enables relevant information sharing with patients in terms of risks and benefits of starting treatment. One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and one individual RCT (ENHANCE) provided evidence relating to the proportion of patients with MS and walking impairment who responded to treatment with PR fampridine versus placebo at 24 weeks follow-up. Clinically meaningful ≥8 point improvement in MSWS-12 score *PR fampridine vs placebo* **At 24 weeks follow-up** • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022; n=765) reported that a greater proportion of patients with MS and walking impairment responded to PR fampridine (44.3%) compared to placebo (33.0%) after 24 weeks of treatment. The difference between treatment groups was *statistically significant*: OR 1.68 (95% CI: 1.23 to 2.29); p<0.001. **(MODERATE)** **One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs provided moderate certainty evidence that a *statistically significant* greater proportion of patients with MS and walking impairment responded to treatment with PR fampridine compared to placebo (measured using thresholds of ≥8 point improvement in MSWS-12 score) at 24 weeks follow-up.**
Safety	

Copyright © NHS England 2024

Outcome	Evidence statement
Complications of PR fampridine therapy **Certainty of evidence:** Low	Safety is important to patients as it reflects the risks involved and allows a risk benefit assessment to be undertaken. The ENHANCE and MOBILE RCTs provided evidence relating to complications of PR fampridine therapy in patients with MS and walking impairment. This analysis compared PR fampridine versus placebo from baseline up to 24 weeks. <u>Any AE</u> *PR fampridine vs placebo* **At 24 weeks follow-up** • The ENHANCE RCT (Hobart et al 2019; n=635) reported that the proportion of patients with MS and walking impairment experiencing any AE was 66% among patients treated with PR fampridine versus 60% in patients treated with placebo. Statistical measures were not reported. **(LOW)** • The MOBILE RCT (Hupperts et al 2016; n=132) reported that the number of patients with MS and walking impairment experiencing any AE was 75% among patients treated with PR fampridine versus 77% in the placebo group. Statistical measures were not reported. **(LOW)** <u>Any treatment-related AE</u> *PR fampridine vs placebo* **At 24 weeks follow-up** The ENHANCE RCT (Hobart et al 2019; n=635) reported that the proportion of patients with MS and walking impairment experiencing any treatment-related AE was 18% for patients treated with PR fampridine and 13% for the placebo group. Statistical measures were not reported. **(LOW)** <u>Any severe AE</u>[30] *PR fampridine vs placebo* **At 24 weeks follow-up** • The ENHANCE RCT (Hobart et al 2019; n=635) reported that the proportion of patients with MS and walking impairment experiencing severe AEs was 3% among patients treated with PR fampridine versus 3% in the placebo group. Statistical measures were not reported. **(LOW)** <u>Any serious AE</u>[31] *PR fampridine vs placebo* **At 24 weeks follow-up** • The ENHANCE RCT (Hobart et al 2019; n=635) reported that the proportion of patients with MS and walking impairment experiencing any serious AE was 8% in patients treated with PR fampridine and 7% in the placebo group. Statistical measures were not reported. **(LOW)** • The MOBILE RCT (Hupperts et al 2016; n=132) reported that the number of patients with MS and walking impairment experiencing any serious AE was 3% in patients treated with PR fampridine and 8% in the placebo group. Statistical measures were not reported. **(LOW)** <u>Any treatment-related serious AE</u> *PR fampridine vs placebo* **At 24 weeks follow-up** • The ENHANCE RCT (Hobart et al 2019; n=635) reported that the proportion of patients with MS and walking impairment experiencing any treatment-related serious AE was 0% in patients receiving PR fampridine versus <1% in patients receiving placebo. Statistical measures were not reported. **(LOW)**

[30] Severe AEs were defined as symptoms causing severe discomfort, incapacitation, or significant impact on daily life.
[31] A serious AE was any untoward medical occurrence that resulted in death/risk of death, hospitalisation/prolonged hospitalisation, persistent or significant disability/incapacity, or resulted in a congenital anomaly/birth defect. There were two deaths, both of which were considered unrelated to study treatment (coronary artery stenosis and acute myocardial infarction), and occurred after the participant had completed study treatment but before completing the 2-week post-treatment follow-up.

Copyright © NHS England 2024

Outcome	Evidence statement
	Any AE leading to dose interruption *PR fampridine vs placebo* **At 24 weeks follow-up** The ENHANCE RCT (Hobart et al 2019; n=635) reported that the proportion of patients with MS and walking impairment experiencing an AE leading to dose interruption was 6% among patients treated with PR fampridine versus 3% in the placebo group. Statistical measures were not reported. **(LOW)** Any AE leading to treatment discontinuation *PR fampridine vs placebo* **At 24 weeks follow-up** • The ENHANCE RCT (Hobart et al 2019; n=635) reported that the proportion of patients with MS and walking impairment discontinuing treatment due to an AE was 7% among patients treated with PR fampridine versus 7% in the placebo group. Statistical measures were not reported. **(LOW)** Any AE leading to study withdrawal *PR fampridine vs placebo* **At 24 weeks follow-up** • The ENHANCE RCT (Hobart et al 2019; n=635) reported that the proportion of patients with MS and walking impairment withdrawing from the study due to an AE was 7% among patients treated with PR fampridine versus 8% in the placebo group. Statistical measures were not reported. **(LOW)** Most common treatment-emergent AEs by MedDRA® Preferred Term (≥ 5% in any treatment group)[32] *PR fampridine vs placebo* **At 24 weeks follow-up** • The ENHANCE RCT (Hobart et al 2019; n=635) reported the proportion of patients with MS and walking impairment experiencing the following AEs: Urinary tract infection: PR fampridine 13% versus placebo 9%; MS relapse: PR fampridine 11% versus placebo 10%; Fall: PR fampridine 8% versus placebo 6%; Back pain: PR fampridine 5% versus placebo 3%; Headache: PR fampridine 5% versus placebo 5%; Nasopharyngitis: PR fampridine 5% versus placebo 6%; Upper respiratory tract infection: PR fampridine 5% versus placebo 3%. Statistical measures were not reported. **(LOW)** **The ENHANCE and MOBILE RCTs provided low certainty evidence that the proportion of patients with MS and walking impairment experiencing any type of adverse event was similar between patients treated with PR fampridine versus placebo at 24 weeks follow-up. The proportions experiencing any AE were 66% for PR fampridine versus 60% for placebo. For any treatment-related AE the proportions were 18% for PR fampridine versus 13% for placebo; and for any serious AE the proportion was 3% in both groups. Reasons for the similar proportions of patients experiencing AEs were not provided in the two RCTs. No statistical measures were reported.**

Abbreviations

ADLs: activities of daily living; AE: adverse event; BBS: Berg balance scale; BSC: best supportive care; CI: confidence interval; EDSS: expanded disability status scale; EQ-5D; EuroQol 5-dimensions; HF: hip flexion; 9-HPT: 9-hole peg test; LSM: least square means; MCID: minimally clinically important difference; MS: multiple sclerosis; MSIS-29 PHYS: multiple sclerosis impact scale-29 physical subscale; MSIS-29 PSYCH: multiple sclerosis impact scale-29 psychological subscale; MSWS-12: multiple sclerosis walking scale-12; MVC: maximal voluntary contraction; Nm: Newton meter; Nm/s: Newton meter per second; NS: not significant; OR: odds ratio; PGIC: patient global impression of change; PR: prolonged release; RCT: randomised controlled trial; SD: standard deviation; SR: slow release; SSST: six spot step test; 5-STS: 5 times sit to stand; T25FW: timed 25 foot walk; TUG: timed up and go; VAS: visual analogue scale.

[32] Listed in descending order of frequency for the PR-fampridine group. Treatment-emergent AEs were defined as AEs that started on or after the first dose of study drug, or pre-existing conditions that worsened in severity after the first dose of study drug; a participant was only counted once within each Preferred Term.

Copyright © NHS England 2024

In people with MS associated walking impairment (EDSS 4 to 7.5), what is the cost-effectiveness of PR fampridine compared with standard care alone or standard care and placebo?

Outcome	Evidence statement
Cost-effectiveness	Two studies considered the cost-effectiveness of PR fampridine plus BSC compared to BSC alone in adults with MS and walking impairment (EDSS 4 to 7). One study was conducted from a Swedish societal perspective and the second study from the Chinese healthcare and societal perspectives. • One study (Acosta et al 2021) was a cost-effectiveness analysis conducted from a Swedish societal perspective. The analysis used a Markov model to estimate accumulated costs and health outcomes, measured by QALYs gained for treatment with PR fampridine plus BSC versus BSC alone. The base case analysis was based on direct (PR-fampridine drug cost, healthcare professionals, hospitalisations, treatment of AEs, cost of care and modifications/aids) and indirect costs (absence from work). The base case analysis showed that PR fampridine plus BSC resulted in an incremental QALY gain of 0.12, incremental cost of 6,982 kronor (€685 and $816), and an ICER of 57,109 kronor per QALY gained (€5,607 and $6,675 per QALY gained) compared to BSC alone over a 20 year time horizon. One-way sensitivity analysis comparing PR fampridine plus BSC compared to BSC alone in adults with MS and walking impairment demonstrated that the ICER was most sensitive to the T25FW score at baseline, the utility value assigned to responders at week 24 and carried forward, the cost of professional care, PR fampridine withdrawal rate and the cost of a day off work. Probabilistic sensitivity analysis results were similar to the deterministic base case analysis, reporting an incremental QALY gain of 0.12 for PR fampridine plus BSC compared with BSC alone, and an ICER of 53,060 kronor per QALY gained (€5,209 and $6,202 per QALY gained). Assuming a willingness-to-pay threshold of 500,000 kronor per QALY gained (€49,088 and $58,445 per QALY gained), there was a 96.76% probability of cost-effectiveness at a price of 1,402.85 kronor per pack (i.e. 56 tablets). Alternative scenario analyses assessing the impact of varying the perspective, costs, utility scores and time horizon resulted in ICERs below the threshold. The healthcare payer perspective resulted in the highest ICER: incremental costs 16,051.87 kronor, incremental QALYs 0.12 and ICER 131,303.57[33] kronor per QALY gained. PR fampridine plus BSC dominated BSC alone when resource use costs were increased by 25%. A lifetime horizon produced an ICER of 57,109 kronor per QALY gained, and a 10 year time horizon resulted in an ICER of 77,605 kronor per QALY gained, indicating that PR fampridine remained cost-effective with a shorter time horizon. • One study (Zhao et al 2022) considered the cost-effectiveness of PR fampridine plus BSC versus BSC alone in Chinese adults with MS and walking disability. The analysis was conducted from both the Chinese societal and healthcare perspectives and used a hybrid decision tree and Markov model to estimate costs and health outcomes, measured by QALYs gained. Base case costs included drug costs, healthcare resource utilisation costs, costs of walking aids and productivity loss of caregivers and patients. The base case analysis used a 10 year time horizon and the response rate from the ENHANCE trial. The QALY difference between PR fampridine plus BSC and BSC alone was calculated based on the pooled EQ-5D values of the ENHANCE and MOBILE trials. Over a 10 year time horizon, PR fampridine plus BSC resulted in an incremental QALY gain of 0.15 and lower total costs of -17,329 Chinese Yuan from the healthcare perspective, which dominated BSC alone with an ICER of -113,488 Chinese Yuan/QALY. PR fampridine plus BSC reduced the cost of healthcare resource utilisation, especially the costs of

[33] There was an unexplained discrepancy in the ICER reported in the text (400,936 kronor/QALY) and table (131,303.57 kronor/QALY).

Copyright © NHS England 2024

Outcome	Evidence statement
	rehabilitation and other supportive drugs. From the societal perspective, PR fampridine plus BSC resulted in reduced total costs of -36,465 Chinse Yuan and dominated BSC alone with an ICER of -238,806 Chinese Yuan/QALY. Zhao et al (2022) also conducted one-way sensitivity analysis in adults with MS and walking disability, which demonstrated consistent results with the base case analysis. The cost-effectiveness results were most sensitive to the cost of rehabilitation and the utility value assigned to the BSC alone group at week 24 and later. Probabilistic sensitivity analysis found that at a WTP threshold of 80,976 Chinese Yuan/QALY, the probability of PR fampridine plus BSC being cost-effective was 100% in patients with MS and walking disability. Alternative scenario analyses exploring the impact of a longer time horizon and different sources of utility values showed that PR fampridine plus BSC dominated BSC alone for all scenarios. When the utilities at different time points were obtained from the MOBILE trial, PR fampridine plus BSC resulted in greater incremental QALY gain (0.39 QALY) compared to the base case analysis (0.15 QALY).
Abbreviations BSC: best supportive care; EDSS: expanded disability scale score; EQ-5D: EuroQol-5 dimensions; ICER: incremental cost-effectiveness ratio; MS: multiple sclerosis; PR: prolonged release; QALY: quality adjusted life years; WTP: willingness-to-pay.	

From the evidence selected, are there any subgroups of patients that may benefit from PR fampridine more than the wider population of interest?

Subgroups	Evidence statement
Walking ability by EDSS score ≤6.0 vs >6.0	One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022) reported subgroup results in patients with MS and walking impairment) by baseline EDSS score ≤6.0 versus >6.0 for the critical outcome walking ability. Improvement in walking ability was defined as a mean MSWS-12 score improvement of ≥8 points over 24 weeks.[34] **Critical Outcomes** **Walking ability** • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022; n=765) reported that there was *no statistically significant* difference in treatment effects for PR fampridine versus placebo on the proportion of patients with MS achieving mean MSWS-12 score improvement of ≥8 points over 24 weeks, by baseline EDSS score of ≤6.0 (47% versus 34%, respectively: OR 1.75 [95% CI: 1.25 to 2.45]) versus baseline EDSS score of >6.0 (31% versus 26%, respectively: OR 1.26 [95% CI: 0.67 to 2.39]): p=0.3766. **One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs reported that there was *no statistically significant* difference in the proportion of patients achieving an MSWS-12 score improvement of ≥8 points over 24 weeks between patients with MS with a baseline EDSS score of ≤6.0 versus >6.0 who were treated with PR fampridine vs placebo. An improvement in the MSWS-12 score of ≥8 is considered to be the MCID.**
Limb mobility/dexterity by EDSS score ≤6.0 vs 6.5 and 7.0	The individual ENHANCE RCT (Hobart et al 2019) reported subgroup results in patients with MS and walking impairment by baseline EDSS score ≤6.0 versus 6.5 and 7.0 for the important outcome limb mobility/dexterity (defined as ABILHAND score).[35] **Important Outcomes** **Limb mobility/dexterity** • The ENHANCE RCT (Hobart et al 2019; ITT n=636; mITT m=633) reported subgroup analysis of ABILHAND by baseline EDSS score ≤6.0 versus 6.5 and

[34] The proportion of patients with MS with a mean improvement in MSWS-12 score exceeding the predetermined threshold (⩾8 points) from baseline over 24 weeks (i.e. people with MS who met the definition of PR-fampridine responders for this analysis).
[35] ABILHAND measures manual ability to manage daily activities among chronic stroke patients. Patients estimate the ease or difficulty of performing each upper limb activity using a 3-level response scale: impossible (0), difficult (1), and easy (2). A higher ABILHAND score represents better manual ability.

Copyright © NHS England 2024

Subgroups	Evidence statement
	7.0 in patients with MS and treated with PR fampridine versus placebo. The authors stated that *"while the differences between the PR-fampridine and placebo groups were not statistically significant, there were small numerical improvements that were larger in the more disabled participants"* [although formal significance testing was not undertaken for subgroup analyses]. EDSS score ≤6.0 difference in LSM change from baseline for PR fampridine versus placebo: 0.10 (95% CI: − 1.04 to 1.24) and EDSS score 6.5 and 7.0 difference in LSM change from baseline for PR fampridine versus placebo: 3.05 (95% CI: -0.09 to 6.19). **The ENHANCE RCT reported that there was *no statistically significant* difference on the ABILHAND score in patients with MS and baseline EDSS score of ≤6.0 versus 6.5 and 7.0 who were treated with PR fampridine versus placebo [although formal significance testing was not undertaken for subgroup analyses].**
Abbreviations CI: confidence interval; EDSS: expanded disability scale score; LSM: least square means; mITT: modified intention-to-treat; MS: multiple sclerosis; MSWS-12: multiple sclerosis walking scale-12; OR: odds ratio; PR: prolonged release; RCT: randomised controlled trial.	

From the evidence selected, what doses, frequency and route of administration of PR fampridine treatment were used and what was the duration of treatment?

Outcome	Evidence statement
PR fampridine regimen	Evidence about PR fampridine regimens was reported in one *post hoc* analysis of the ENHANCE and MOBILE RCTs, three RCTs (reported in four papers) and three prospective case series. • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022) and the individual ENHANCE and MOBILE RCTs (reported in three papers: Gasperini et al 2016, Hobart et al 2019, Hupperts et al 2016) administered PR fampridine 10 mg tablets twice daily to patients with MS and walking impairment over a 24-week treatment period. • One RCT (Jensen et al 2016) administered SR fampridine 10 mg tablets twice daily to SR fampridine naïve patients with MS and walking impairment over a period of 26 to 28 days. Treatment responders then underwent a one week washout period before recommencing treatment with fampridine for four weeks. • One prospective case series (Alvarez-Payero et al 2017) administered fampridine 10 mg twice daily for the first time to patients with MS and walking impairment. The duration of treatment was not explicitly stated but patients were followed up for six months. • One prospective case series (Fragoso et al 2016) administered fampridine 10 mg twice a day to patients with MS and gait dysfunction. This study reported a median duration of treatment with fampridine of nine months (range one to 30 months). • One prospective case series (Marzal-Alfaro et al 2018) reported that patients with MS and walking impairment initially received fampridine 10 mg twice daily for 14 days, at which point patients who responded to treatment were selected and continued treatment up to six months. **One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs, three RCTs (including ENHANCE and MOBILE) (four papers) and three prospective case series administered adults with MS and walking impairment with PR fampridine 10 mg twice daily. Treatment durations varied across the different studies, with most ranging between four weeks and six months, and one prospective case series reporting a median treatment duration of nine months.**
Abbreviations	

Copyright © NHS England 2024

Outcome	Evidence statement
MS: multiple sclerosis; MSWS-12: multiple sclerosis walking scale-12; PR: prolonged release; RCT: randomised controlled trial; SR: slow release; T25FW: timed 25 foot walk.	

From the evidence selected, what definition of treatment responder was used, how was responder status measured, and at what time point after initiating treatment was this assessed?

Outcome	Evidence statement
Treatment responders	Evidence about definitions for patients with MS and walking impairment who responded to treatment with PR fampridine (i.e. treatment responders) was reported in one *post hoc* analysis of the ENHANCE and MOBILE RCTs, three RCTs including the ENHANCE and MOBILE RCTs (reported in four papers) and three prospective case series. • One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022) and the individual ENHANCE and MOBILE RCTs (reported in three papers: Gasperini et al 2016, Hobart et al 2019, Hupperts et al 2016) defined treatment responders as patients with MS and walking impairment who achieved mean improvement in MSWS-12 score of ≥ 8 points from baseline over 24 weeks after treatment with PR fampridine. • One RCT (Jensen et al 2016) categorised treatment responders as patients with MS and walking impairment (the top 40%) who showed the most marked improvements on SSST after treatment with SR fampridine over a period of 26 to 28 days. Treatment responders were identified after 26 to 28 days of treatment, these patients then underwent a one week washout period before recommencing treatment with fampridine for four weeks. • One prospective case series (Alvarez-Payero et al 2017) considered a patient with MS and walking impairment to be a treatment responder when they achieved a decrease in time of at least 20% in the T25FW and a decrease of ≥4 points on the MSWS-12 score. After each clinical visit (two weeks, and three and six months), only patients who were considered responders continued to receive fampridine. • One prospective case series (Fragoso et al 2016) defined efficacy (i.e. responders to treatment with fampridine) as patients achieving ≥20% speed improvement in the T25FW test (measured in seconds) after one month of treatment. • One prospective case series (Marzal-Alfaro et al 2018) defined treatment responders as patients who did not experience significant adverse events, who reported a favourable response to fampridine, and showed an improvement of at least 20% in T25FW and any improvement in MSWS-12. These patients continued to receive treatment and were assessed at two weeks, and three and six months. **One *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs, the individual ENHANCE and MOBILE RCTs, and three prospective case series defined treatment responders measured using T25FW test (a decrease of at least 20%) and/or the MSWS-12 score, but different thresholds for the MSWS-12 score were used to define treatment responders (improvement in MSWS-12 score of ≥ 8 points, decrease of ≥4 points or any percentage improvement in MSWS-12 score). The third RCT (not included in the integrated analysis) defined treatment responders as patients (the top 40%) showing the greatest improvements on SSST.**
Abbreviations MSWS-12: multiple sclerosis walking scale-12; PR: prolonged release; RCT: randomised controlled trial; SR: slow release; SSST: six spot step test; T25FW: timed 25-foot walk.	

From the evidence selected, what were the standard care practices for walking impairment for patients receiving PR fampridine and those receiving standard care alone?

Copyright © NHS England 2024

<table>
<tr><th>Outcome</th><th>Evidence statement</th></tr>
<tr><td>Standard care practices</td><td>Details about standard care practices for walking impairment in patients receiving PR fampridine and those receiving standard care alone were reported in one post hoc analysis of the ENHANCE and MOBILE RCTs, and three individual RCTs (reported in four papers).
• One post hoc integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022) reported that concomitant physiotherapy and concomitant DMT use were permitted in the two RCTs. Concomitant DMTs included alemtuzumab, fingolimod, dimethyl fumarate, glatiramer acetate, interferon beta-1a, interferon beta-1b, natalizumab, and teriflunomide. No further details were provided.

• The ENHANCE RCT (Hobart et al 2019) reported that patients with MS and walking impairment could receive concomitant use of approved disease-modifying treatments for fatigue or spasticity if the drug and dose remained stable throughout the study; physiotherapy and rehabilitation therapy were also permitted.
<table>
<tr><th>Concomitant therapy</th><th>PR-fampridine (n = 316)</th><th>Placebo (n = 319)</th></tr>
<tr><td>Any concomitant medication</td><td>276 (87)</td><td>287 (90)</td></tr>
<tr><td>Most common concomitant medications[36]</td><td></td><td></td></tr>
<tr><td>Baclofen</td><td>65 (21)</td><td>65 (20)</td></tr>
<tr><td>Colecalciferol</td><td>47 (15)</td><td>48 (15)</td></tr>
<tr><td>Tizanidine</td><td>36 (11)</td><td>37 (12)</td></tr>
<tr><td>Ibuprofen</td><td>33 (10)</td><td>31 (10)</td></tr>
<tr><td>Methylprednisolone</td><td>35 (11)</td><td>29 (9)</td></tr>
<tr><td>Paracetamol</td><td>31 (10)</td><td>30 (9)</td></tr>
<tr><td>Any concomitant non-drug therapy[37]</td><td>43 (14)</td><td>51 (16)</td></tr>
<tr><td>Most common concomitant non-drug therapies[4]</td><td></td><td></td></tr>
<tr><td>Physiotherapy</td><td>16 (5)</td><td>19 (6)</td></tr>
<tr><td>Bladder catheterisation</td><td>0</td><td>9 (3)</td></tr>
<tr><td>Rehabilitation therapy</td><td>3 (< 1)</td><td>5 (2)</td></tr>
</table>
• The MOBILE RCT (Gasperini et al 2016; Hupperts et al 2016) reported that patients with MS and walking impairment could receive the most stable concomitant treatments for MS, but no details were provided on standard care practices for walking impairment for patients receiving PR fampridine and those receiving standard care alone.

• One RCT (Jensen et al 2016) did not specifically state standard care practices for walking impairment for patients receiving PR fampridine and those receiving standard care alone. The only details provided were that patients receiving concomitant treatment with carvedilol, propranolol, or metformin were not eligible for inclusion in the study.

The ENHANCE RCT provided details on concomitant medications and non-drug treatments for patients receiving PR fampridine versus placebo. One post hoc integrated analysis of the ENHANCE and MOBILE RCTs and two RCTs (reported in three papers) provided limited information about standard care practices for walking impairment in patients receiving PR fampridine and those receiving standard care alone.</td></tr>
<tr><td colspan="2">Abbreviations
DMT: disease-modifying therapy; MS: multiple sclerosis; PR: prolonged release; RCT: randomised controlled trial.</td></tr>
</table>

[36] Medication used in ≥ 10% of patients in either treatment group.
[37] Therapy received in ≥ 2% of patients in either treatment group.

Copyright © NHS England 2024

6. Discussion

This review examined the clinical effectiveness, safety and cost-effectiveness of prolonged release (PR) fampridine compared to standard care alone or standard care and placebo in adults with multiple sclerosis (MS) and walking impairment (as defined by Expanded Disability Status Score [EDSS] 4 to 7.5). The critical outcomes of interest were walking ability, physical impact of MS, and health related quality of life (HRQoL). The important outcomes of interest were limb mobility/dexterity, activities of daily living (ADLs), proportion of treatment responders, and safety.

Evidence for the clinical effectiveness of PR fampridine and safety was available from one *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs (Hupperts et al 2022), three individual RCTs reported in four papers (Gasperini et al 2016, Hobart et al 2019, Hupperts et al 2016, Jensen et al 2016), and three prospective case series (Alvarez-Payero et al 2017, Fragoso et al 2016, Marzal-Alfaro et al 2018). Two of the individual RCTs (Hobart et al 2019 [ENHANCE], Hupperts et al 2016 [MOBILE]) were included in the *post hoc* integrated analysis but were also included separately in this evidence review as they provided additional outcome data not reported in the integrated analysis. Where outcomes were reported in higher level evidence (for example, the integrated analysis of two RCTs) they were not also reported from studies of lower level evidence (for example, the individual RCTs). The *post hoc* integrated analysis (Hupperts et al 2022) and the three individual RCTs, reported in four papers (Gasperini et al 2016, Hobart et al 2019, Hupperts et al 2016, Jensen et al 2016) provided comparative evidence (PR fampridine versus placebo) for critical outcomes (walking ability, physical impact of MS, HRQoL) and important outcomes (limb mobility/dexterity, proportion of treatment responders) and safety. The three prospective case series (Alvarez-Payero et al 2017, Fragoso et al 2016, Marzal-Alfaro et al 2018) provided non-comparative evidence for one important outcome (activities of daily living [ADLs]) for which no evidence was identified from comparative studies. As higher level evidence from comparative studies was identified for the other outcomes stated in the PICO document, only findings relating to ADLs reported by the case series are presented in this evidence review.

The *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs, three individual RCTs (reported in four papers) and three prospective case series included in this evidence review were all undertaken in adults (sample sizes ranged from 30 to 765 patients). One individual study each was conducted in Brazil, China, Southern Denmark or Sweden, and two RCTs (reported in four papers) were conducted in multiple countries (including Belgium, Canada, Italy, The Netherlands, Sweden and the UK in the MOBILE RCT and not specified in the ENHANCE RCT). Where reported, the included study populations were in patients with different types of MS (primary progressive, progressive-relapsing, relapsing-remitting, and secondary progressive MS), and proportions for each type varied across and within the included studies. Furthermore, the populations included patients with EDSS scores ranging from 4.0 to 7.0,[38] which reflects different walking ability and support requirements (e.g. EDSS 4. 0 to 5.5 [able to walk/no support], 6.0 [unilateral support], and 6.5 to 7.0 [bilateral support]). The proportion of patients in each EDSS level was not always reported which means that it is unclear whether some studies may have included a greater proportion of patients with higher levels of disability. Follow-up assessments were performed at four weeks in one RCT, up to 24 weeks in the ENHANCE and

[38] The EDSS score is a rating scale that assesses the degree of neurological disability taking into account eight functional systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and other) in MS patients. The scale ranges from 0 (normal) to 10 (death due to MS). EDSS values between 4.0 and 7.0 reflect a growing negative impact on the walking ability.

Copyright © NHS England 2024

MOBILE RCTs (reported in three papers and the *post hoc* integrated analysis), and at one and six months in the three prospective case series.

The included studies administered PR fampridine 10 mg twice daily, but treatment durations varied across the different studies, with most ranging between four weeks and six months, and one prospective case series reporting a median treatment duration of nine months. The included studies did not provide specific details on standard care practices for walking impairment in patients receiving PR fampridine and those receiving standard care alone. The ENHANCE RCT provided details on concomitant use of approved disease-modifying treatments (DMTs) for fatigue or spasticity and use of physiotherapy and rehabilitation therapy. This was generally similar in the PR fampridine and placebo treatment groups: any concomitant medication (87% versus 90%, respectively) and any concomitant non-drug therapy (14% versus 16%, respectively). One RCT reported that patients receiving concomitant treatment with carvedilol, propranolol, or metformin were not eligible for inclusion in the study, but no further details were provided. The remaining studies reported that concomitant physiotherapy and/or DMTs were permitted, but did not provide any further details.

Treatment responders were defined differently across the included studies: one *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs, the individual ENHANCE and MOBILE RCTs (three papers) and three prospective case series measured responders using T25FW test (a decrease of at least 20%) and/or the MSWS-12 score, but different thresholds for the MSWS-12 score were used to define treatment responders (improvement in MSWS-12 score of ≥ 8 points, decrease of ≥4 points or any percentage improvement in MSWS-12 score. Although the T25FW test is an objective measure, the MSWS-12 score is a subjective measure. Inherent problems (such as stability and interpretability) are associated with self-reported measures, and this was acknowledged in the *post hoc* integrated analysis of the ENHANCE and MOBILE RCTs and the individual ENHANCE and MOBILE RCTs: *"the definition of a responder in both studies was based on a magnitude of change in a self-reported measure with response options that are subject to individual interpretation."* The authors also acknowledged that one of the biases of responder analyses is that patients with MS and walking impairment who respond on one measure are more likely to show a positive response on other outcome measures, which may introduce bias. One RCT (Jensen et al 2016) defined responders as patients (the top 40%) showing the greatest improvements on the Six Spot Step Test (SSST), but the authors acknowledged that this criterion had not been validated.

The individual ENHANCE and MOBILE RCTs were similar in design and baseline demographics (age, sex, and body mass index) and clinical characteristics were generally comparable between the treatment groups, with the exception that the MOBILE RCT included more patients with secondary-progressive MS and the ENHANCE RCT included more patients with relapsing-remitting MS. Although formal statistical tests for heterogeneity (e.g. I^2 test) were not conducted in the *post hoc* integrated analysis (Hupperts et al 2022), subgroup analyses were performed to determine whether treatment effects in treatment responders (i.e. patients with mean MSWS-12 score improvement of ≥8 points over 24 weeks) were heterogeneous across subgroups (stratified by demographic and clinical characteristics at baseline). The authors indicated that there was no heterogeneity of effect of PR fampridine across the different subgroups. The only subgroup of interest, as stated in the PICO, was EDSS score ≤6.0 versus >6.0 and only findings for these subgroups are reported in this evidence review. The increased sample size (n=765) in the *post hoc* integrated analysis provided greater power in terms of evaluating treatment differences between PR fampridine and placebo. The integrated data were analysed using appropriate methods to adjust for covariates and imputation for missing data. Sensitivity analyses were also conducted (an analysis without adjustments and one using observed data only) to assess the impact of adjusting for covariates or imputing data on the findings. Findings from the sensitivity analyses were similar to the pre-specified analyses, which

Copyright © NHS England 2024

the authors reported indicated that the data were not imbalanced and data imputation did not influence the findings. The authors acknowledged that because the EQ-5D measure is not specific to MS, it may not appropriately capture all changes in quality of life in patients with MS who are treated with PR fampridine. In addition, the authors acknowledged that the EQ-5D-3L may not be sufficiently sensitive to measure the impact of walking changes in patients with MS and walking impairments treated with PR fampridine. The impact of these limitations on the findings remains unclear. The *post hoc* integrated analysis (Hupperts et al 2022) reported that improvements in outcomes were consistently greater with PR fampridine versus placebo, although the differences were not always statistically significant.

Responder analysis was also conducted in the *post hoc* integrated analysis (Hupperts et al 2022) and one RCT (Gasperini et al 2016). The *post hoc* integrated analysis assessed outcomes in patients with MS who would remain on PR fampridine over the longer term in real-world clinical practice. Patients with MS who met the criteria of a PR fampridine MSWS-12 responder (defined as patients achieving a mean improvement of ≥8 points in MSWS-12 score from baseline over 24 weeks) were compared to MSWS-12 non-responders and patients receiving placebo. Greater improvements were reported for all outcomes (MSWS-12 score, TUG speed, BBS score, MSIS-29 PHYS score, EQ-5D utility and VAS scores) in PR fampridine MSWS-12 responders compared to non-responders and placebo treated patients over 24 weeks. Statistically significant greater improvements were reported in PR fampridine MSWS-12 responders compared to non-responders ($p<0.001$) and compared to placebo treatment patients ($p<0.001$) for the proportion of patients achieving ≥15% mean improvement in TUG speed. Statistical measures were not reported for the remaining outcomes, but as the 95% confidence intervals for the differences between the groups (i.e. PR fampridine responders versus non-responders and versus placebo treated patients) did not cross zero, statistically significant differences are indicated in favour of PR fampridine responders. The RCT (Gasperini et al 2016) also reported greater improvements in PR fampridine MSWS-12 improvers compared to non-improvers and compared to placebo treated patients in MSIS-29 PSYCH scores over 24 weeks, but no statistical measures were reported. Responder analysis should be interpreted with caution as this type of analysis does not reveal the underlying factors involved in the reasons why some patients respond to treatment and others do not. Responders were identified over 24 weeks of treatment; hence the definition of responders did not allow the responder group to be defined ahead of treatment.

Both the ENHANCE and MOBILE RCTs indicated that PR fampridine was well tolerated, but the duration of follow-up was insufficient to enable conclusions to be drawn on the longer-term effectiveness and safety in patients with MS. Furthermore both RCTs highlighted that when patients discontinued treatment with PR fampridine therapy after the trial duration (24 weeks), any improvements in outcome measures (MSWS-12, TUG speed, and BBS score) disappeared and patients approached pre-treatment levels within two weeks (i.e. at 26 weeks follow-up). .

One RCT (Jensen et al 2016) included a small number of patients and was underpowered, which limits the ability to draw accurate conclusions about the findings. This RCT included an open label enrichment phase whereby patients received slow release (SR) fampridine for 26 to 28 days; only patients considered to be responders to treatment (i.e. patients [the top 40%] showing the greatest improvements on the Six Spot Step Test [SSST]) were included in the randomised controlled trial (RCT). The main uncertainty relates to the very serious selection bias due to the inclusion of only patients who responded to SR fampridine in the RCT and the impact this may have on the reliability of the conclusions. Although the study population did not clearly match the PICO eligibility criteria, the evidence was included in this review but downgraded due to very serious indirectness.

Copyright © NHS England 2024

The three prospective case series (Alvarez-Payero et al 2017, Fragoso et al 2016, Marzal-Alfaro et al 2018) provided non-comparative evidence relating to ADLs in patients with MS and walking impairment. One of these case series (Alvarez-Payero 2017) reported EDSS scores in responders (defined as a decrease in time of at least 20% in the T25FW and a decrease of ≥4 points on the MSWS-12 score) who completed six months of treatment with fampridine (n=25). This case series did not report EDSS scores for non-responders (n=5), which suggests reporting bias may have been introduced. Alvarez-Payero (2017) also reported that eight of 55 patients who had been classified as treatment responders at two weeks follow-up, were then considered non-responders at three and six months follow-up. The main limitation of the three prospective case series was the lack of a comparator group to enable a comparison in outcomes between patients who did and did not receive fampridine. Additional limitations for the three prospective case series included the small sample sizes, which limits the potential to generalise the findings to the wider population of interest, and the duration of follow-up, which was acknowledged by the authors to be insufficient to draw conclusions on longer-term effectiveness and safety in patients with MS.

The certainty in the clinical effectiveness evidence was very low to moderate for one critical outcome (walking ability), low to moderate for two critical outcomes (HRQoL and physical impact of MS). The certainty in the evidence was very low to moderate for one important outcome (limb mobility/dexterity), very low for one important outcome (ADLs), moderate for the important outcome, proportion of treatment responders, and low for safety. Factors reducing confidence in the outcomes reported include the very serious limitations in the *post hoc* integrated analysis as it did not follow standard systematic review methods and procedures, although the certainty of the evidence was only partially downgraded because the searches for this evidence review did not identify any other RCTs that met the PICO eligibility criteria and our own risk of bias assessment/critical appraisal of the two RCTs found serious (but not very serious) risk of bias due to unclear methods used to assess reliability of the outcomes reported in the integrated *post hoc* analysis. Additional factors reducing the confidence in the outcomes include the very serious risk of bias in one RCT and two prospective case series (due to, for example, potential selection bias, unclear study methods and incomplete outcome reporting) and serious indirectness due to one RCT including only patients who had previously responded to treatment with SR fampridine, and the lack of a comparator in the three prospective case series. Further limitations include the small numbers of patients included in some of the studies and serious or very serious risk of bias for all included studies due to, for example, unclear study methods, potential selection bias, and the number of patients lost to follow-up or discontinuing treatment. All the studies included in this evidence review reported outcomes in terms of clinical relevance, measured using different methods and thresholds and the duration of follow-up was insufficient to enable conclusions to be drawn on the longer-term effectiveness and safety in patients with MS and walking impairment.

Evidence for the cost-effectiveness of PR fampridine for the treatment of walking impairment in adults with MS was available from two studies (Acosta et al 2021, Zhao et al 2022). The cost-effectiveness studies used effectiveness, costs, utilities and adverse event data, clinical trials of PR fampridine (including the ENHANCE and MOBILE RCTs), published sources and clinical expert interviews to develop models, which were used to calculate the costs and QALYs gained for PR fampridine plus best supportive care (BSC) compared to BSC alone. The cost-effectiveness studies varied in terms of the perspectives (whether from a Swedish or Chinese healthcare or societal perspective) and time horizons (whether for 10 years, 20 years, or over a lifetime). Both studies used an appropriate model to calculate costs and health outcomes and tested assumptions using one-way and probabilistic sensitivity analysis. The results are unlikely to be generalisable to current patients in England, as costs in the two studies are based on those in Sweden and China and the willingness-to-pay (WTP) thresholds used in the studies

Copyright © NHS England 2024

differ from those used by the National Institute of Health and Care Excellence (NICE) in England.

Copyright © NHS England 2024

7. Conclusion

The very low to moderate certainty evidence from the four comparative clinical effectiveness studies included in this review suggests that, overall, PR fampridine in adults with MS and walking impairment improves self-perceived physical and psychological impacts of MS compared to placebo, although the differences between treatment groups were not always statistically significant. Both the ENHANCE and MOBILE RCTs indicated that PR fampridine was well tolerated, but when patients discontinued treatment with PR fampridine therapy after the trial duration, any improvements in outcome measures disappeared and patients approached pre-treatment levels within two weeks. Comparative evidence on one important outcome (ADLs) was not available and was therefore provided by three non-comparative prospective case series. The findings from the three case series were mixed, with two studies reporting no differences in ADLs pre- and post-treatment with PR fampridine, and one study reporting a statistically significant improvement, but this was only reported in treatment responders. Although the increased sample size in the *post hoc* integrated analysis provided greater power in terms of evaluating treatment differences between PR fampridine and placebo, the limitations of some of the included studies reduce the confidence in the findings. Limitations include the very serious indirectness for one RCT due to its including only patients who had previously responded to treatment with SR fampridine, and the lack of a comparator in the three prospective case series. Further limitations include the small numbers of patients included in some of the studies and the serious or very serious risk of bias for all included studies associated with, for example, unclear study methods (or not following standard systematic review methods and procedures in the *post hoc* integrated analysis), potential selection bias, and the number of patients lost to follow-up or discontinuing treatment.

Evidence for the cost-effectiveness of PR fampridine for the treatment of walking impairment in adults with MS was available from two studies. The cost-effectiveness studies varied in terms of the perspectives (whether from a Swedish or Chinese healthcare or societal perspective) and time horizons (whether for 10 years, 20 years, or over a lifetime). The results are unlikely to be generalisable to current patients in England, as costs in the two studies are based on those in Sweden and China and the willingness-to-pay (WTP) thresholds used in the studies differ from those used by the National Institute of Health and Care Excellence (NICE) in England.

Copyright © NHS England 2024

Appendix A PICO document

The review questions for this evidence review are:

1. In people with MS associated walking impairment (EDSS 4 to 7.5), what is the clinical effectiveness of PR fampridine compared with standard care alone or standard care and placebo?
2. In people with MS associated walking impairment (EDSS 4 to 7.5), what is the safety of PR fampridine compared with standard care alone or standard care and placebo?
3. In people with MS associated walking impairment (EDSS 4 to 7.5), what is the cost-effectiveness of PR fampridine compared with standard care alone or standard care and placebo?
4. From the evidence selected, are there any subgroups of patients that may benefit from PR fampridine more than the wider population of interest?
5. From the evidence selected, what doses, frequency and route of administration of PR fampridine treatment were used and what was the duration of treatment?
6. From the evidence selected, what definition of treatment responder was used, how was responder status measured, and at what time point after initiating treatment was this assessed?
7. From the evidence selected what were the standard care practices for walking impairment for patients receiving PR fampridine and those receiving standard care alone?

P – Population and Indication	Patients of all ages with: - Diagnosis of Multiple Sclerosis (MS) (any subtype) AND - MS associated walking impairment as defined by Expanded Disability Status Score (EDSS) score of 4-7.5 Subgroups: EDSS <6 vs ≥6
I – Intervention	Prolonged release (PR) fampridine in addition to standard care. [PR fampridine is generally prescribed as oral, 10 mg twice a day or 10mg once a day for impaired renal function, however all doses and formulations should be included.] [The following term may be used interchangeably with PR fampridine: dalfampridine] [Standard care includes standard care for both the MS and the walking impairment. MS standard care includes, but is not limited to, approved disease-modifying therapies, medications for fatigue or spasticity. Standard care for walking impairment may constitute any therapy that could potentially impact or assist with walking impairment, including but not limited to any of: walking aids, exercise regimes, physiotherapy and/or spasticity treatments. Any of these measures may together be regarded as best supportive care. Standard care for walking impairment may vary according to mobility at baseline]
C – Comparator(s)	- Standard care alone - Standard care plus placebo
O – Outcomes	**Clinical Effectiveness**

Copyright © NHS England 2024

	Unless stated for the outcome, minimally clinically important differences (MCIDs) are unknown. Outcomes ideally measured at 2-4 weeks and 16-24 weeks as well as long-term outcomes. *Critical to decision making* • **Walking ability** *This outcome is important to patients because walking impairment reduces independence and negatively impacts health-related quality of life, productivity, and daily activities.* [Measures of walking ability may be subjective (patient-assessed or self-reported) or objective (clinician-assessed). They may be linked to walking speed, stamina, gait or overall function. Measures include the 12-item multiple sclerosis walking scale (12MSWS), timed walk tests e.g., 10- or 25-foot walk (T25FW). The MCID for mean improvement in 12MSWS is ≥ 8 points. The MCID for improvement in T25FW from baseline is estimated to be 20%.] • **Physical impact of MS** *This outcome is important to patients as it measures functional mobility, and links to enablement, independence and active participation* [For example, as measured by timed up and go test (TUG test speed/time), Multiple Sclerosis Impact Scale physical impact subscale (MSIS-29 PHYS). The MCID for TUG test is ≥ 15% improvement from baseline.] • **Health related quality of life (HRQL)** *This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment* [Other terms used to describe or indicate quality of life include but are not limited to; patient-reported quality of life outcomes, health related quality of life. Examples of metrics to assess quality of life include but are not limited to: Short Form (SF-36), Multiple Sclerosis Quality of Life-54 (MSQOL-54), Multiple Sclerosis Impact Scale (MSIS-29). Other methods of assessing quality of life include but are not limited to subjective/self-reported/carer reported quality of life experiences.] *Important to decision-making:* • **Limb mobility/dexterity** *This outcome is important to patients because a reduction in upper and lower limb mobility and dexterity, which is associated with MS, reduces independence and negatively impacts health-related quality of life, productivity, and daily activities.* [Examples of relevant measures include the lower extremity manual muscle test (LEMMT). Limb mobility/dexterity includes manual ability e.g. as assessed by 56-item ABILHAND, the 9 hole PEG test] • **Activities of daily living** *This outcome is important to patients because it reflects daily functioning and how well people can engage in education, employment and recreational activities.*

Copyright © NHS England 2024

	• **Proportion of treatment responders** *This outcome enables relevant information sharing with patients in terms of risks and benefits of starting treatment.* **<u>Safety</u>** • **Complications of fampridine therapy** *Safety is important to patients as it reflects the risks involved and allows a risk benefit assessment to be undertaken* [Other terms used to describe or indicate safety include, but are not limited to; adverse events, serious/ major adverse events. Examples may include but are not limited to; hypersensitivity, anaphylaxis, and anaphylactoid events, adverse events leading to drug discontinuation, seizures, headaches, falls, fractures, confusion, urinary tract infections] **<u>Cost-effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2009 – 2023 Date limits have been extended to capture the initial reports of the key trials.
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, preprints and guidelines
Study design	Case reports, resource utilisation studies

Copyright © NHS England 2024

Appendix B Search strategy

Medline, Embase, the Cochrane Library and TRIP database were searched limiting the search to papers published in English language in the last 14 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, guidelines, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2009 to 24 November 2023

Medline search strategy

1	exp Multiple Sclerosis/dt [Drug Therapy]
2	exp Multiple Sclerosis/
3	(multiple sclerosis or ms).ti,ab,kf.
4	2 or 3
5	walking/ or dependent ambulation/ or exp gait/ or stair climbing/
6	mobility limitation/
7	(walk* or mobile or mobility or gait or ambulat* or ((motor or physical*) adj funtion?)).ti,ab,kf.
8	(expanded disability status scale or edss or msws).ti,ab,kf.
9	5 or 6 or 7 or 8
10	4 and 9
11	1 or 10
12	exp 4-Aminopyridine/
13	Potassium Channel Blockers/tu [Therapeutic Use]
14	(4-Aminopyridine or 4Aminopyridine or fampridine or dalfampridine or ampyra or fampyra).ti,ab,kf.
15	potassium channel blocker?.ti.
16	12 or 13 or 14 or 15
17	11 and 16
18	exp animals/ not humans/
19	17 not 18
20	limit 19 to (meta analysis or "systematic review")
21	(comment or editorial or letter or news or review).pt. or case report.ti.
22	19 not 21
23	20 or 22
24	limit 23 to (english language and yr="2009 -Current")

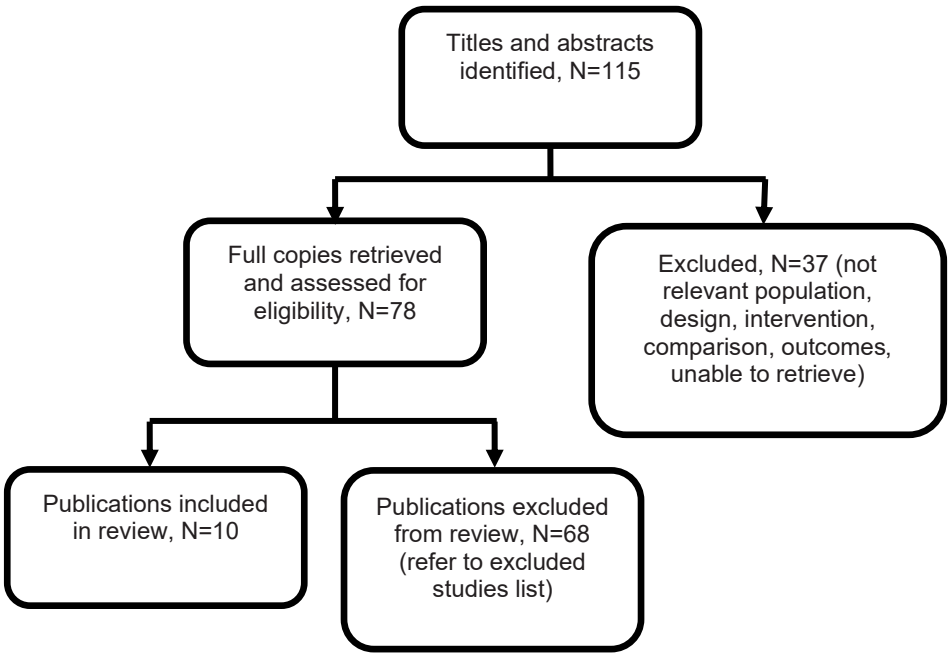
Copyright © NHS England 2024

Copyright © NHS England 2024

Appendix C Evidence selection

The literature searches identified 115 references. These were screened using their titles and abstracts and 78 references were obtained in full text and assessed for relevance. Of these, 10 references are included in the evidence summary. The remaining 68 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Hobart J, Ziemssen T, Feys P, Linnebank M, Goodman AD, Farrell R, Hupperts R, Blight AR, Englishby V, McNeill M, Chang I, Lima G, Elkins J; ENHANCE study investigators. Assessment of Clinically Meaningful Improvements in Self-Reported Walking Ability in Participants with Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III ENHANCE Trial of Prolonged-Release Fampridine. CNS Drugs. 2019 Jan;33(1):61-79. doi: 10.1007/s40263-018-0586-5.	Include
Hupperts R, Gasperini C, Lycke J, Ziemssen T, Feys P, Xiao S, Acosta C, Koster T, Hobart J. Efficacy of prolonged-release fampridine versus placebo on walking ability, dynamic and static balance, physical impact of multiple sclerosis, and quality of life: an integrated analysis of MOBILE and ENHANCE. Ther Adv Neurol Disord. 2022 May 18;15:17562864221090398. doi: 10.1177/17562864221090398.	Include
Goodman AD, Bethoux F, Brown TR, Schapiro RT, Cohen R, Marinucci LN, Henney HR 3rd, Blight AR; MS-F203, MS-F204, and Extension Study Investigators. Long-term safety and efficacy of dalfampridine for walking impairment in patients with multiple sclerosis: Results of open-label extensions of two Phase 3 clinical trials. Mult Scler. 2015 Sep;21(10):1322-31. doi: 10.1177/1352458514563591. Epub 2015 Jan 12.	Exclude Results from open-label extensions of two Phase 3 clinical trials. Original publications for both extension studies (Goodman 2009, Goodman 2010) excluded due to out of scope population (EDSS score 1.5 to 7 not 4 to 7.5).

Copyright © NHS England 2024

Appendix D Excluded studies table

Study reference	Reason for exclusion
Ahdab R, Shatila MM, Shatila AR, Khazen G, Freiha J, Salem M, et al. Cortical Excitability Measures May Predict Clinical Response to Fampridine in Patients with Multiple Sclerosis and Gait Impairment. Brain Sciences. 2019;9(12):05.	Non-comparative study. Population out of scope and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Allart E, Benoit A, Blanchard-Dauphin A, Tiffreau V, Thevenon A, Zephir H, et al. Sustained-released fampridine in multiple sclerosis: effects on gait parameters, arm function, fatigue, and quality of life. Journal of Neurology. 2015;262(8):1936-45.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Amini Harandi A, Pakdaman H, Karamiani F, Mohammadi F, Shirzadeh Barough S, Siavoshi F, et al. Fampridine in multiple sclerosis patients with acute phase of cervical transverse myelitis: a double-blind, randomized placebo-controlled trial. Neurological Sciences. 2023;44(1):393-6.	Population out of scope - There was no indication that the study's included population had an EDSS score of between 4 and 7.5 as specified in the PICO framework for this review (the only mention of EDSS score related to an exclusion criterion of EDSS <0.5 before the attack.)
Applebee A, Goodman AD, Mayadev AS, Bethoux F, Goldman MD, Klingler M, et al. Effects of Dalfampridine Extended-release Tablets on 6-minute Walk Distance in Patients With Multiple Sclerosis: A Post Hoc Analysis of a Double-blind, Placebo-controlled Trial. Clinical Therapeutics. 2015;37(12):2780-7.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (mean [SD] EDSS score for patients treated with 10 mg fampridine was 5 [1.4])).
Arreola-Mora C, Silva-Pereyra J, Fernandez T, Paredes-Cruz M, Bertado-Cortes B, Grijalva I. Effects of 4-aminopyridine on attention and executive functions of patients with multiple sclerosis: Randomized, double-blind, placebo-controlled clinical trial. Preliminary report. Multiple Sclerosis and Related Disorders. 2019;28:117-24.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population. (EDSS score range between 3 and 7 for patients in both treatment arms); focus on neuropsychological tests rather than walking ability.
Bakirtzis C, Konstantinopoulou E, Langdon DW, Grigoriadou E, Minti F, Nikolaidis I, et al. Long-term effects of prolonged-release fampridine in cognitive function, fatigue, mood and quality of life of MS patients: The IGNITE study. Journal of the Neurological Sciences. 2018;395:106-12.	Non-comparative study. Unclear population and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Behm K, Morgan P. The effect of symptom-controlling medication on gait outcomes in people with multiple sclerosis: a systematic review. Disability & Rehabilitation. 2018;40(15):1733-44.	Systematic review that included studies with out of scope population in terms of EDSS score and studies that assessed out of scope treatments.
Broicher SD, Filli L, Geisseler O, Germann N, Zorner B, Brugger P, Linnebank M. Positive effects of fampridine on cognition, fatigue and depression in patients with multiple sclerosis over 2 years. Journal of Neurology. 2018;265(5):1016-25.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population. Includes patients with EDSS score range between 3 and 7.
Brown TR, Simnad VI. A Randomized Crossover Trial of Dalfampridine Extended Release for Effect on Ambulatory Activity in People with Multiple Sclerosis. International Journal of Ms Care. 2016;18(4):170-6.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (mean [SE] EDSS score for patients treated with dalfampridine was 5.1 [0.3]; range not reported; inclusion criteria EDSS score 0 to 6.5).
Cameron MH, Fitzpatrick M, Overs S, Murchison C, Manning J, Whitham R. Dalfampridine improves walking speed, walking endurance, and community participation	Non-comparative study. Unclear population and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)

Copyright © NHS England 2024

Study reference	Reason for exclusion
in veterans with multiple sclerosis: a longitudinal cohort study. Multiple Sclerosis. 2014;20(6):733-8.	
Castelnovo G, Gerlach O, Freedman MS, Bergmann A, Sinay V, Castillo-Trivino T, et al. Safety, Patient-Reported Well-Being, and Physician-Reported Assessment of Walking Ability in Patients with Multiple Sclerosis for Prolonged-Release Fampridine Treatment in Routine Clinical Practice: Results of the LIBERATE Study. CNS Drugs. 2021;35(9):1009-22.	Non-comparative study. Population out of scope and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Costa-Arpin E, Pato A, Rodriguez-Regal A, Midaglia L, Yanez R, Munoz D, et al. Clinical response and tolerability of fampridine in clinical practice. Neurodegenerative Disease Management. 2016;6(2):99-105.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Crayton H, Sidovar M, Wulf S, Guo A. Patient perspectives and experience with dalfampridine treatment in multiple sclerosis-related walking impairment: the step together program. The Patient: Patient-Centered Outcomes Research. 2015;8(3):283-91.	Non-comparative study. Unclear population and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
De Giglio L, De Luca F, Gurreri F, Ferrante I, Prosperini L, Borriello G, et al. Effect of dalfampridine on information processing speed impairment in multiple sclerosis. Neurology. 2019;93(8):e733-e46.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (median [range] EDSS scores for patients treated with dalfampridine was 4 [1 to 6]).
Etemadifar M, Saboori M, Chitsaz A, Nouri H, Salari M, Khorvash R, et al. The effect of fampridine on the risk of seizure in patients with multiple sclerosis. Multiple Sclerosis and Related Disorders. 2020;43:102188.	Non-comparative study. Population out of scope and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Filli L, Werner J, Beyer G, Reuter K, Petersen JA, Weller M, et al. Predicting responsiveness to fampridine in gait-impaired patients with multiple sclerosis. European Journal of Neurology. 2019;26(2):281-9.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population. Includes patients with EDSS score 2.5 to 6.5.
Filli L, Zorner B, Kapitza S, Reuter K, Lorincz L, Weller D, et al. Monitoring long-term efficacy of fampridine in gait-impaired patients with multiple sclerosis. Neurology. 2017;88(9):832-41.	Non-comparative study (extension study assessing long-term efficacy of fampridine). Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (mean [SD] EDSS score 5.3 [1.2]).
Fjeldstad C, Suarez G, Klingler M, Henney HR, 3rd, Rabinowicz AL, Pardo G. Dalfampridine Effects Beyond Walking Speed in Multiple Sclerosis. International Journal of Ms Care. 2015;17(6):275-83.	Non-comparative study. Unclear population and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Ghorbanpour S, Rahimibarghani S, Rohani S, Rastkar M, Ghajarzadeh M. Fampridine for gait imbalance in patients with multiple sclerosis (MS): a systematic review and meta-analysis. Neurological Sciences. 2023;44(9):3059-69.	Systematic review that included studies with out of scope population in terms of EDSS score and outcomes not reported separately for studies with in scope populations.
Goodman AD, Bethoux F, Brown TR, Schapiro RT, Cohen R, Marinucci LN, et al. Long-term safety and efficacy of dalfampridine for walking impairment in patients with multiple sclerosis: Results of open-label extensions of two Phase 3 clinical trials. Multiple Sclerosis. 2015;21(10):1322-31.	Reports outcomes for two open label extension studies but both studies include out of scope populations in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population median [range] EDSS score was 6.0 [1.5 to 7] in study 1 and 6.0 [2 to 7] in study 2).

Copyright © NHS England 2024

Study reference	Reason for exclusion
Goodman AD, Brown TR, Edwards KR, Krupp LB, Schapiro RT, Cohen R, et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. Annals of Neurology. 2010;68(4):494-502.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population – (mean [range] EDSS score for patients receiving ER dalfampridine was 5.6 [1.5 to 7]).
Goodman AD, Brown TR, Krupp LB, Schapiro RT, Schwid SR, Cohen R, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet. 2009;373(9665):732-8.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (mean [range] EDSS score in patients receiving SR fampridine was 5.8 [2.5 to 7]).
Hobart J, Blight AR, Goodman A, Lynn F, Putzki N. Timed 25-foot walk: direct evidence that improving 20% or greater is clinically meaningful in MS. Neurology. 2013;80(16):1509-17.	Pooled data from two RCTs that include out of scope populations in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (range (2.5 to 7.0) in one study and (1.5 to 7.0) in the second study).
Jacques F, Schembri A, Nativ A, Paquette C, Kalinowski P. Prolonged-Release Fampridine as Adjunct Therapy to Active Motor Training in MS Patients: A Pilot, Double-Blind, Randomized, Placebo-Controlled Study. Multiple Sclerosis Journal Experimental Translational & Clinical. 2018;4(1):2055217318761168.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (mean [SD] EDSS score in patients receiving PR fampridine was 4.62 [1.05]).
Jensen H, Ravnborg M, Mamoei S, Dalgas U, Stenager E. Changes in cognition, arm function and lower body function after slow-release Fampridine treatment. Multiple Sclerosis. 2014;20(14):1872-80.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Kantor D, Chancellor MB, Snell CW, Henney HR, 3rd, Rabinowicz AL. Assessment of confirmed urinary tract infection in patients treated with dalfampridine for multiple sclerosis. Postgraduate Medicine. 2015;127(2):218-22.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (mean [SD] EDSS score in patients receiving dalfampridine 10 mg was 4.7 [1.5]).
Keune PM, Cocks AJ, Young WR, Burschka JM, Hansen S, Hofstadt-van Oy U, et al. Dynamic walking features and improved walking performance in multiple sclerosis patients treated with fampridine (4-aminopyridine). BMC Neurology. 2015;15:171.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Korsen M, Kunz R, Schminke U, Runge U, Kohlmann T, Dressel A. Dalfampridine effects on cognition, fatigue, and dexterity. Brain and Behavior. 2017;7(1):e00559.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Lecat M, Decavel P, Magnin E, Lucas B, Gremeaux V, Sagawa Y. Multiple Sclerosis and Clinical Gait Analysis before and after Fampridine: A Systematic Review. European Neurology. 2017;78(5-6):272-86.	Systematic review including 17 RCTs and non-RCTs. EDSS score was not always referred to in study inclusion criteria and where it was mentioned it was not always within the range of EDSS scores specified in the PICO framework for this review. Eligible studies have been identified and included in this review.
Lo AC, Ruiz JA, Koenig CM, Anderson BM, Olson KM, Triche EW. Effects of dalfampridine on multi-dimensional aspects of gait and dexterity in multiple sclerosis among timed walk responders and non-responders. Journal of the Neurological Sciences. 2015;356(1-2):77-82.	Non-comparative study. Population out of scope and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)

Copyright © NHS England 2024

Study reference	Reason for exclusion
Macdonell R, Nagels G, Laplaud DA, Pozzilli C, de Jong B, Martins da Silva A, et al. Improved patient-reported health impact of multiple sclerosis: The ENABLE study of PR-fampridine. Multiple Sclerosis. 2016;22(7):944-54.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Magnin E, Sagawa Y, Jr., Chamard L, Berger E, Moulin T, Decavel P. Verbal Fluencies and Fampridine Treatment in Multiple Sclerosis. European Neurology. 2015;74(5-6):243-50.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Mamoei S, Jensen HB, Dalgas U, Zijdewind I, Pedersen AK, Nygaard MKE, et al. A cross-sectional comparison of performance, neurophysiological and MRI outcomes of responders and non-responders to fampridine treatment in multiple sclerosis - An explorative study. Journal of Clinical Neuroscience. 2020;82(Pt A):179-85.	Non-comparative study. Unclear population and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Marion S, Leonid C, Belinda B, Joanne D, Elise H, Leeanne C, Richard M. Effects of modified-release fampridine on upper limb impairment in patients with Multiple Sclerosis. Multiple Sclerosis and Related Disorders. 2020;40:101971.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (EDSS score 0 to 3 [mild] or moderate [3.5 to 5.5]); focus is on upper limb dexterity.
Mejuto B, Castellano P, Castro C, Lopez LM. Assessment of the efficacy and safety of fampridine. Farmacia Hospitalaria. 2017;41(2):283-91.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Mitsikostas DD, Doskas T, Gkatzonis S, Fakas N, Maltezou M, Papadopoulos D, et al. A Prospective, Observational, Cohort Study to Assess the Efficacy and Safety of Prolonged-Release Fampridine in Cognition, Fatigue, Depression, and Quality of Life in Multiple Sclerosis Patients: The FAMILY Study. Advances in Therapy. 2021;38(3):1536-51.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Olmo G, Farolfi F, Miola F, Giorgi S, Sapio AD, Bertolotto A. The reliability of objective fatigue measures in Multiple Sclerosis Patients. Biomedical Signal Processing and Control. 2020;56:101696.	Non-comparative study. Population out of scope and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Pavsic K, Pelicon K, Ledinek AH, Sega S. Short-term impact of fampridine on motor and cognitive functions, mood and quality of life among multiple sclerosis patients. Clinical Neurology & Neurosurgery. 2015;139:35-40.	Non-comparative study. Population out of scope and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Pickering H, Murray J, Lin CS, Cormack C, Martin A, Kiernan MC, Krishnan AV. Fampridine treatment and walking distance in multiple sclerosis: A randomised controlled trial. Clinical Neurophysiology. 2017;128(1):93-9.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population. Of the total cohort, 32% had an EDSS score between 0 and 2, 44% had an EDSS score between 2.5 and 4, and 24% had an EDSS score between 4.5 and 6.
Plummer P, Markovic-Plese S, Giesser B. Dalfampridine for Mobility Limitations in People With Multiple Sclerosis May Be Augmented by Physical Therapy: A Non-randomized Two-Group Proof-of-Concept Pilot Study. Frontiers in Rehabilitation Sciences. 2021;2:795306.	Non-comparative study. Population out of scope and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Plummer P. Critical Appraisal of Evidence for Improving Gait Speed in People with Multiple Sclerosis: Dalfampridine Versus Gait Training. International Journal of Ms Care. 2016;18(3):105-15.	Not a formal systematic review. Includes out of scope studies in terms of population and treatments.

Copyright © NHS England 2024

Study reference	Reason for exclusion
Pozzilli C, Prosperini L, Tommasin S, Gasperini C, Barbuti E, De Giglio L. Dalfampridine improves slowed processing speed in multiple sclerosis patients with mild motor disability: post hoc analysis of a randomized controlled trial. Therapeutic Advances in Neurological Disorders. 2021;14:17562864211011286.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (median [range] EDSS for full responders (n=34) 3 [1.5 to 4.5]; partial responders (n=37) 4 [3 to 5]).
Prosperini L, Castelli L, De Giglio L, Bonanno V, Gasperini C, Pozzilli C. Dalfampridine to Improve Balance in Multiple Sclerosis: Substudy from a Randomized Placebo-Controlled Trial. Neurotherapeutics. 2020;17(2):704-9.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population. Study inclusion criteria for patients able to stand upright without any support and to be still ambulant, scoring <6 on EDSS (range in the study is 1.5 to 5.5).
Prosperini L, Gianni C, Fortuna D, Marchetti MR, Pozzilli C. Oral dalfampridine improves standing balance detected at static posturography in multiple sclerosis. Multiple Sclerosis International. 2014;2014:802307.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Prugger M, Berger T. Assessing the long-term clinical benefit of prolonged-release fampridine tablets in a real-world setting: a review of 67 cases. Patient Related Outcome Measures. 2013;4:75-85.	Non-comparative study. Population out of scope and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Rabadi MH, Kreymborg K, Vincent AS. Sustained-release fampridine (4-aminopyridine) in multiple sclerosis: efficacy and impact on motor function. Drugs in R & D. 2013;13(3):175-81.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Rodriguez-Leal FA, Haase R, Akgun K, Eisele J, Proschmann U, Schultheiss T, et al. Nonwalking response to fampridine in patients with multiple sclerosis in a real-world setting. Therapeutic Advances in Chronic Disease. 2019;10:2040622319835136.	Non-comparative study. Population out of scope and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Rodriguez-Leal FA, Haase R, Thomas K, Eisele JC, Proschmann U, Schultheiss T, et al. Fampridine response in MS patients with gait impairment in a real-world setting: Need for new response criteria? Multiple Sclerosis. 2018;24(10):1337-46.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Ruck T, Bittner S, Simon OJ, Gobel K, Wiendl H, Schilling M, Meuth SG. Long-term effects of dalfampridine in patients with multiple sclerosis. Journal of the Neurological Sciences. 2014;337(1-2):18-24.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Sadeqi Y, Baghbanian SM, Bazi A, Ghazaeian M, Fallah S. The effectiveness of amantadine and dalfampridine in improving fatigue in patients with multiple sclerosis: A randomized, double-blind, clinical trial. Current Journal of Neurology. 2022;21(4):211-6.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (mean EDSS score in patients receiving dalfampridine was 1.14).
Sagawa Y, Jr., Magnin E, Paillot L, Moulin T, Decavel P. Fampridine and quality of life in individuals with multiple sclerosis. Springerplus. 2016;5(1):1070.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Satchidanand N, Drake A, Smerbeck A, Hojnacki D, Kolb C, Patrick K, et al. Dalfampridine benefits ambulation but not cognition in multiple sclerosis. Multiple Sclerosis. 2020;26(1):91-8.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (median [range] EDSS score in patients receiving dalfampridine was 3.5 [1 to 6.5]).

Copyright © NHS England 2024

Study reference	Reason for exclusion
Savin Z, Lejbkowicz I, Glass-Marmor L, Lavi I, Rosenblum S, Miller A. Effect of Fampridine-PR (prolonged released 4-aminopyridine) on the manual functions of patients with Multiple Sclerosis. Journal of the Neurological Sciences. 2016;360:102-9.	Non-comparative study. Unclear population and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Shi J WXCY. Study on Dalfampridine in the treatment of Multiple Sclerosis Mobility Disability: A meta-analysis. PloS one. 2020:e0222288.	Systematic review including 10 RCTs comparing dalfampridine vs placebo. RCTs include out of scope patients in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (EDSS scores 1.5 to 7 or NA).
Skov CD, Sorensen CB, Thorning M, Lambertsen KL, Frich LH, Jensen HB, et al. Evaluation of functional outcome measures after fampridine treatment in patients with multiple sclerosis - An interventional follow-up study. Multiple Sclerosis and Related Disorders. 2022;66:104034.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Stolyarov ID, Petrov AM, Boyko AN. Efficacy and safety of Kinezia (fampridine) in the complex therapy of multiple sclerosis. Zhurnal nevrologii i psikhiatrii imeni SS Korsakova. 2020;120(11):45-52.	Non-English language publication (in Russian)
Thaera GM, Wingerchuk DM, Carter JL. Positive neurologic phenomena with initiation of dalfampridine for multiple sclerosis. Multiple Sclerosis and Related Disorders. 2014;3(1):107-9.	Non-comparative study. Unclear population and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Thorning M, Nielsen HH, Frich LH, Jensen HB, Lambertsen KL, Holsgaard-Larsen A. Gait quality and function after fampridine treatment in patients with multiple sclerosis - A prospective cohort study. Clinical Biomechanics. 2022;100:105826.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Triche EW, Ruiz JA, Olson KM, Lo AC. Changes in Cognitive Processing Speed, Mood, and Fatigue in an Observational Study of Persons With Multiple Sclerosis Treated With Dalfampridine-ER. Clinical Neuropharmacology. 2016;39(2):73-80.	Non-comparative study. Unclear population and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Valet M. Effects of Fampridine in People with Multiple Sclerosis: A Systematic Review and Meta-analysis. CNS drugs. 2020:1087-99.	Systematic review including 20 RCTs comparing PR fampridine vs placebo. Some of the individual studies included patients with EDSS scores ranging from 1 to 7.5. Outcomes not reported separately for eligible studies with EDSS scores 4 to 7.
Valet M, El Sankari S, Van Pesch V, Detrembleur C, Lejeune T, Stoquart G. Effects of prolonged-release fampridine on multiple sclerosis-related gait impairments. A crossover, double-blinded, placebo-controlled study. Clinical Biomechanics. 2021;86:105382.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (baseline EDSS score 4 with an IQR 4 to 5). ADL outcome data reported but not separately for in scope population.
van Munster CEP, Kaya L, Lam KH, Kalkers NF, Killestein J, Uitdehaag BMJ. Responder rates to fampridine differ between clinical subgroups of MS patients and patient reported outcome influences treatment decision making. Multiple Sclerosis and Related Disorders. 2020;38:101489.	Non-comparative study. ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)

Copyright © NHS England 2024

Study reference	Reason for exclusion
Vollmer T, Blight AR, Henney HR, 3rd. Steady-state pharmacokinetics and tolerability of orally administered fampridine sustained-release 10-mg tablets in patients with multiple sclerosis: a 2-week, open-label, follow-up study. Clinical Therapeutics. 2009;31(10):2215-23.	Non-comparative study. Unclear population and ADL outcomes not reported. (Results for all other outcomes of interest were available from comparative studies.)
Weller D, Lorincz L, Sutter T, Reuter K, Linnebank M, Weller M, et al. Fampridine-induced changes in walking kinetics are associated with clinical improvements in patients with multiple sclerosis. Journal of the Neurological Sciences. 2020;416:116978.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population –(total cohort mean [range] EDSS was 4.6 [2.5 to 6.5]).
Yapundich R, Applebee A, Bethoux F, Goldman MD, Hutton GJ, Mass M, et al. Evaluation of Dalfampridine Extended Release 5 and 10 mg in Multiple Sclerosis: A Randomized Controlled Trial. Int J MS Care. 2015;17(3):138-45.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (mean [SD] EDSS score in patients receiving dalfampridine 10 mg was 4.7 [1.5]).
Zhang E, Tian X, Li R, Chen C, Li M, Ma L, et al. Dalfampridine in the treatment of multiple sclerosis: a meta-analysis of randomised controlled trials. Orphanet Journal Of Rare Diseases. 2021;16(1):87.	Systematic review including nine RCTs comparing dalfampridine vs placebo. RCTs include out of scope patients in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population.
Ziemssen T, Prosser C, Haas JS, Lee A, Braun S, Landsman-Blumberg P, et al. Healthcare resource use and costs of multiple sclerosis patients in Germany before and during fampridine treatment. BMC Neurology. 2017;17(1):62.	Unclear population - reports MS-related healthcare costs before and during fampridine treatment but does not state whether population costs are based on a population with an EDSS score between 4 and 7.5.
Zorner B, Filli L, Reuter K, Kapitza S, Lorincz L, Sutter T, et al. Prolonged-release fampridine in multiple sclerosis: Improved ambulation effected by changes in walking pattern. Multiple Sclerosis. 2016;22(11):1463-75.	Population out of scope in terms of EDSS score stated in the PICO framework for this review and outcomes not reported separately for the in scope population (mean [range] EDSS score at baseline was 4.9 [2.5 to 6.5]).

Copyright © NHS England 2024

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Acosta C, Gianinazzi M, Dort T, Armstrong N, Ryder S, Lundqvist T, et al. Modeling the cost-effectiveness of prolonged-release fampridine for the treatment of walking impairment in patients with multiple sclerosis in Sweden. Journal of Medical Economics. 2021;24(1):770-80. **Study location** Sweden **Study type** Cost-effectiveness analysis from a Swedish societal perspective, reporting health outcomes in terms of QALYs and ICERs **Study aim** To evaluate the cost-effectiveness of PR fampridine plus BSC versus BSC alone in the treatment of adults in Sweden with MS and walking impairment	**Inclusion criteria** Adults with MS and EDSS scores between 4 and 7[39] **Exclusion Criteria** None stated **Total sample size** Not stated **No. of participants in each treatment group** Not stated **Baseline characteristics** The modelled patient population matched the ENHANCE phase III study population, which included adult MS patients with EDSS scores between 4 and 7 Mean age (years): 48.9	**Interventions** PR fampridine 10 mg tablet twice daily plus BSC **Comparators** BSC alone BSC includes all supportive care that could be used concomitantly to manage MS symptoms.	**Important outcomes** **Cost-effectiveness[40]** Base case cost-effectiveness (costs per treatment and QALYs, LYs at a discounted cost (at a rate of 3.0%) for patients with MS and walking impairment, over a 20 year horizon) (Swedish kronor) **QALYs** PR fampridine plus BSC: 9.27 BSC: 9.15 Incremental: 0.12 **LYs:** PR fampridine plus BSC: 14.58 BSC: 14.58 Incremental: 0.00 Total costs (kronor) ([1 kronor = €0.0981762 on 8 April 2021; 1 kronor = $0.116890 on 8 April 2021]): PR fampridine plus BSC: 3,451,840.03 (€338,888.54; $403,485.58) BSC alone: 3,444,858.51 (€338,203.12; $402,669.51)	**Comments:** This is a cost-effectiveness analysis comparing PR fampridine plus BSC to BSC alone in Swedish adults with MS and walking impairment. The economic evaluation was conducted from a Swedish societal perspective to capture all direct costs (PR fampridine drug cost, healthcare professionals, hospitalisations, treatment of AEs, cost of care and modifications/aids) and indirect costs (absence from work) associated with MS related walking impairment. Model parameters were based on four studies evaluating PR

[39] The EDSS score is a rating scale that assesses the degree of neurological disability taking into account eight functional systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and other) in MS patients. The scale ranges from 0 (normal) to 10 (death due to MS). EDSS values between 4.0 and 7.0 reflect a growing negative impact on the walking ability.
[40] Current conversion rate of 1.00 Swedish krona = 0.07 British pounds (dated 22nd January 2024).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study dates Cost-effectiveness based on ENHANCE trial population and sources published between 2009 and 2019	Mean time since diagnosis (months): 137 Sex, % (male): 42 Because the model also included T25FW, which was not measured in the ENHANCE (or MOBILE) trials, this was derived from the baseline values observed in the MS-F203 (Goodman et al 2009) and MS-F204 (Goodman et al 2010) trials: T25FW (feet/second): 2.1		Incremental: 6,981.52 (€685.42; $816.07) <u>Above costs based on the following unit costs (Swedish kronor)</u> <u>Total drug cost</u> PR fampridine plus BSC: 52,092.25 (€5,114.22; $6,089.06) BSC alone: 0 Incremental: 52,092.25 (€5,114.22; $6,089.06) <u>Direct costs</u> PR fampridine plus BSC: 2,084,141.07 (€204,613.05; $243,615.25) BSC alone: 2,120,181.45 (€208,151.36; $247,828.01) Incremental: -36,040.38 (€-3,538.31; $-4,212.76) <u>Indirect costs</u> PR fampridine plus BSC: 1,315,606.71 (€129,161.27; $153,781.27) BSC alone: 1,324,677.06 (€130,051.76; $154,841.50) Incremental: -9,070.35 (€-890.49; $-1,060.23) **ICER (Swedish kronor): 57,108.51 (€5,606.70; $6,675.41)** <u>Sensitivity analysis</u> One-way sensitivity analyses were performed comparing PR fampridine plus BSC versus BSC alone. All sensitivity analyses resulted in ICERs below the WTP threshold (500,000 Swedish kronor; (€49,088 and $58,445) The most sensitive parameters were the T25FW score at baseline, the	fampridine vs placebo in patients with MS and walking impairment (it was unclear how published sources were identified): MS-F203, MS-F204, ENHANCE and MOBILE clinical studies; and one study (IMPACT trial) that captured T25FW in patients with advanced MS, but compared interferon beta-1a intramuscular versus placebo. The authors stated that the use of the placebo arm from the IMPACT trial could be considered conservative as these patients experienced the slowest published rate of T25FW decline, and may therefore have underestimated the true impact of PR fampridine. The cost-utility analysis was based on a Markov model with PR fampridine treatment responders defined in the model using the MSWS-12, T25FW scores, accumulated costs and QALYs in Swedish patients with

<table>
<tr><th>Study details</th><th>Population</th><th>Interventions</th><th>Study outcomes</th><th>Appraisal and funding</th></tr>
<tr><td></td><td></td><td></td><td>utility value assigned to responders at week 24 and carried forward, the cost of professional care, PR fampridine withdrawal rate and the cost of a day off work.

Probabilistic sensitivity analyses were also performed using 5,000 iterations and varying 172 parameters (including baseline patient characteristics, multiple disease related parameters, comorbidity factors, healthcare resources and costs, adverse events, utilities and treatment effectiveness parameters).

Probabilistic sensitivity analyses were similar to the base-case analysis with an incremental QALY gain or 0.12 for PR fampridine plus BSC vs BSC alone and an ICER of 53,060 kronor/QALY (€5,209/QALY and $6,202/QALY)

Probability of a 56 pack of PR fampridine at a cost of 1,402.85 kronor being cost-effective for patients with MS and walking impairment at a WTP threshold of 500,000 kronor/QALY (€49,088/QALY and $58,445/QALY): 96.76%

<u>Cost-effectiveness scenario analysis for PR fampridine plus BSC vs BSC alone</u>
<table>
<tr><th></th><th>Incremental costs (kronor)</th><th>Incremental QALYs</th><th>ICER (kronor/QALY)</th></tr>
<tr><td colspan="4">Time horizon</td></tr>
<tr><td>Lifetime (100 years)</td><td>6,981.52</td><td>0.12</td><td>57,108.51</td></tr>
<tr><td>10 years</td><td>9,029.37</td><td>0.12</td><td>77,604.64</td></tr>
</table>
</td><td>MS-related walking impairment. The model included 4 weeks of treatment costs in all patients starting PR fampridine. The base case scenario used a 20 year time horizon. Discounting was applied at rate of 3% per year for all costs and outcomes, in accordance with Swedish guidelines.

The primary outcome was ICERs per QALY gained for PR fampridine plus BSC compared with BSC alone. QALYs were reported for responders and non-responders to treatment, and appropriate sensitivity analyses were performed to test the assumptions used. Scenario analyses were also performed to assess the impact of varying the perspective, costs, utility scores and time horizon.

The study used appropriate methodology and tested assumptions</td></tr>
</table>

Study details	Population	Interventions	Study outcomes				Appraisal and funding
			Discounting rates for costs and health outcomes				using one-way and probabilistic sensitivity analyses. Limitations of the study (as acknowledged by the authors) included the model not capturing non-responders; the potential for cost savings on unnecessary PR fampridine treatment in these individuals; and the need to extrapolate data on T25FW to model long term treatment effect due to lack of availability of long term data. In addition, the probability sensitivity analyses did not account for possible pairwise correlations between relevant inputs, which may overestimate the variability of the results reported for cost-effectiveness. **Source of funding:** Biogen
			0%	5,082.17	0.14	36,301.21	
			5%	7,930.27	0.11	72,093.33	
			Perspective				
			Healthcare payer	16,051.87	0.12	131,303.57[41]	
			Clinical trial scenarios[42]				
			MOBILE	6,981.52	0.44	15,668.02	
			Pooled ENHANCE and MOBILE	7,032.63	0.15	46,359.31	
			ENHANCE BSC adjusted	6,981.52	0.04	163,202.35	
			Variations in costs – increase in resource use costs				
			+25%	-3,934.85	0.12	PR fampridine dominates	
			-25%	17,897.89	0.12	146,403.93	

[41] There was an unexplained discrepancy in the ICER reported in the text (400,936 kronor/QALY) and table (131,303.57 kronor/QALY).
[42] The authors stated that as EQ-5D is not a disease-specific instrument, it is likely to lack the sensitivity required to appropriately capture all quality of life changes experienced by MS patients on PR-fampridine. They therefore conducted scenario analyses to input EQ-5D-5L values from the MOBILE study and integrated analysis combining data from the ENHANCE and MOBILE studies. The authors also stated that utility values for BSC and PR fampridine responders showed a numerical difference at baseline, even if patients were evenly distributed on most of the baseline clinical characteristics in the ENHANCE study, and a scenario analysis was conducted to investigate the impact of such difference in baseline utility values (i.e. ENHANCE BSC adjusted).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Alvarez-Payero M, Valeiras-Munoz C, Lion-Vazquez S, Pineiro-Corrales G, Munoz-Garcia D, Midaglia L. Experience with fampridine in clinical practice: analysis of a possible marker of clinical response. International Journal of Neuroscience. 2017;127(10):915-22. **Study location** Spain **Study type** Prospective case series **Study aim** To assess the efficacy and safety of fampridine in daily clinical practice in patients with MS and gait disorders **Study dates** May to September 2014	**Inclusion criteria** Patients aged ≥18 years with MS and evidence of affected gait (EDSS 4 to 7) **Exclusion Criteria** History of epilepsy, creatinine clearance <80 mL/min, concomitant treatment with organic cation transporter 2 inhibitors and relapse during the previous 60 days **Total sample size** N=55 **No. of participants in each treatment group** Fampridine: N=55 Control: None **Baseline characteristics** Age (years), mean (±SD): 51.73 (11.1) Sex (female), n (%): 37 (67.3) Progressive form of MS, n (%)	**Interventions** Fampridine: 10 mg twice daily **Comparators** No comparator group Disease-modifying treatments could be administered concomitantly with fampridine (e.g. interferons, azathioprine).	Follow-up at six months **Important outcomes** **Activities of daily living** Defined as EDSS score in treatment responders,[43, 44] mean (±SD) Before fampridine (n=25): 6.1 (0.9 [range 4.0 to 7.0]) After fampridine (n=25): 5.6 (0.1) *Difference between pre- and post-treatment scores: p<0.05* For the study population followed up at six months (n=25 responders and n=5 non-responders), improvements resulted in a reduction in the number of supports needed for walking in 9.1% of patients	This study was appraised using the JBI Critical Appraisal Tool for case series 1. Yes 2. Unclear 3. Unclear 4. Yes 5. No 6. Yes 7. Yes 8. No 9. Yes 10. Yes **Other comments:** This was a prospective case series including 55 consecutively recruited patients with MS and walking difficulties treated with fampridine. Valid methods were used to measure outcomes in accordance with the Spanish (Galicia) health agency's guidelines. Baseline

[43] Variations of 0.5 points, between EDSS 4 and 7, were considered of clinical impact because this range on the scale reflects important changes in walking ability, corresponding EDSS 4 to a restricted walking up to 500 m and EDSS 7.0 to a severely affected deambulation, no more than 5 m without a walking aid.
[44] Response was defined as increased gait speed (≥20%) using the T25FW test and decreased MSWS-12 score (≥4 points).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	PPMS: 8 (14.5) RRMS: 31 (56.4) SPMS: 16 (29.1) <u>EDSS score - all patients</u> Mean (±SD): 5.8 (1.0) [range 4.0 to 7.0] Levels, n (%): 4 to 5.5 (able to walk/no support): 20 (36.4) 6 (unilateral support): 17 (30.9) 6.5 to 7.0 (bilateral support): 18 (32.7)			characteristics were reported for the 55 patients, but only 30 patients completed follow-up at 6 months (n=25 responders vs n=5 non-responders). Patients was considered responders when they reached a decrease in time of at least 20% in the T25FW and a decrease of ≥4 points on the MSWS-12 scale. After each visit, only patients who were considered responders continued on treatment. The decrease in EDSS score was observed in responders who completed six months of treatment with fampridine and was not reported for non-responders, which could introduce reporting bias. Other outcomes were reported for both responders and non-responders. Twenty eight (50.9%) of patients received concomitant disease-modifying treatments.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				The authors reported outcomes in two patients who were initially considered treatment responders, but lost response during follow-up, for whom fampridine was withdrawn and then reintroduced after a washout period of one month. These data are not reported in this review. In total, 10 patients (18.2%) were withdrawn from treatment due to intolerance, 8 of whom withdrew within the first 2 weeks. The authors stated that the improvement observed among responders was seen as a significant decrease in the EDSS score. "*In clinical terms, this means that some patients no longer need to use a cane or crutch for support or pass to use one support instead of two (20% of responders). They benefit from increased autonomy, which would*

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				have a very positive impact on ADLs." **Source of funding:** None.
Fragoso YD, Adoni T, Alves-Leon SV, Apostolos-Pereira SL, Barreira AA, Brooks JB, et al. Real-life experience with fampridine (Fampyra R) for patients with multiple sclerosis and gait disorders. Neurorehabilitation. 2016;39(2):301-4. **Study location** Brazil **Study type** Prospective case series **Study aim** To assess the *"real-life"* efficacy and safety of fampridine in patients with MS and gait disorders **Study dates** Not stated	**Inclusion criteria** Patients with MS who were receiving fampridine for treatment of gait disorders **Exclusion Criteria** Not stated **Total sample size** N=89 **No. of participants in each treatment group** Fampridine: N=89 Control: None **Baseline characteristics** Age (years), median (range): 44 (26 to 78) Sex (male/female), n: 34/55 Duration of MS (years), median (range): 12 (2 to 46)	**Interventions** Fampridine: 10 mg twice daily **Comparators** No comparator group The median duration of treatment with fampridine was nine months (range 1 to 30 months).	Follow-up a**t** one month **Important outcomes** **Activities of daily living** Defined as improvement of disability assessed by EDSS from baseline, mean (±SD) Before fampridine (n=NR): 5.2 (1.1) After fampridine (n=NR): 5.0 (1.4) *Difference between pre- and post-treatment EDSS scores: p=0.29* The authors stated that *"improvement of disability assessed by means of EDSS if the score decreased by at least 1.0 point after one month of treatment. This improvement was observed in 14 patients (17.5%)"*[45]	This study was appraised using the JBI Critical Appraisal Tool for case series 1. No 2. Unclear 3. Unclear 4. Unclear 5. Unclear 6. Yes 7. No 8. Yes 9. No 10. Yes **Other comments:** This was a prospective case series including data from 89 patients with MS and gait impairment treated with fampridine; study dates were not reported and it was unclear whether

[45] The number of patients assessed by EDSS was not reported; although 89 patients were included in the study, the observed improvements in 14 (17.5%) patients suggests that not all patients were assessed. The authors did not provide an explanation as to why not all patients were included in the outcome assessments.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	EDSS, mean (±SD): 5.2 (1.1)			patients were recruited consecutively. Clinical data on patients with MS were collected by Brazilian neurologists. Limited study details and baseline characteristics were reported. Efficacy (i.e. responders to treatment) was defined as patients achieving ≥20% speed improvement in the T25FW test, measured in seconds. Fampridine was withdrawn from all patients who did not improve on treatment, those with seizures and those who reported experiencing worse balance after using fampridine; no further details were provided. The authors acknowledged the potential for selection bias, due to fampridine not being fully provided by the public health system in Brazil, the authors may have selected patients with greater chances of improving with fampridine.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				Source of funding: The study was conducted without any financial support.
Gasperini C, Hupperts R, Lycke J, Short C, McNeill M, Zhong J, Mehta LR. Prolonged-release fampridine treatment improved subject-reported impact of multiple sclerosis: Item-level analysis of the MSIS-29. Journal of the Neurological Sciences. 2016;370:123-31. **Study location** Canada and Europe **Study type** *Post hoc* analysis of Phase II double-blind RCT (MOBILE) **Study aim** To evaluate the physical and psychological health outcomes of patients with progressing or relapsing MS from individual items of the Multiple Sclerosis Impact Scale (MSIS-29) **Study dates** See Hupperts et al (2016)	**Inclusion criteria** See Hupperts et al (2016) **Exclusion Criteria** See Hupperts et al (2016) **Total sample size** N=132 **No. of participants in each treatment group** PR fampridine: n=68 Placebo: n=64 **Baseline characteristics** See Hupperts et al (2016)	**Interventions** PR fampridine: 10 mg tablets twice daily **Comparators** Placebo twice daily See Hupperts et al (2016) for concomitant treatments	**Critical outcomes** **Walking ability** See Hupperts et al (2022) **Physical impact of MS** See Hupperts et al (2022) **HRQoL** Defined as difference in the change in MSIS-29 PSYCH mean subscale score[46] from baseline At week 4 Difference between PR fampridine and placebo groups in the mean reduction in MSIS-29 PSYCH subscale scores from baseline: 42% At week 12 Difference between PR fampridine and placebo groups in the mean reduction in MSIS-29 PSYCH subscale scores from baseline: 57% At week 24 Difference between PR fampridine and placebo groups in the mean reduction in MSIS-29 PSYCH subscale scores from baseline: 148%	See Hupperts et al (2016) for JBI Critical Appraisal Tool for RCTs assessment 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Unclear 7. No 8. Yes 9. Unclear 10. No 11. Yes 12. Unclear 13. Yes **Other comments:** This was a *post hoc* analysis of the MOBILE RCT. The analysis

[46] For each visit, MSIS-29 PSYCH scores were calculated by totalling the nine individual items and transforming to a scale with a range of 0 (no impact of MS) to 100 (extreme impact of MS). The percentage of study participants who reported any mean improvement or worsening in the MSIS-29 PSYCH individual items by visit were also analysed.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			A greater proportion of patients treated with PR-fampridine versus placebo showed mean improvements in six of the nine PSYCH items over 12 and 24 weeks; the difference was statistically significant for one item *"worries related to your MS"* at 12 weeks (p=0.044) and 24 weeks (p=0.006). A greater proportion of patients treated with placebo versus PR fampridine showed mean improvements in the remaining three PSYCH items over 12 and 24 weeks, but the difference was not statistically significant. ***Post hoc* analysis** <u>At week 24</u> Difference between PR fampridine MSWS-12 improvers (n=33)[47] and placebo groups (n=64)[48] in the mean reduction in MSIS-29 PSYCH subscale scores from baseline: 111% Improvements in MSIS-29 PSYCH subscale scores from baseline were also greater in the PR fampridine MSWS-12 improver population compared to MSWS-12 non-improvers (n=35), but no further details were provided. A greater proportion of PR fampridine MSWS-12 improvers versus placebo showed mean improvements in eight of nine MSIS-29 PSYCH items over weeks 2 to 24. The two items with the greatest percentage difference (>25%) in mean reductions in the MSWS-12 improver group versus placebo group over weeks 2 to 24 were *"feeling mentally fatigued"* and *"worries related to your MS"*. A higher proportion of PR fampridine MSWS-12 improvers compared with MSWS-12 non-improvers	evaluated the physical and psychological health outcomes of patients with progressing or relapsing MS using individual items of the MSIS-29 score. Only data on MSIS-29 PSYCH subscale scores are presented here as data on MSIS-29 PHYS subscale scores are reported in the *post hoc* integrated analysis (Hupperts et al 2022). Missing data were imputed using the last observation carried forward method when at least one post-baseline value was available. Differences between treatment groups were assessed using logistic regression, adjusting for mean baseline item score. For all analyses of individual items, observed data were used. The authors presented the proportion of patients with mean

[47] Patients were defined as improvers if they achieved a ≥8 point mean reduction in MSWS-12 score over 24 weeks; non-improvers were defined as those with <8 point mean reduction over 24 weeks, no change, or an increase in MSWS-12 score.
[48] Due the small number of patients in the placebo group who showed clinically meaningful improvement on the MSWS-12, analyses were conducted on the placebo group as a whole.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			showed mean reductions in scores across all MSIS-29 PSYCH items over weeks 2 to 24.	improvement in each MSIS-29 PSYCH subscale item, but only statistically significant items are reported in this review. *Post hoc* analyses for MSIS-29 PSYCH subscale scores were also conducted in patients who improved on PR fampridine measured using the MSWS-12 score vs PR fampridine non-responders. Findings from these analyses are not reported here as they are presented in the *post hoc* integrated analysis (Hupperts et al 2022). **Source of funding:** Biogen
Hobart J, Ziemssen T, Feys P, Linnebank M, Goodman AD, Farrell R, et al. Assessment of Clinically Meaningful Improvements in Self-Reported Walking Ability in Participants with Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III ENHANCE Trial of Prolonged-Release	**Inclusion criteria** Patients aged 18 to 70 years with a diagnosis of PPMS, SPMS, PRMS, or relapsing-remitting MS ≥ 3 months' duration; EDSS score of 4.0 to 7.0; and investigator-assessed walking impairment	**Interventions** PR fampridine: 10 mg tablets twice daily **Comparators** Matching placebo Concomitant use of approved disease-modifying treatments for fatigue or spasticity were allowed in both treatment arms if the drug and dose remained	Follow-up at 24 weeks, unless otherwise stated **Critical outcomes** **Walking ability** <u>Defined as the proportion of patients with a clinically meaningful improvement in MSWS-12 (≥10 points) from baseline</u> PR fampridine (n=315) 38**%** Placebo (n=318) 27%	This study was appraised using the JBI Critical Appraisal Tool for RCTs. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Fampridine. CNS Drugs. 2019;33(1):61-79. **Study location** Multicentre (92 centres in 11 countries) **Study type** Phase III double-blind RCT (ENHANCE) **Study aim** To assess whether PR fampridine has a clinically meaningful impact on self-reported walking ability in patients with MS and impaired walking **Study dates** September 2014 to February 2016	**Exclusion Criteria** Patients with recent exacerbation of MS (within 60 days of screening visit), recent initiation/change in the dosing of approved immunomodulatory therapies, and any history of seizure, epilepsy, or other convulsive disorder[49] **Total sample size** N=636 (mITT:[50] n=633) **No. of participants in each treatment group** PR fampridine: n=317[51] (mITT: n=315) Placebo: n=319 (mITT: n=318) **Baseline characteristics -mITT population** Age (years), mean (±SD): PR fampridine	stable throughout the study; physiotherapy and rehabilitation therapy were also permitted.	*Difference between PR fampridine vs placebo: p=0.003* At 26 weeks [i.e. two week post-dosing follow-up visit after 24 weeks of fampridine treatment] The authors reported that *"within 2 weeks of stopping PR-fampridine treatment., the effects of PR-fampridine on the MSWS-12 dissipated"*. **Physical impact of MS** See Hupperts et al (2022) **HRQoL** See Hupperts et al (2022) **Important outcomes** **Limb mobility/dexterity** Defined as ABILHAND score (range 0 to 100)[52] change from baseline[53] LSM change from baseline (95% CI): PR fampridine (n=312) 1.49 (0.36 to 2.61); Placebo (n=315) 0.75 (−0.41 to 1.91) *LSM difference in change from baseline for PR fampridine vs. placebo (95% CI): 0.74 (−0.38 to 1.86); p=0.197*	6. Yes 7. Yes 8. Yes 9. Unclear 10. No 11. Yes 12. Yes 13. Yes **Other comments:** Patients were randomised on a 1:1 basis and were stratified by EDSS score (≤6 or 6.5 to 7); a protocol amendment in December 2014 added stratification by prior aminopyridine use due to concerns regarding potential bias. As some inclusion criteria were left to the discretion of the study investigators (e.g. drug or alcohol

[49] Additional exclusion criteria included: a wide range of comorbidities (e.g. acute or chronic hepatitis, pulmonary disease); any relevant allergy; clinically significant abnormal laboratory values; use of certain treatments (e.g. mitoxantrone or cyclophosphamide)or change in current medication; history of drug or alcohol abuse (as defined by the investigator) within the two years before the screening visit; pregnancy or breastfeeding (see full paper for details).
[50] Modified intention-to-treat (mITT) analyses included randomised patients who received at least one dose of study treatment and had findings for at least one post-baseline efficacy assessment.
[51] One patient randomised to PR fampridine withdrew consent before receiving treatment.
[52] ABILHAND measures manual ability to manage daily activities among chronic stroke patients. Patients estimate the ease or difficulty of performing each upper limb activity using a 3-level response scale: impossible (0), difficult (1), and easy (2). A higher ABILHAND score represents better manual ability.
[53] Based on a mixed-effects model for repeated measures using a common variance/covariance matrix structure.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	49.0 (9.8); Placebo 48.8 (10.5) Sex (female), n (%): PR fampridine 186 (59); Placebo 180 (57) <u>Disease course, n (%)</u> • RRMS: PR fampridine 169 (54); Placebo 155 (49) • SPMS: PR fampridine 95 (30); Placebo 99 (31) • PPMS: PR fampridine 41 (13); Placebo 45 (14) • PRMS: PR fampridine 10 (3); Placebo 19 (6) EDSS score (mean, ±SD): PR fampridine 5.49 (0.92); Placebo 5.48 (0.91) EDSS score (median, range): PR fampridine 6.0 (4.0 to 7.0); Placebo 5.5 (4.0 to 7.0) EDSS score ≤ 6.0, n (%): PR fampridine 246 (78); Placebo 246 (77)		<u>Subgroup analysis of ABILHAND score stratified by baseline EDSS score</u> EDSS score ≤ 6.0 (mean ABILHAND scores at baseline, ±SD): PR fampridine (n=244) 89.98 (12.96), range 25.5 to 100.0; Placebo (n=244) 88.17 (14.09), range 30.7 to 100.0 LSM change from baseline over 24 weeks: PR fampridine (n=244) 1.32; Placebo (n=244) 1.22 *LSM difference in change from baseline for PR fampridine vs. placebo (95% CI): 0.10 (−1.04 to 1.24); p=NS* EDSS score 6.5 and 7.0 (mean ABILHAND scores at baseline, ±SD): PR fampridine (n=68) 83.84 (15.90; range 43.2 to 100.0); Placebo (n=71) 78.30 (17.53; range 36.2 to 100.0) LSM change from baseline over 24 weeks: PR fampridine (n=68) 2.10; Placebo (n=71) –0.95 *LSM difference in change from baseline for PR fampridine vs. placebo (95% CI): 3.05 (−0.09 to 6.19); p=NS* The authors stated that *"while the differences between the PR-fampridine and placebo groups were not statistically significant, there were " small numerical improvements that were larger in the more disabled participants"* [although formal significance testing was not undertaken for subgroup analyses] **Safety – complications of fampridine therapy, n (%)** <u>Defined as any AE</u> PR fampridine (n=316): 207 (66) Placebo (n=319): 190 (60)	abuse) and clinically significant abnormal results may be subjective, selection bias may have been introduced. All patients, investigators, site personnel, and funder personnel were masked to treatment assignment. It was unclear whether all outcomes were measured in a reliable way – most were self-reported and no details were provided on the reliability of measurements. Follow-up was incomplete: 16% of patients withdrew from PR fampridine treatment arm and 20% from the placebo arm, although reasons for withdrawals were provided and missing data were imputed. The study included a 2-week screening period, a 24-week double-blind treatment period, and a 2-week post-dosing follow-up visit. Concomitant medication was used in 276/315 (87%) patients

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	EDSS score 6.5 and 7.0, n (%): PR fampridine 69 (22); Placebo 72 (23) TUG time, feet/second (mean, ±SD): PR fampridine 24.9 (26.6, range 6.3 to 239.8; Placebo 27.1 (42.0), range 0 to 436.8 Self-reported outcomes ABILHAND score (mean, ±SD): PR fampridine 86.9 (15.8), range 0.9 to 100.0; Placebo 84.3 (16.5), range 26.0 to 100.0		Defined as any severe AE[54] PR fampridine (n=316): 9 (3) Placebo (n=319): 8 (3) Defined as any treatment-related AE[55] PR fampridine (n=316): 56 (18) Placebo (n=319): 43 (13) Defined as serious AE[56] PR fampridine (n=316): 25 (8) Placebo (n=319): 21 (7) Defined as any treatment-related serious AE[55, 56] PR fampridine (n=316): 0 (0) Placebo (n=319): 1 (<1) Defined as AE leading to dose interruption PR fampridine (n=316): 9 (6) Placebo (n=319): 11 (3) Defined as AE leading to treatment discontinuation PR fampridine (n=316): 21 (7) Placebo (n=319): 23 (7) Defined as AE leading to study withdrawal PR fampridine (n=316): 22 (7) Placebo (n=319): 24 (8)	receiving PR fampridine and in 287/319 (90%) patients receiving placebo. Concomitant non-drug treatment (including, but not limited to physiotherapy, bladder catheterisation, rehabilitation therapy) was used in 43/316 (14%) patients receiving PR fampridine and in 51/319 (16%) patients receiving placebo. Data from one site (n=10 patients) were deemed unreliable due to serious Good Clinical Practice non-compliance and were excluded from the analyses before unblinding. The authors conducted pre-specified sensitivity analyses to compare the results with and without the data from these ten participants, which revealed no

[54] Severe AEs were defined as symptoms causing severe discomfort, incapacitation, or significant impact on daily life.
[55] Investigators assessed whether the AE was related to study drug.
[56] A serious AE was any untoward medical occurrence that resulted in death/risk of death, hospitalisation/prolonged hospitalisation, persistent or significant disability/incapacity, or resulted in a congenital anomaly/birth defect. There were two deaths, both of which were considered unrelated to study treatment (coronary artery stenosis and acute myocardial infarction), and occurred after the participant had completed study treatment but before completing the 2-week post-treatment follow-up.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Defined as most common treatment-emergent AEs by MedDRA® Preferred Term (≥ 5% in any treatment group)[57] Urinary tract infection: PR fampridine (n=316) 41 (13); Placebo (n319) 30 (9) MS relapse: PR fampridine (n=316) 34 (11); Placebo (n=319) 33 (10) Fall: PR fampridine (n=316) 24 (8); Placebo (n=319) 19 (6) Back pain: PR fampridine (n=316) 16 (5); Placebo (n=319) 11 (3) Headache: PR fampridine (n=316) 15 (5); Placebo (n=319) 15 (5) Nasopharyngitis: PR fampridine (n=316) 15 (5); Placebo (n=319) 18 (6) Upper respiratory tract infection: PR fampridine (n=316) 15 (5); Placebo (n=319) 10 (3)	appreciable differences across all outcomes. Based on the mITT sample (n=633), the following levels of post-baseline data were missing and were imputed for efficacy outcomes: MSWS-12 score: 12% (PR fampridine, 10%; placebo, 14%); TUG speed: 9% (PR fampridine, 7%; placebo, 12%); and ABILHAND score: 9% (PR fampridine, 8%; placebo, 11%). Fifty one patients withdrew from the PR fampridine treatment arm (AE: n=21; lost to follow-up: n=2; non-compliance: n=6; self-perceived lack of efficacy: n=2; consent withdrawn: n=7; investigator decision: n=1; death: n=1; Other: n=11. Sixty five patients withdrew from the placebo treatment arm (AE: n=23; lost to follow-up: n=4; pregnancy: n=1; non-

[57] Listed in descending order of frequency for the PR-fampridine group. Treatment-emergent AEs were defined as AEs that started on or after the first dose of study drug, or pre-existing conditions that worsened in severity after the first dose of study drug; a participant was only counted once within each Preferred Term.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				compliance: n=10; self-perceived lack of efficacy: n=10; consent withdrawn: n=11; death: n=1; Other: n=5. Mean (SD) compliance with dosing of study treatment was 98.7% (3.9%) in the PR fampridine group and 98.4% (4.6%) in the placebo group for the ITT population (n=633). Mean compliance rates were the same for each treatment group in the safety population (n=635). Subgroup analysis of ABILHAND outcomes were also reported based on normal (≥ 80) vs abnormal (<80) ABILHAND scores at baseline. ***Post hoc* analyses of all outcomes were also conducted in patients who responded to PR fampridine measured using the MSWS-12 score vs PR fampridine non-responders and vs placebo treated patients. Findings from these analyses**

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				are not reported here as they are presented in the *post hoc* integrated analysis (Hupperts et al 2022).Source of funding: Biogen.
Hupperts R, Lycke J, Short C, Gasperini C, McNeill M, Medori R, et al. Prolonged-release fampridine and walking and balance in MS: randomised controlled MOBILE trial. Multiple Sclerosis. 2016;22(2):212-21. **Study location** Belgium, Canada, Italy, The Netherlands, Sweden and the UK (24 centres) **Study type** Phase II double-blind RCT (MOBILE) **Study aim** To assess the effect of PR fampridine on self-assessed walking disability, dynamic/static balance and safety in patients with progressing or relapsing MS **Study dates**	**Inclusion criteria** Adults aged 18 to 70 years with an EDSS score of 4.0 to 7.0; diagnosis of PPMS, SPMS, PRMS or RRMS of ⩾3 months' duration. **Exclusion Criteria** 4-aminopyridine or 3, 4-diaminopyridine in any formulation ⩽30 days before screening; known allergy to pyridine-containing substances; any history of seizure, epilepsy or other convulsive disorder; renal impairment (creatinine clearance <80 ml/min); onset of MS exacerbation ⩽60 days before screening; BMI ⩾40 kg/m^2.	**Interventions** PR fampridine: 10 mg tablets every 12 hours **Comparators** Matching placebo every 12 hours Most stable concomitant therapies for treatment of MS were permitted, but no further details were provided.	Follow-up at 24 weeks, unless otherwise stated **Critical outcomes** **Walking ability** <u>Defined as number of patients reporting improvement on PGIC[58] at two weeks follow-up, n (%) (*post hoc* analysis)</u> PR fampridine (n=68): 31 (46); Placebo (n=64): 16 (26); p=0.023 <u>Defined as mean MSWS-12 score improvement of ≥1 points from baseline, n (%)</u> PR fampridine (n=68): 44 (64.7) Placebo (n=64): 35 (54.7) *Difference between PR fampridine vs placebo: p=NS* <u>Defined as mean MSWS-12 score improvement of ≥2 points from baseline, n (%)</u> PR fampridine (n=68): 42 (61.8) Placebo (n=64): 33 (51.6) *Difference between PR fampridine vs placebo: p=NS*	This study was appraised using the JBI Critical Appraisal Tool for RCTs. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Unclear 7. Yes 8. Yes 9. Unclear 10. No 11. Yes 12. Yes 13. Yes

[58] The PGIC is a global assessment of the patient's impression of how the study drug affected their overall walking during the preceding seven days. The PGIC was scored on a seven-point scale (from 1 = very much worse to 7 = very much improved).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
August 2012 to August 2013	**Total sample size** N=132 (ITT) **No. of participants in each treatment group** PR fampridine: n=68 Placebo: n=64 **Baseline characteristics** Age (years), mean: PR fampridine 49.8; Placebo 49.8 Sex (female), n (%): PR fampridine 38 (56); Placebo 33 (52) Disease course, n (%) RRMS: PR fampridine 24 (35); Placebo 20 (31) SPMS: PR fampridine 31 (46); Placebo 37 (58) PPMS: PR fampridine 12 (18); Placebo 6 (9) PRMS: PR fampridine 1 (1); Placebo 1 (2) EDSS score, mean (median): PR fampridine 5.6 (6.0); Placebo 5.9 (6.0)		Defined as mean MSWS-12 score improvement of ≥3 points from baseline, n (%) PR fampridine (n=68): 42 (61.8) Placebo (n=64): 32 (50.0) *Difference between PR fampridine vs placebo: p=NS* Defined as mean MSWS-12 score improvement of ≥4 points from baseline, n (%) PR fampridine (n=68): 42 (61.8) Placebo (n=64): 30 (46.9) *Difference between PR fampridine vs placebo: p=NS* Defined as mean MSWS-12 score improvement of ≥5 points from baseline, n (%) PR fampridine (n=68): 37 (54.4) Placebo (n=64): 26 (40.6) *Difference between PR fampridine vs placebo: p=NS* Defined as mean MSWS-12 score improvement of ≥6 points from baseline, n (%) PR fampridine (n=68): 35 (51.5) Placebo (n=64): 23 (35.9) *Difference between PR fampridine vs placebo: p=NS* Defined as mean MSWS-12 score improvement of ≥7 points from baseline, n (%) PR fampridine (n=68): 34 (50.0) Placebo (n=64): 20 (31.3)	**Other comments:** Patients were randomised on a 1:1 basis. All patients and trial staff, including the principal investigator, were blinded to patient treatment assignments. It was unclear whether all outcomes were measured in a reliable way as no details were provided on the reliability of measurements. Follow-up was incomplete: 19% of patients withdrew from each treatment arm, although reasons for withdrawals were provided and missing data were imputed by the last observation carried forward method when at least one post-baseline value was available. The study included a 24-week double-blind treatment period, and a 2-week post-dosing follow-up visit. Twelve patients discontinued PR fampridine treatment (AE: n=5; lack of efficacy: n=1; Other:

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Difference between PR fampridine vs placebo: p<0.0275 Defined as mean MSWS-12 score improvement of ≥9 points from baseline, n (%) PR fampridine (n=68): 33 (48.5) Placebo (n=64): 17 (26.6) *Difference between PR fampridine vs placebo: p<0.0088* Defined as mean MSWS-12 score improvement of ≥10 points from baseline, % PR fampridine (n=68): 28 (41.2) Placebo (n=64): 17 (26.6) *Difference between PR fampridine vs placebo: p=NS* At 26 weeks [i.e. two week post-dosing follow-up visit after 24 weeks of fampridine treatment] The authors reported that *"after treatment discontinuation at week 24, improvements declined and approached zero by the week 26 follow-up visit in the PR-fampridine group"* **Physical impact of MS** Defined as TUG speed at 26 weeks [i.e. two week post-dosing follow-up visit after 24 weeks of fampridine treatment] The authors reported that *"after treatment discontinuation at week 24, improvements declined and approached zero by the week 26 follow-up visit in the PR-fampridine group"* See also Hupperts et al (2022) **HRQoL**	n=6 [CrCI out of range: n=4; unacceptable concomitant medication required: n=2]). Thirteen patients discontinued from the placebo arm (AE: n=7; lack of efficacy: n=1; consent withdrawal: n=2; Other: n=3 [CrCI out of range: n=1; unacceptable concomitant medication required: n=2]). Although the PGIC was assessed at weeks 2, 4, 8, 12, 16, 20 and 24, because it is designed to assess change since the previous visit, week 2 was the only time point that was valid for between-group comparisons of treatment effect. **Source of funding:** Biogen.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			See Hupperts et al (2022) **Important outcomes** **Limb mobility/dexterity** Defined as BBS score at 26 weeks [i.e. two week post-dosing follow-up visit after 24 weeks of fampridine treatment] The authors reported that *" after treatment discontinuation at week 24, improvements declined and approached zero by the week 26 follow-up visit in the PR-fampridine group"* See also Hupperts et al (2022) **Safety**[59] Defined as number of patients with AEs, n (%) PR fampridine (n=68): 51 (75); Placebo (n=64) 49 (77) Defined as number of patients with SAEs, n (%) PR fampridine (n=68): 2 (3); Placebo (n=64) 5 (8)	
Hupperts R, Gasperini C, Lycke J, Ziemssen T, Feys P, Xiao S, et al. Efficacy of prolonged-release fampridine versus placebo on walking ability, dynamic and static balance, physical impact of multiple sclerosis, and quality of life: an integrated analysis of MOBILE and ENHANCE. Therapeutic Advances in	**Inclusion criteria** Two RCTs comparing PR fampridine vs placebo in adults aged 18 to 70 years with an EDSS score of 4.0 to 7.0; diagnosis of PPMS, SPMS, PRMS or RRMS of ⩾3 months' duration. **Exclusion Criteria**	**Interventions** PR fampridine: 10 mg tablets every 12 hours **Comparators** Matching placebo every 12 hours In the pooled MOBILE and ENHANCE studies, concomitant disease-modifying treatments	Follow-up at 24 weeks, unless otherwise stated **Critical outcomes** **Walking ability** Defined as MSWS-12 score change from baseline, LSM PR fampridine (n=383) 59.2 (SE 0.8); Change from baseline, LSM (95% CI): −6.9 (−8.5 to −5.4) Placebo (n=382) 62.9 (SE 0.8); Change from baseline, LSM (95% CI): -3.2 (-4.8 to -1.6)	This study was assessed using the JBI Critical Appraisal Tool for Systematic Reviews and Research Syntheses. 1. Yes 2. No 3. No

[59] Defined as treatment-emergent AEs reported for ≥5% of patients.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Neurological Disorders. 2022;15:17562864221090398. **Study location** Multicentre 92 centres in 11 countries (1 RCT), 24 centres in 6 countries (1 RCT) **Study type** Pooled data from two double-blind RCTs (ENHANCE and MOBILE) **Study aim** To further explore the effects of PR fampridine on walking ability, dynamic and static balance, physical impact of MS, and quality of life, using a *post hoc* integrated efficacy analysis **Study dates** See Hobart et al (2019) and Hupperts et al (2016)	Not stated. **Total sample size** N=765 **No. of participants in each treatment group** PR fampridine: n=383 Placebo: n=382 **Baseline characteristics – pooled data [PR fampridine: n=383; Placebo: n=382, unless otherwise stated]** Age (years), mean (95% CI): PR fampridine 49.1 (48.1 to 50.1); Placebo 49.0 (47.9 to 50.0) Sex (female), % (95% CI): PR fampridine 58 (53.6 to 63.4); Placebo 56 (50.8–60.7) Disease course, % (95% CI) RRMS: PR fampridine 50	included alemtuzumab, fingolimod, dimethyl fumarate, glatiramer acetate, interferon beta-1a, interferon beta-1b, atalizumab, and teriflunomide.	*LSM difference in change from baseline for PR fampridine vs. placebo (95% CI):* −3.70 (−5.61 to −1.79); p<0.001 Defined as clinically meaningful ≥8 improvement in MSWS-12 score[61] from baseline[62] PR fampridine (n=383): 44.3% Placebo (n=382): 33.0% Difference between treatment groups: OR 1.68 (95% CI: 1.23 to 2.29); p<0.001 *Sensitivity analyses (analysis not adjusted for baseline covariates)*: OR 1.62 (95% CI: 1.19 to 2.19); p<0.0019 Subgroup data for MSWS-12 responders (mean improvement ≥8 points from baseline) based on EDSS at baseline, n/N (%) EDSS ≤6.0: PR fampridine 140/296 (47); Placebo 96/283 (34) *Difference between treatment groups:* OR 1.75 (95% CI: 1.25 to 2.45) EDSS >6.0: PR fampridine 27/87 (31); Placebo 26/99 (26) *Difference between treatment groups:* OR 1.26 (95% CI: 0.67 to 2.39); *Difference between EDSS ≤6.0 vs >6.0; p=0.3766*	4. No 5. No 6. No 7. No 8. Unclear 9. NA 10. No 11. Yes **Other comments:** This was a *post hoc* integrated analysis of two RCTs and therefore did not follow standard systematic review methods and processes, i.e. did not include a systematic search of the literature to identify all relevant evidence. The analysis did not include a critical appraisal of the quality of the two RCTs and it was unclear whether efforts were made by the review authors to minimise bias or systematic errors by

[61] The proportion of patients with MS with a mean improvement in MSWS-12 score exceeding the predetermined threshold (⩾8 points) from baseline over 24 weeks (i.e. people with MS who met the definition of PR-fampridine responders for this analysis), analysed using a logistic regression model with treatment group as the classification variable and study, baseline MSWS-12 score, baseline TUG speed, age, and screening EDSS score as covariates.

[62] Percentage based on binomial proportions. OR, 95% CI, and p value calculated using logistic regression model adjusted for study, baseline MSWS-12 score, baseline TUG speed, age, and screening EDSS score (missing data imputed using multiple imputation).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	(45.4 to 55.4); Placebo 46 (40.8 to 50.8) SPMS: PR fampridine 33 (28.2 to 37.6); Placebo 36 (30.8 to 40.4) PPMS: PR fampridine 14 (10.4 to 17.3); Placebo 13 (9.9 to 16.8) PRMS: PR fampridine 3 (1.2 to 4.5); Placebo 5 (3.0 to 7.5) EDSS score, mean (95% CI): PR fampridine 5.51 (5.41 to 5.60); Placebo 5.54 (5.45 to 5.63) MSWS-12 score, mean (±SD) PR fampridine: 65.04 (21.46); Placebo: 67.15 (21.91) TUG speed (metres/second), mean (±SD) PR fampridine: 0.38 (0.18); Placebo: 0.37 (0.20)		*Post hoc* analyses for MSWS-12 score[63] PR fampridine responder (n=170) 47.1 (SE 0.9); Change from baseline, LSM (95% CI): -19 (-20.9 to -17.2) PR fampridine non-responder (n=213) 69.2 (SE 0.9); Change from baseline, LSM (95% CI): 3.1 (1.4 to 4.8) Placebo (n=382) 63.0 (SE 0.7); Change from baseline, LSM (95% CI): -3.1 (-4.4 to -1.7) *LSM difference in change from baseline for PR fampridine responder vs non-responder (95% CI): -22.1 (-24.4 to -19.8)* *LSM difference in change from baseline for PR fampridine responder vs placebo (95% CI): -16.0 (-18.0 to -13.9)* **Physical impact of MS** Defined as TUG speed (metres/second) change from baseline, LSM (SE) PR fampridine (n=383) 0.43 (0.004); Change from baseline, LSM (95% CI): 15.5 (12.77 to 18.23) Placebo (n=382) 0.40 (0.004); Change from baseline, LSM (95% CI): 11.09 (8.21 to 13.97) *LSM difference in change from baseline for PR fampridine vs placebo (95% CI):* 4.40 (0.97 to 7.83); p=0.012 Defined as proportion of patients with ≥15% improvement in TUG speed (metres/second) from baseline	conducting all data extraction in duplicate and independently. The two studies included a 24-week double-blind treatment period, and a 2-week post-dosing follow-up visit. The two studies were considered by the authors to be similar in design to enable pooling of individual-level data, although statistical heterogeneity was not formally assessed. For the pooled analysis for each visit, if ⩾50% of the MSWS-12 component items were answered but ⩾1 was not answered, item scores from the unanswered items were imputed using the respondent-specific mean score using the scores from answered items. If < 50% of the MSWS-12 component items were answered, then those unanswered component items were considered missing

[63] *Post hoc* analyses were conducted using the pooled data to evaluate each outcome in patients who met the criteria of a PR fampridine MSWS-12 responder (defined as achieving a mean improvement of ≥8 points in MSWS-12 score from baseline over 24 weeks) compared with PR fampridine MSWS-12 non-responders and placebo-treated patients.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	BBS score, mean (±SD) PR fampridine: 40.62 (11.67); Placebo: 40.05 (11.91) MSIS-29 PHYS score, mean (±SD) PR fampridine: 52.17 (20.81); Placebo: 54.90 (20.72) EQ-5D utility index score,[60] mean (±SD) PR fampridine (n=380): 0.60 (0.21); Placebo (n=380): 0.59 (0.21) EQ-5D VAS, mean (±SD) PR fampridine (n=380): 61.04 (17.96); Placebo (n=379): 57.33 (18.55)		PR fampridine (n=383): 44.1% Placebo (n=382): 34.5% *Difference between treatment groups:* OR 1.54 (95% CI: 1.13 to 2.11); p=0.007 *Sensitivity analyses (analysis not adjusted for baseline covariates):* OR 1.50 (95% CI: 1.10 to 2.03); p = 0.0094 *Post hoc* analyses for TUG speed (metres/second) change from baseline, LSM (SE)[63] PR fampridine responder (n=170) 0.45 (0.01); Change from baseline, LSM (95% CI): 22.40 (18.72 to 26.07) PR fampridine non-responder (n=213) 0.41 (SE 0.01); Change from baseline, LSM (95% CI): 9.70 (6.23 to 13.18) Placebo (n=382) 0.40 (SE 0.004); Change from baseline, LSM (95% CI): 10.91 (8.07 to 13.75) *LSM difference in change from baseline for PR fampridine responder vs non-responder (95% CI): 12.69 (7.99 to 17.40)* *LSM difference in change from baseline for PR fampridine responder vs placebo (95% CI): 11.48 (7.25 to 15.72)* Proportion of patients with ≥15% mean improvement in TUG speed PR fampridine responder: 53.9% PR fampridine non-responder: 36.5% Placebo: 34.5%	(and therefore, the total score would be missing, as well) for that visit. Missing data were imputed using the Markov Chain Monte Carlo method. A similar analysis compared the proportion of patients with MS with a ⩾15% mean improvement in TUG speed between treatment groups, and missing TUG speed individual post-baseline scores were handled as for the MSWS-12 score. Sensitivity analyses were conducted to explore the impact of adjustments and imputation on the results, and subgroup analyses were also performed. Recommendations for policy and/or practice were not discussed, but there was limited discussion around gaps in the research that would benefit from further research. **Source of funding:**

[60] MOBILE used the EQ-5D-5L; ENHANCE used the EQ-5D-3L; and the pooled analysis used the 'crosswalk' method, developed by the EuroQol Group, to map the EQ-5D-5L data to the EQ-5D-3L UK value set before calculating the utility index score.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			PR fampridine responder vs non-responder: OR 2.33 (95% CI 1.50 to 3.61); p<0.001 *PR fampridine responder vs placebo: OR 2.46 (95% CI 1.66 to 3.65); p<0.001* Defined as MSIS-29 PHYS score change from baseline, LSM PR fampridine (n=383) 46.5 (SE 0.7); Change from baseline, LSM (95% CI): −7.0 (−8.4 to −5.7) Placebo (n=382) 49.7 (SE 0.7); Change from baseline, LSM (95% CI): −3.8 (−5.2 to −2. 5) *LSM difference in change from baseline for PR fampridine vs placebo (95% CI):* −3.18 (95% CI: −4.84 to −1.52); p<0.001 *Post hoc* analyses for MSIS-29 PHYS score[63] PR fampridine responder (n=170) 37.9 (SE 0.9); Change from baseline, LSM (95% CI): −15.6 (−17.3 to −13.9) PR fampridine non-responder (n=213) 53.7 (SE 0.8); Change from baseline, LSM (95% CI): 0.2 (−1.4 to 1.7) Placebo (n=382) 49.9 (SE 0.6); Change from baseline, LSM (95% CI): −3.6 (−4.9 to −2.4) *LSM difference in change from baseline for PR fampridine responder vs non-responder (95% CI): −15.8 (−17.9 to −13.7)* *LSM difference in change from baseline for PR fampridine responder vs placebo (95% CI): −12.0 (−13.9 to −10.1)* **HRQoL**	Biogen.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Defined as EQ-5D-3L utility index score,[64] LSM PR fampridine (n=383) 0.612 (SE 0.009); Change from baseline, LSM (95% CI): 0.014 (−0.003 to 0.031) Placebo (n=382) 0.592 (SE 0.009); Change from baseline, LSM (95% CI): −0.006 (−0.023 to 0.012) *LSM difference in change from baseline for PR fampridine vs placebo (95% CI):* 0.020 (−0.001 to 0.041); p=NS *Post hoc* analyses for EQ-5D-3L utility index score[63] PR fampridine responder (n=167) 0.649 (SE 0.0117); Change from baseline, LSM (95% CI): 0.052 (0.029 to 0.075) PR fampridine non-responder (n=213) 0.580 (SE 0.0108); Change from baseline, LSM (95% CI): −0.017 (−0.038 to 0.004) Placebo (n=380) 0.591 (SE 0.009); Change from baseline, LSM (95% CI): −0.007 (−0.024 to 0.011) *LSM difference in change from baseline for PR fampridine responder vs non-responder (95% CI): 0.069 (0.040 to 0.098)* *LSM difference in change from baseline for PR fampridine responder vs placebo (95% CI): 0.059 (0.033 to 0.084)* Defined as EQ-5D VAS, LSM PR fampridine (n=383) 61.5 (SE 0.8); Change from baseline, LSM (95% CI): 2.2 (0.7 to 3.8)	

[64] Data were pooled from the ENHANCE and MOBILE RCTs using the 'crosswalk' method, developed by the EuroQol Group, and the EQ-5D-5L data was mapped to the EQ-5D-3L UK value set before calculating the combined utility index score. Analysis includes only those visits that were common between the MOBILE ENHANCE studies.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Placebo (n=382) 60.7 (SE 0.8); Change from baseline, LSM (95% CI): 1.4 (−0.3 to 3.0) *LSM difference in change from baseline for PR fampridine vs placebo (95% CI):* 0.9 (−1.0 to 2.8); p=NS *Post hoc* analyses for EQ-5D VAS score[63] PR fampridine responder (n=167) 63.9 (SE 1.1); Change from baseline, LSM (95% CI): 4.6 (2.5 to 6.7) PR fampridine non-responder (n=213) 59.6 (SE 1.0); Change from baseline, LSM (95% CI): 0.3 (−1.7 to 2.3) Placebo (n=379) 60.6 (SE 0.8); Change from baseline, LSM (95% CI): 1.3 (−0.3 to 2.9) *LSM difference in change from baseline for PR fampridine responder vs non-responder (95% CI): 4.3 (1.6 to 7.0)* *LSM difference in change from baseline for PR fampridine responder vs placebo (95% CI): 3.3 (0.9 to 5.7)* **Important outcomes** **Limb mobility/dexterity** Defined as BBS score change from baseline, LSM PR fampridine (n=383) 42.7 (SE 0.2); Change from baseline, LSM (95% CI): 2.3 (1.9 to 2.8) Placebo (n=382) 42.1 (SE 0.2); Change from baseline, LSM (95% CI): 1.7 (1.3 to 2.2) *LSM difference in change from baseline for PR fampridine vs placebo (95% CI):* 0.62 (0.09 to 1.14); p=0.021	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Post hoc analyses for BBS score[63] PR fampridine responder (n=170) 43.3 (SE 0.3); Change from baseline, LSM (95% CI): 3.0 (2.4 to 3.6) PR fampridine non-responder (n=213) 42.1 (SE 0.3); Change from baseline, LSM (95% CI): 1.8 (1.2 to 2.3) Placebo (n=382) 42.0 (SE 0.2); Change from baseline, LSM (95% CI): 1.7 (1.3 to 2.1) *LSM difference in change from baseline for PR fampridine responder vs non-responder (95% CI): 1.3 (0.5 to 2.0)* *LSM difference in change from baseline for PR fampridine responder vs placebo (95% CI): 1.3 (0.7 to 2.0)* **Proportion of treatment responders** Defined as proportion of patients with clinically meaningful ≥8 improvement in MSWS-12 score from baseline PR fampridine (n=383): 44.3% Placebo (n=382): 33.0% Difference between treatment groups: OR 1.68 (95% CI: 1.23 to 2.29); p<0.001 *Sensitivity analyses (analysis not adjusted for baseline covariates): OR 1.62 (95% CI: 1.19 to 2.19); p<0.0019* **Safety[65]**	

[65] Safety analyses were based on the safety sample (i.e. all participants randomised and exposed to study treatment). Any AE with a missing onset date and a resolution date after the first dose of study treatment was considered treatment emergent.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			See Hobart et al (2019) and Hupperts et al (2016) for safety data.	
Jensen HB, Nielsen JL, Ravnborg M, Dalgas U, Aagaard P, Stenager E. Effect of slow release-Fampridine on muscle strength, rate of force development, functional capacity and cognitive function in an enriched population of MS patients. A randomized, double blind, placebo controlled study. Multiple Sclerosis and Related Disorders. 2016;10:137-44. **Study location** Southern Denmark **Study type** Double blind RCT **Study aim** To assess the effect of slow release (SR) fampridine on muscle strength, rate of force development, functional capacity and cognitive function in people with MS **Study dates** Not reported	**Inclusion criteria** Adults aged 18 to 60 years meeting the McDonald criteria for MS; EDSS between 4 and 7 with a pyramidal functional subscore ≥2, and fulfil the responder criterion[66] **Exclusion Criteria** History of epileptic seizures; MS relapse or change in immunomodulatory treatment within 60 days; cancer within five years, clinically important systemic disease or concomitant treatment with carvedilol, propranolol, or metformin **Total sample size** N=37 (ITT) **No. of participants in each treatment group** SR fampridine: n=17 Placebo: n=20	**Interventions** SR fampridine 10 mg twice daily **Comparators** Placebo twice daily The authors did not state whether use of concomitant treatments [other than those stated in the exclusion criteria] were permitted.	Follow-up duration four weeks **Critical outcomes** **Walking ability** <u>Defined as functional capacity measured using T25FW, mean (±SD)</u> SR fampridine: 11.3 (9.2); mean change from baseline (±SD) [% change from baseline (±SD)]: −3.3 (9.5) [−13.6 (18.3)] Placebo: 8.3 (3.8); mean change from baseline (±SD) [% change from baseline (±SD)]: 0.3 (1.8) [4.7 (24.1)] *Between group difference in mean change from baseline: p=0.02* <u>Functional capacity measured using SSST, mean (±SD)</u> SR fampridine: 20.2 (14.8); mean change from baseline (±SD) [% change from baseline (±SD)]: −3.25 (8.0) [−11.4 (17.7)] Placebo: 14.5 (7.4); mean change from baseline (±SD) [% change from baseline (±SD)]: 0.6 (3.2) [3.8 (19.6)] *Between group difference in mean change from baseline: p=0.005* **Important outcomes** **Limb mobility/dexterity**	This study was appraised using the JBI Critical Appraisal Tool for RCTs. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Unclear 7. Unclear 8. Yes 9. Unclear 10. Yes 11. Yes 12. Unclear 13. Yes **Other comments:** The RCT was preceded by an open label enrichment phase; responders to SR fampridine were included in this RCT after a one week

[66] Responders were defined as patients who had previously responded to SR-Fampridine treatment (i.e. the top 40% of patients showing the most marked improvements on SSST).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Baseline characteristics Age (years), mean (±SD): SR fampridine 50.8 (6.5); Placebo: 48.4 (6.4) Sex (female), %: SR fampridine 47; Placebo 65 EDSS score, mean (±SD): SR fampridine 5.8 (0.8); Placebo: 5.5 (0.7) Functional capacity measured using T25FW, mean (±SD) SR fampridine: 14.1 (17.0); Placebo: 8.3 (3.8) Functional capacity measured using SSST, mean (±SD) SR fampridine: 20.2 (14.8); Placebo: 13.9 (6.5) Functional capacity measured using 5-STS, mean (±SD)		Functional capacity measured using 5-STS, mean (±SD) SR fampridine: 13.9 (5.2); mean change from baseline (±SD) [% change from baseline (±SD)]: −2.5 (4.0) [−7.6 (37.1)] Placebo: 13.8 (5.0); mean change from baseline (±SD) [% change from baseline (±SD)]: 0.2 (2.3) [1.6 (13.7)] *Between group difference in mean change from baseline: p=0.006* Hand dexterity measured using 9-HPT, mean (±SD) SR fampridine: 29.1 (11.2); mean change from baseline (±SD) [% change from baseline (±SD)]: −0.3 (2.6) [−1.0 (8.4)] Placebo: 28.5 (9.3); mean change from baseline (±SD) [% change from baseline (±SD)]: 0.6 (4.4) [4.1 (12.0)] *Between group difference in mean change from baseline: p=0.1* Defined as composite scores for maximal concentric and isometric muscle strength using isokinetic dynamometry, mean (±SD)[67] *Weakest leg – MVC (Nm)* *Knee extension* SR fampridine: 283.6 (103.4); mean change from baseline (±SD) (% change from baseline [±SD]): 29.5 (63.6) [11.6 (24.1)]	washout period. Responders were defined as patients (the top 40%) showing the most marked improvements on SSST. Including only responders to treatment introduces serious selection bias. It was unclear whether treatment groups were treated identically (other than the intervention of interest) as the authors did not state whether concomitant treatments were permitted and, if so, whether there were differences across treatment groups. Although the RCT was double-blind it was unclear whether outcome assessors were blind to treatment assignment. Details on the reliability of the measurements used, e.g. the number of raters, training of raters, the intra-rater

[67] Maximal concentric and isometric muscle strength for the knee extension (KE), knee flexion (KF) and hip flexion (HF) were determined using isokinetic dynamometry. Both legs were tested separately. Concentric KE and KF strength was evaluated at slow (30°/s) and fast (180°/s) angular velocities at a range of motion (ROM) of 90–20° (full extension=0°). Concentric HF strength was tested at slow (30°/s) and moderate (120°/s) angular velocities, using a ROM of 0–45° (neutral standing=0°). Isometric KE/KF strength tests were performed at a fixed knee joint angle of 70°, while isometric HF strength was tested at 20° fixed hip flexion angle.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	SR fampridine: 16.4 (6.2); Placebo: 13.6 (4.9) <u>Hand dexterity measured using 9-HPT, mean (±SD)</u> SR fampridine: 29.2 (10.7); Placebo: 28.9 (11.4) <u>Composite scores for maximal concentric and isometric muscle strength using isokinetic dynamometry, mean (±SD)</u> *Weakest leg – MVC (Nm)* *Knee extension* SR fampridine: 258.0 (80.1) Placebo: 254.3 (141.9) *Knee flexion* SR fampridine: 128.1 (51.0) Placebo: 114.4 (63.4) *Hip flexion* SR fampridine: 195.1 (77.1) Placebo: 212.0 (95.3)		Placebo: 247.0 (126.6); mean change from baseline (±SD) (% change from baseline [±SD]): −7.3 (28.1) [−0.8 (11.3)] *Between group difference in mean change from baseline: p=0.03* *Knee flexion* SR fampridine: 143.1 (69.8); mean change from baseline (±SD) (% change from baseline [±SD]): 15.6 (43.1) [11.2 (29.5)] Placebo: 112.2 (68.3); mean change from baseline (±SD) (% change from baseline [±SD]): −2.2 (12.4) [−4.8 ± 12.9)] *Between group difference in mean change from baseline: p=0.03* *Hip flexion* SR fampridine: 277.7 (100.7); mean change from baseline (±SD) (% change from baseline [±SD]): 29.9 (42.6) [14.3 (14.9)] Placebo: 201.6 (89.1); mean change from baseline (±SD) (% change from baseline [±SD]): −2.8 (41.3) [−1.3 (20.5)] *Between group difference in mean change from baseline: p=0.05* *Weakest leg – Rate of force development (Nm/second)* *Knee extension* SR fampridine: 1,132.3 (687.4); mean change from baseline (±SD) (% change from baseline [±SD]): 221.9 (408.5) [23.3 (32.2)]	and the inter-rater reliability within the study, were not reported. The study was underpowered as n=25 patients were needed in each treatment arm, which can reduce the validity of the study findings. One patient in each treatment arm was lost to follow-up. The authors reported data separately for concentric and isometric muscle strength and rate of force development, for the weakest and strongest leg, but we have only reported data for the composite scores, The authors also measured cognitive function using the SDMT, but data are not reported here as this was not an outcome of interest. **Source of funding:** Region of Southern Denmark, the Research Fund of the MS-clinic of Southern

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Weakest leg – Rate of force development (Nm/s) *Knee extension* SR fampridine: 947.7 (651.3) Placebo: 951.9 (654.4) *Knee flexion* SR fampridine: 268.2 (231.9) Placebo: 248.7 (179.2) *Hip flexion* SR fampridine: 777.6 (552.5) Placebo: 774.0 (597.0) *Strongest leg – MVC (Nm)* *Knee extension* SR fampridine: 292.5 (95.2) Placebo: 329.4 (146.9) *Knee flexion* SR fampridine: 154.0 (60.5) Placebo: 160.9 (81.6) *Hip flexion*		Placebo: 900.6 (670.4); mean change from baseline (±SD) (% change from baseline [±SD]): −51.3 (311.2) [−2.2 (30.3)] *Between group difference in mean change from baseline: p=0.002* *Knee flexion* SR fampridine: 349.6 (263.1); mean change from baseline (±SD) (% change from baseline [±SD]): 93.1 (119.4) [34.7 (43.0)] Placebo: 217.8 (170.9); mean change from baseline (±SD) (% change from baseline [±SD]): −30.8 (85.7) [−6.7 (32.2)] *Between group difference in mean change from baseline: p<0.001* *Hip flexion* SR fampridine: 874.4 (651.7); mean change from baseline (±SD) (% change from baseline [±SD]): 96.8 (557.8) [12.4 (51.2)] Placebo: 612.9 (482.3); mean change from baseline (±SD) (% change from baseline [±SD]): −138.6 (259.0) [−8.4 (54.4)] *Between group difference in mean change from baseline: p=0.09* *Strongest leg – MVC (Nm)* *Knee extension* SR fampridine: 318.7 (87.8); mean change from baseline (±SD) (% change from baseline [±SD]): 19.0 (36.7) [8.3 (13.4)]	Jutland, and Biogen Idec.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	SR fampridine: 241.4 (107.0) Placebo: 268.8 (132.2) *Strongest leg – Rate of force development (Nm/s)* *Knee extension* SR fampridine: 1,199.0 (860.6) Placebo: 1,434.4 (964.2) *Knee flexion* SR fampridine: 425.8 (92.6) Placebo: 527.6 (299.7) *Hip flexion* SR fampridine: 1,000.2 (703.8) Placebo 993.9 (747.3)		Placebo: 334.7 (147.3); mean change from baseline (±SD) (% change from baseline [±SD]): 5.3 (20.1) [1.5 (6.3)] *Between group difference in mean change from baseline: p=0.06* *Knee flexion* SR fampridine: 177.6 (67.9); mean change from baseline (±SD) (% change from baseline [±SD]): 20.5 (26.5) [13.7 (16.5)] Placebo: 170.0 (89.0); mean change from baseline (±SD) (% change from baseline [±SD]): 9.2 (27.3) [4.1 (19.6)] *Between group difference in mean change from baseline: p=0.08* *Hip flexion* SR fampridine: 257.8 (97.7); mean change from baseline (±SD) (% change from baseline [±SD]): 16.5 (72.0) [10.9 (28.2)] Placebo: 281.9 (122.8); mean change from baseline (±SD) (% change from baseline [±SD]): 13.2 (45.7) [8.3 (16.4)] *Between group difference in mean change from baseline: p=0.9* *Strongest leg – Rate of force development (Nm/second)* *Knee extension* SR fampridine: 1,402.6 (610.6); mean change from baseline (±SD) (% change from baseline [±SD]): 159.1 (498.0) [13.3 (32.3)]	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Placebo: 1,528.6 (961.9); mean change from baseline (±SD) (% change from baseline [±SD]): 94.2 (371.9) [14.6 (36.4)] *Between group difference in mean change from baseline: p=0.2* *Knee flexion* SR fampridine: 609.2 (413.3); mean change from baseline (±SD) (% change from baseline [±SD]): 175.4 (270.7) [41.2 (63.5)] Placebo: 559.6 (381.8); mean change from baseline (±SD) (% change from baseline [±SD]): 32.0 (190.2) [18.6 (56.1)] *Between group difference in mean change from baseline: p=0.1* *Hip flexion* SR fampridine: 1,241.5 (1,140.9); mean change from baseline (±SD) (% change from baseline [±SD]): 241.4 (947.8) [33.4 (93.9)] Placebo: 1,010.3 (697.1); mean change from baseline (±SD) (% change from baseline [±SD]): 16.3 (303.2) [1.6 (8.8)] *Between group difference in mean change from baseline: p=0.3*	
Marzal-Alfaro MB, Martin Barbero ML, Garcia Dominguez J, Romero-Delgado F, Martinez Gines ML, Herranz A, Sanjurjo-Saez M. Impact of fampridine on quality of life: clinical benefit in real-world practice. European Journal	**Inclusion criteria** Patients with diagnosed MS, EDSS >4 and <7, absence of seizure disorder antecedents and normal renal function	**Interventions** Fampridine: 10 mg twice daily **Comparators** No comparator group Immunomodulatory treatments (e.g.	**Important outcomes** **Activities of daily living** <u>EDSS score for all patients (i.e. fampridine responders and non-responders), mean (±SD)</u> At baseline (n=30): 5.8 (0.9) At 2 weeks (n=27): 5.8 (NR)	This study was appraised using the JBI Critical Appraisal Tool for case series 1. Yes 2. Unclear 3. Unclear

Study details	Population	Interventions	Study outcomes	Appraisal and funding
of Hospital Pharmacy Science & Practice. 2018;25(3):138-43. **Study location** Spain **Study type** Prospective case series **Study aim** To assess the efficacy and safety of fampridine in patients with MS and walking impairment in clinical practice **Study dates** May 2014 to May 2015 (including follow-up)	(creatinine clearance >80 mL/min) **Exclusion Criteria** Disease instability as evidenced by recent MS relapse or change in immunomodulatory therapy **Total sample size** N=30 **No. of participants in each treatment group** Fampridine: N=30 Control: None **Baseline characteristics** Age (years) mean (±SD): 39.1 (9.7) Sex (female), n (%): 14 (46.7) Duration of MS (years), mean (±SD): 13.7 (6.4) <u>MS types, n (%)</u> RRMS: 17 (56.7%) SPMS: 9 (30%) PPMS: 3 (10%) PRMS: 1 (3.3%)	natalizumab, fingolimod) were used concomitantly in patients.	At 3 months (n=26): 5.8 (NR) At 6 months (n=18): 5.7 (NR)	4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:** This was a prospective case series including data from 30 consecutively recruited patients with MS and walking impairment treated with fampridine. Details were provided on study methods and statistical analyses. Baseline characteristics were presented for all patients and reasons for loss to follow-up were reported. Patients initially received fampridine for 14 days, at which point patients who responded to treatment were selected. Patients who did not experience significant adverse effects, who reported a

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Use of walking aids, mean (±SD): 24 (80%) EDSS, mean (±SD): 5.8 (0.9)			favourable response to fampridine and showed an improvement of at least 20% in T25FWand any percentage in MSWS-12 continued taking fampridine. Eight of 30 patients (27%) discontinued treatment with fampridine: 3 after 15 days of treatment, 2 after 3 months and 3 after 6 months. Reasons for withdrawal were perceived lack of effectiveness in four patients (50%), poor tolerability in three patients (37.5%) and both poor effectiveness and tolerability in one patient (12.5%). **Source of funding:** Not commissioned.
Zhao X, Yang H, Wei T, Zhao J, Liu J, Huang Z, et al. Cost-effectiveness analysis of prolonged-release fampridine to treat walking disability of multiple sclerosis in China. Journal of Comparative	**Inclusion criteria** Chinese adults with MS and EDSS scores between 4 and 7 **Exclusion Criteria** None stated	**Interventions** PR fampridine 10 mg tablet plus BSC **Comparators** BSC alone BSC includes other supportive drugs,	**Important outcomes** **Cost-effectiveness**[68] <u>Base case analysis (costs per treatment for patients with MS and walking impairment, over a 10 year horizon) (Chinese Yuan)</u> Total costs included the cost of PR fampridine (27,769 Chinese Yuan), healthcare professional and	**Comments:** This is a cost-effectiveness analysis comparing PR fampridine plus BSC to BSC alone in Chinese adults with MS and walking impairment.

[68] Current conversion rate 1.00 Chinese Yuan = 0.10 British pounds (dated 22nd January 2024).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Effectiveness Research. 2022;11(14):1057-69. **Study location** China **Study type** Cost-effectiveness analysis from Chinese societal and healthcare perspectives, reporting health outcomes in terms of QALYs and ICERs **Study aim** To evaluate the cost-effectiveness of PR fampridine plus BSC versus BSC alone in the treatment of adults in China with MS and walking impairment **Study dates** Cost-effectiveness based on sources published between 2002 and 2022	**Total sample size** Not stated **No. of participants in each treatment group** Not stated **Baseline characteristics** The starting age of the modelled cohort was calculated using the mean age of MS diagnosis in China from a published source and the mean duration from the diagnosis of MS in patient to treatment with PR fampridine in the ENHANCE study (i.e. 170 months): Mean age at MS diagnosis (years): 34.1 Sex, % (male): 36 Time from MS diagnosis to taking PR fampridine (months): 170 Time T25FW (feet/second): 2.1	examinations and laboratory tests, hospitalisation, rehabilitation, neurologist visits and other outpatient visits.	hospital visits, tests and examinations, other supportive drugs, adverse event costs, walking aids, and loss of productivity Total costs from the healthcare perspective: PR fampridine plus BSC 713,746; BSC alone 731,075 Total costs from the societal perspective: PR fampridine plus BSC 979,551; BSC alone 1,016,016 Total QALY (QALYs): PR fampridine plus BSC 4.94; BSC alone 4.79 **Incremental** Δ Cost from the healthcare perspective: PR fampridine plus BSC -17,329 Δ Cost from the societal perspective: PR fampridine plus BSC -36,465 Δ QALY (QALYs): PR fampridine plus BSC 0.15 ICER from the healthcare perspective (Chinese Yuan/QALY): PR fampridine plus BSC Dominant (-113,488) ICER from the societal perspective (Chinese Yuan/QALY): PR fampridine plus BSC Dominant (-238,806) <u>Sensitivity analysis</u> One-way sensitivity analyses were performed comparing PR fampridine plus BSC versus BSC alone. The most sensitive parameters were the cost of rehabilitation and the utility value assigned to the BSC group at week 24 and later. Probabilistic sensitivity analyses were also performed using 5,000 iterations. Uncertainty around model parameter estimates was based on	Model parameters were based on clinical studies evaluating PR fampridine vs placebo in patients with MS and walking impairment, published sources and clinical expert interviews. It was unclear how published sources were identified. The cost-effectiveness analysis was based on a hybrid decision tree (for response assessment in the first 4 weeks of treatment) and a Markov model with a cycle length of 4 weeks, allowing health outcomes and costs to be accumulated over time. The analysis was conducted from Chinese societal and healthcare perspectives, over a 10 year time horizon. Discounting for costs and QALYs was applied at a rate of 5%, and a half-cycle correction was applied in accordance with Chinese pharmacoeconomic guidelines.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			their calculated or reported patient counts, standard deviations or ranges, depending on the parameter. Probability of PR fampridine plus BSC being considered to be cost-effective versus BSC alone using a WTP threshold of 80,976 Chinese Yuan/QALY gained: 100% <u>Cost-effectiveness scenario analysis for PR fampridine plus BSC vs BSC alone (Chinese Yuan)</u> **Scenario 1: 20 year time horizon** Total costs from the healthcare perspective: PR fampridine plus BSC 1,175,633; BSC alone 1,193,502 Total costs from the societal perspective: PR fampridine plus BSC 1,586,671; BSC alone 1,625,765 Total QALY (QALYs): PR fampridine plus BSC 7.63; BSC alone 7.45 ICER from the healthcare perspective (Chinese Yuan/QALY): PR fampridine plus BSC Dominant (-96,522) ICER from the societal perspective (Chinese Yuan/QALY): PR fampridine plus BSC Dominant (-211,175) **Scenario 2: utilities from ENHANCE trial** Total costs from the healthcare perspective: PR fampridine plus BSC 713,746; BSC alone 731,075 Total costs from the societal perspective: PR fampridine plus BSC 979,551; BSC alone 1,016,016 Total QALY (QALYs): PR fampridine plus BSC 5.02; BSC alone 4.92	In the base case analysis, treatment response was defined as a mean improvement of ≥8 on the MSWS-12 scale (from the ENHANCE study) and was applied to calculate the first 4 weeks' effectiveness of PR fampridine. Disease progression was measured using T25FW scores obtained from placebo arms in the IMPACT and ASCEND studies. The primary outcomes were QALYs gained and ICERs/QALY. The QALY difference between PR fampridine plus BSC and BSC alone was calculated based on pooled EQ-5D values from the ENHANCE and MOBILE studies. Appropriate one-way and probabilistic sensitivity analyses were performed to test the assumptions used. Scenario analyses were also performed to assess the impact of varying the time horizon and different

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			ICER from the healthcare perspective (Chinese Yuan/QALY): PR fampridine plus BSC Dominant (-169,756) ICER from the societal perspective (Chinese Yuan/QALY) PR fampridine plus BSC Dominant (-357,210) **Scenario 3: utilities from MOBILE trial** Total costs from the healthcare perspective: PR fampridine plus BSC 713,746; BSC alone 731,075 Total costs from the societal perspective: PR fampridine plus BSC 979,551; BSC alone 1,016,016 Total QALY (QALYs): PR fampridine plus BSC 4.53; BSC alone 4.14 ICER from the healthcare perspective (Chinese Yuan/QALY): PR fampridine plus BSC Dominant (-44,251) ICER from the societal perspective (Chinese Yuan/QALY); PR fampridine Dominant (-93,115)	sources of utility values. Limitations of the study (as acknowledged by the authors) included the need to extrapolate data on T25FW to model long term treatment effect due to lack of availability of long term data for MSWS-12. In addition, because there were no available data regarding the utilities for PR fampridine responders and BSC beyond 24 weeks, it was assumed that there were no utility changes for patients in the subsequent weeks, which may not reflect that there may be variation in utility values. **Source of funding:** Biogen China

Abbreviations

ADLs: activities of daily living; AE: adverse event; BBS: Berg balance scale; BSC: best supportive care; BMI: body mass index; CI: confidence interval; CrCl: creatinine clearance; EDSS: expanded disability status scale; EQ-5D; EuroQol 5-dimensions; HF: hip flexion; 9-HPT: 9-hole peg test; HRQoL: health related quality of life; ICER: incremental cost-effectiveness ratio; ITT: intention to treat; KE: knee extension; KF: knee flexion; LSM: least square means; LY: life years; mITT: modified intention-to-treat; MS: multiple sclerosis; MSIS-29 PHYS: multiple sclerosis impact scale-29 physical subscale; MSIS-29 PSYCH: multiple sclerosis impact scale-29 psychological subscale; MSWS-12: multiple sclerosis walking scale-12; MVC: maximal voluntary contraction; n: number; Nm: Newton meter; NR: not reported; NS: not significant; OR: odds ratio; PGIC: patient global impression of change; PICO: population, intervention, comparator, outcomes; PPMS: primary progressive multiple sclerosis; PR: prolonged release; PRMS: progressive-relapsing multiple sclerosis; QALY: quality adjusted life years; RCT: randomised controlled trial; RRMS: relapsing-remitting multiple sclerosis; SAE: serious adverse event; SD: standard deviation; SE: standard

Study details	Population	Interventions	Study outcomes	Appraisal and funding
error; SPMS: secondary progressive multiple sclerosis; SR: slow release; SSST: six spot step test; 5-STS: 5 times sit to stand; T25FW: timed 25 foot walk; TUG: timed up and go; VAS: visual analogue scale; WTP: willingness to pay.				

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses

1. Is the review question clearly and explicitly stated?
2. Were the inclusion criteria appropriate for the review question?
3. Was the search strategy appropriate?
4. Were the sources and resources used to search for studies adequate?
5. Were the criteria for appraising studies appropriate?
6. Was critical appraisal conducted by two or more reviewers independently?
7. Were there methods to minimize errors in data extraction?
8. Were the methods used to combine studies appropriate?
9. Was the likelihood of publication bias assessed?
10. Were recommendations for policy and/or practice supported by the reported data?
11. Were the specific directives for new research appropriate?

JBI Critical Appraisal Checklist for Randomised Controlled Trials

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were treatment groups treated identically other than the intervention of interest?
7. Were outcome assessors blind to treatment assignment?
8. Were outcomes measured in the same way for treatment groups?
9. Were outcomes measured in a reliable way?
10. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?
11. Were participants analysed in the groups to which they were randomised?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate and any deviations from the standard RCT design (individual randomisation, parallel groups) accounted for in the conduct and analysis of the trial?

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

For abbreviations and footnotes see end of table

In people with MS and associated walking impairment (as defined by EDSS 4 to 7.5), what is the clinical effectiveness of PR fampridine compared to standard care alone or standard care and placebo?

Table 2: PR fampridine vs placebo

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	PR fampridine	Placebo	Result		
Walking ability – 1 *post hoc* integrated analysis of 2 RCTs, 3 RCTs									
Patients reporting improvement on PGIC[a] n (%) at two weeks follow-up (post hoc analysis) [higher numbers indicate benefit]									
1 RCT (MOBILE) Hupperts et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 31 (46) Placebo: 16 (26) *Difference between PR fampridine vs placebo: p=0.023*	Critical	MODERATE
T25FW,[b] mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [negative values indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: −3.3 (9.5) [−13.6 (18.3)] Placebo: 0.3 (1.8) [4.7 (24.1)] *Difference between PR fampridine vs placebo: p=0.02*	Critical	VERY LOW
SSST,[c] mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [negative values indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: −3.25 (8.0) [−11.4 (17.7)] Placebo: 0.6 (3.2) [3.8 (19.6)] *Difference between PR fampridine vs placebo: p=0.005*	Critical	VERY LOW
MSWS-12 score,[d] LSM (95% CI) change from baseline to 24 weeks follow-up [higher negative values indicate benefit]									
1 *post hoc* integrated analysis of 2 RCTs	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	383	382	PR fampridine: -6.9 (-8.5 to -5.4) Placebo: -3.2 (-4.8 to -1.6)	Critical	MODERATE

(ENHANCE, MOBILE) Hupperts et al 2022							*Difference between PR fampridine vs placebo: −3.70 (−5.61 to −1.79); p<0.001*		
MSWS-12 score, mean improvement of ≥1 point from baseline to 24 weeks follow-up, n (%) [higher numbers indicate benefit]									
1 RCT (MOBILE) Hupperts et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 44 (64.7) Placebo: 35 (54.7) *Difference between PR fampridine vs placebo: p=NS*	Critical	MODERATE
MSWS-12 score, mean improvement of ≥2 points from baseline to 24 weeks follow-up, n (%) [higher numbers indicate benefit]									
1 RCT (MOBILE) Hupperts et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 42 (61.8) Placebo: 33 (51.6) *Difference between PR fampridine vs placebo: p=NS*	Critical	MODERATE
MSWS-12 score, mean improvement of ≥3 points from baseline to 24 weeks follow-up, n (%) [higher numbers indicate benefit]									
1 RCT (MOBILE) Hupperts et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 42 (61.8) Placebo: 32 (50.0) *Difference between PR fampridine vs placebo: p=NS*	Critical	MODERATE
MSWS-12 score, mean improvement of ≥4 points from baseline to 24 weeks follow-up, n (%) [higher numbers indicate benefit]									
1 RCT (MOBILE) Hupperts et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 42 (61.8) Placebo: 30 (46.9) *Difference between PR fampridine vs placebo: p=NS*	Critical	MODERATE
MSWS-12 score, mean improvement of ≥5 points from baseline to 24 weeks follow-up, n (%) [higher numbers indicate benefit]									
1 RCT (MOBILE) Hupperts et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 37 (54.4) Placebo: 26 (40.6) *Difference between PR fampridine vs placebo: p=NS*	Critical	MODERATE
MSWS-12 score, mean improvement of ≥6 points from baseline to 24 weeks follow-up, n (%) [higher numbers indicate benefit]									

1 RCT (MOBILE) Hupperts et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 35 (51.5) Placebo: 23 (35.9) *Difference between PR fampridine vs placebo: p=NS*	Critical	MODERATE
MSWS-12 score, mean improvement of ≥7 points from baseline to 24 weeks follow-up, n (%) [higher numbers indicate benefit]									
1 RCT (MOBILE) Hupperts et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 34 (50.0) Placebo: 20 (31.3) *Difference between PR fampridine vs placebo: p<0.0275*	Critical	MODERATE
MSWS-12 score, mean improvement of MCID ≥8 points from baseline to 24 weeks follow-up, (%; n not reported)[e] [higher numbers indicate benefit]									
1 *post hoc* integrated analysis of 2 RCTs (ENHANCE, MOBILE) Hupperts et al 2022	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	383	382	PR fampridine: 44.3 Placebo: 33.0 *Difference between PR fampridine vs placebo: OR 1.68 (95% CI: 1.23 to 2.29); p<0.001*	Critical	MODERATE
MSWS-12 score, mean improvement of ≥9 points from baseline to 24 weeks follow-up, n (%) [higher numbers indicate benefit]									
1 RCT (MOBILE) Hupperts et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 33 (48.5) Placebo: 17 (26.6) *Difference between PR fampridine vs placebo: p<0.0088*	Critical	MODERATE
MSWS-12 score, mean improvement of ≥10 points from baseline to 24 weeks follow-up, n (%) [higher numbers indicate benefit]									
1 RCT (MOBILE) Hupperts et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 28 (41.2) Placebo: 17 (26.6) *Difference between PR fampridine vs placebo: p=NS*	Critical	MODERATE
1 RCT (ENHANCE)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	315	318	PR fampridine: n not reported (38) Placebo: n not reported (27)	Critical	MODERATE

Hobart et al 2019							*Difference between PR fampridine vs placebo: p=0.003*		
MSWS-12 score at 26 weeks follow-up (two weeks after discontinuation of treatment with PR fampridine									
1 RCT (MOBILE) Hupperts et al 2016	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	68	64	The authors stated that *"after treatment discontinuation at week 24, improvements declined and approached zero by the week 26 follow-up visit in the PR-fampridine group"*	Critical	LOW
1 RCT (ENHANCE) Hobart et al 2019	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	315	318	The authors stated that *"within 2 weeks of stopping PR-fampridine treatment, the effects of PR-fampridine on the MSWS-12 dissipated"*	Critical	LOW
Physical impact of MS - 1 *post hoc* integrated analysis of 2 RCTs									
TUG speed (metres/second),[f] LSM (95% CI) change from baseline to 24 weeks follow-up [higher scores indicate benefit]									
1 *post hoc* integrated analysis of 2 RCTs (ENHANCE, MOBILE) Hupperts et al 2022	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	383	382	PR fampridine: 15.5 (12.77 to 18.23) Placebo: 11.09 (8.21 to 13.97) *LSM difference in change from baseline between PR fampridine vs placebo: 4.40 (0.97 to 7.83); p=0.012*	Critical	MODERATE
Proportion of patients achieving MCID ≥15% improvement in TUG speed (metres/second), change from baseline to 24 weeks follow-up (OR, 95% CI) [higher scores indicate benefit]									
1 *post hoc* integrated analysis of 2 RCTs (ENHANCE, MOBILE) Hupperts et al 2022	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	383	382	PR fampridine: 44.1% Placebo: 34.5% *LSM difference in change from baseline between PR fampridine vs placebo: 1.54 (91.13 to 2.11); p=0.007*	Critical	MODERATE
MSIS-29 PHYS score,[g] LSM (95% CI) change from baseline to 24 weeks follow-up									

1 *post hoc* integrated analysis of 2 RCTs (ENHANCE, MOBILE) Hupperts et al 2022	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	383	382	PR fampridine −7.0 (−8.4 to −5.7) Placebo: −3.8 (−5.2 to −2. 5) *LSM difference in change from baseline between PR fampridine vs placebo: −3.18 (95% CI: −4.84 to −1.52); p<0.001*	Critical	MODERATE
TUG speed at 26 weeks follow-up (two weeks after discontinuation of treatment with PR fampridine									
1 RCT (MOBILE) Hupperts et al 2016	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	68	64	The authors stated that *"after treatment discontinuation at week 24, improvements declined and approached zero by the week 26 follow-up visit in the PR-fampridine group"*	Critical	LOW
HRQoL - 1 *post hoc* integrated analysis of 2 RCTs, 1 *post hoc* analysis of 1 RCT									
EQ-5D-3L utility index score, LSM (95% CI) change from baseline to 24 weeks follow-up [higher positive scores indicate benefit]									
1 *post hoc* integrated analysis of 2 RCTs (ENHANCE, MOBILE) Hupperts et al 2022	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	383	382	PR fampridine: 0.014 (−0.003 to 0.031) Placebo: −0.006 (−0.023 to 0.012) *LSM difference in change from baseline between PR fampridine vs placebo: 0.020 (−0.001 to 0.041); p=NS*	Critical	MODERATE
EQ-5D VAS, LSM (95% CI) change from baseline to 24 weeks follow-up [higher positive scores indicate benefit]									
1 *post hoc* integrated analysis of 2 RCTs (ENHANCE, MOBILE) Hupperts et al 2022	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	383	382	PR fampridine: 2.2 (0.7 to 3.8) Placebo: 1.4 (−0.3 to 3.0) *LSM difference in change from baseline between PR fampridine vs placebo: 0.9 (−1.0 to 2.8); p=NS*	Critical	MODERATE
MSIS-29 PSYCH score,[h] % difference in mean reduction in score from baseline to four weeks follow-up [greater percentage indicates benefit]									

1 *post hoc* analysis of 1 RCT (MOBILE) Gasperini et al 2016	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	68	64	Difference between PR fampridine vs placebo in the mean reduction in scores from baseline: 42%	Critical	LOW
MSIS-29 PSYCH score,[h] % difference in mean reduction in score from baseline to 12 weeks follow-up [greater percentage indicates benefit]									
1 *post hoc* analysis of 1 RCT (MOBILE) Gasperini et al 2016	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	68	64	Difference between PR fampridine vs placebo in the mean reduction in scores from baseline: 57%	Critical	LOW
MSIS-29 PSYCH score,[h] proportion of patients showing mean improvement in individual item scores from baseline to 12 weeks follow-up									
1 *post hoc* analysis of 1 RCT (MOBILE) Gasperini et al 2016	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	68	64	A greater proportion of patients treated with PR fampridine versus placebo showed mean improvements in six of the nine PSYCH items; the difference was statistically significant for one item *"worries related to your MS"* ; p=0.044	Critical	LOW
MSIS-29 PSYCH score,[h] % difference in mean reduction in score from baseline to 24 weeks follow-up [greater percentage indicates benefit]									
1 *post hoc* analysis of 1 RCT (MOBILE) Gasperini et al 2016	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	68	64	Difference between PR fampridine vs placebo in the mean reduction in scores from baseline: 148%	Critical	LOW
MSIS-29 PSYCH score,[h] proportion of patients showing mean improvement in individual item scores from baseline to 24 weeks follow-up									
1 *post hoc* analysis of 1 RCT (MOBILE) Gasperini et al 2016	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	68	64	A greater proportion of patients treated with PR-fampridine versus placebo showed mean improvements in six of the nine PSYCH items; the difference was statistically significant for one item *"worries related to your MS;"* p=0.006	Critical	LOW

							A greater proportion of patients treated with placebo versus PR fampridine showed mean improvements in the remaining three PSYCH items over 12 and 24 weeks, but the difference was not statistically significant.		
Limb mobility/dexterity – iml									
5-STS (for functional capacity),[i] mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [negative values indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: −2.5 (4.0) [−7.6 (37.1)] Placebo: 0.2 (2.3) [1.6 (13.7)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.006*	Important	VERY LOW
9-HPT (for hand dexterity),[j] mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [negative values indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: −0.3 (2.6) [−1.0 (8.4)] Placebo: 0.6 (4.4) [4.1 (12.0)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.1*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – weakest leg (MVC [Nm] – knee extension), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 29.5 (63.6) [11.6 (24.1)] Placebo: −7.3 (28.1) [−0.8 (11.3)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.03*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – weakest leg (MVC [Nm] – knee flexion), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 15.6 (43.1) [11.2 (29.5)] Placebo: −2.2 (12.4) [−4.8 ± 12.9)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.03*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – weakest leg (MVC [Nm] – hip flexion), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									

1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 29.9 (42.6) [14.3 (14.9)] Placebo: −2.8 (41.3) [−1.3 (20.5)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.05*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – weakest leg (rate of force development [Nm/s] – knee extension), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 221.9 (408.5) [23.3 (32.2)] Placebo: −51.3 (311.2) [−2.2 (30.3)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.002*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – weakest leg (rate of force development [Nm/s] – knee flexion), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 93.1 (119.4) [34.7 (43.0)] Placebo: −30.8 (85.7) [−6.7 (32.2)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p<0.001*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – weakest leg (rate of force development [Nm/s] – hip flexion), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 96.8 (557.8) [12.4 (51.2)] Placebo: −138.6 (259.0) [−8.4 (54.4)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.09*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – strongest leg (MVC [Nm] – knee extension), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 19.0 (36.7) [8.3 (13.4)] Placebo: 5.3 (20.1) [1.5 (6.3)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.06*	Important	VERY LOW

Composite scores for maximal concentric and isometric muscle strength – strongest leg (MVC [Nm] – knee flexion), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 20.5 (26.5) [13.7 (16.5)] Placebo: 9.2 (27.3) [4.1 (19.6)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.08*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – strongest leg (MVC [Nm] – hip flexion), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 16.5 (72.0) [10.9 (28.2)] Placebo: 13.2 (45.7) [8.3 (16.4)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.9*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – strongest leg (rate of force development [Nm/s] – knee extension), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 159.1 (498.0) [13.3 (32.3)] Placebo: 94.2 (371.9) [14.6 (36.4)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.2*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – strongest leg (rate of force development [Nm/s] – knee flexion), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 175.4 (270.7) [41.2 (63.5)] Placebo: 32.0 (190.2) [18.6 (56.1)] *Difference in mean change from baseline between PR fampridine vs placebo*: *p=0.1*	Important	VERY LOW
Composite scores for maximal concentric and isometric muscle strength – strongest leg (rate of force development [Nm/s] – hip flexion), mean (±SD) [% (±SD)] change from baseline to four weeks follow-up [higher numbers indicate benefit]									
1 RCT Jensen et al 2016	Very serious limitations[2]	Very serious indirectness[3]	Not applicable	Not calculable	17	20	SR fampridine: 241.4 (947.8) [33.4 (93.9)] Placebo: 16.3 (303.2) [1.6 (8.8)]	Important	VERY LOW

							Difference in mean change from baseline between PR fampridine vs placebo: *p=0.3*		
ABILHAND score,[k] LSM (95% CI) change from baseline to 24 weeks follow-up [higher scores indicate benefit]									
1 RCT (ENHANCE) Hobart et al 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	312	315	PR fampridine: 1.49 (0.36 to 2.61) Placebo: 0.75 (−0.41 to 1.91) *LSM difference in change from baseline between PR fampridine vs placebo: 0.74 (−0.38 to 1.86); p=0.197*	Important	MODERATE
BBS score,[l] LSM (95% CI) change from baseline to 24 weeks follow-up [higher scores indicate benefit]									
1 *post hoc* integrated analysis of 2 RCTs (ENHANCE, MOBILE) Hupperts et al 2022	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	383	382	PR fampridine: 2.3 (1.9 to 2.8) Placebo: 1.7 (1.3 to 2.2) *LSM difference in change from baseline between PR fampridine vs placebo: 0.62 (0.09 to 1.14); p=0.021*	Important	MODERATE
BBS score at 26 weeks follow-up (two weeks after discontinuation of treatment with PR fampridine									
1 RCT (MOBILE) Hupperts et al 2016	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	68	64	The authors stated that *"after treatment discontinuation at week 24, improvements declined and approached zero by the week 26 follow-up visit in the PR-fampridine group"*	Important	LOW
Proportion of treatment responders – 1 *post hoc* integrated analysis of 2 RCTs, 1 RCT									
Proportion of patients (%) achieving clinically meaningful ≥8 point improvement in MSWS-12 score at 24 weeks follow-up [higher percentages indicate benefit]									
1 *post hoc* integrated analysis of 2 RCTs (ENHANCE, MOBILE) Hupperts et al 2022	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	383	382	PR fampridine: 44.3 Placebo: 33.0[m] *Difference between PR fampridine vs placebo: OR 1.68 (95% CI: 1.23 to 2.29); p<0.001*	Important	MODERATE
Safety – 2 RCTs									

Any AE, (n, %) at 24 weeks follow-up [lower percentages indicate benefit]									
1 RCT (ENHANCE) Hobart et al 2019	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	316	319	PR fampridine: 207 (66) Placebo: 190 (60)	Important	LOW
1 RCT (MOBILE) Hupperts et al 2016	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 51 (75) Placebo: 49 (77)	Important	LOW
Any treatment-related AE, (n, %) at 24 weeks follow-up [lower percentages indicate benefit]									
1 RCT (ENHANCE) Hobart et al 2019	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	316	319	PR fampridine: 56 (18) Placebo: 43 (13)	Important	LOW
Any severe AE,[n] (n, %) at 24 weeks follow-up [lower percentages indicate benefit]									
1 RCT (ENHANCE) Hobart et al 2019	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	316	319	PR fampridine: 9 (3) Placebo: 8 (3)	Important	LOW
Any serious AE, (n, %) at 24 weeks follow-up [lower percentages indicate benefit]									
1 RCT (ENHANCE) Hobart et al 2019	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	316	319	PR fampridine: 25 (8)[o] Placebo: 21 (7)	Important	LOW
1 RCT (MOBILE) Hupperts et al 2016	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	68	64	PR fampridine: 2 (3) Placebo: 5 (8)	Important	LOW
Any treatment-related serious AE, (n, %) at 24 weeks follow-up [lower percentages indicate benefit]									
1 RCT (ENHANCE)	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	316	319	PR fampridine: 0 (0) Placebo: 1 (<1)	Important	LOW

Hobart et al 2019									
Any AE leading to dose interruption, (n, %) at 24 weeks follow-up [lower percentages indicate benefit]									
1 RCT (ENHANCE) Hobart et al 2019	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	316	319	PR fampridine: 9 (6) Placebo: 11 (3)	Important	LOW
Any AE leading to treatment discontinuation, (n, %) at 24 weeks follow-up [lower percentages indicate benefit]									
1 RCT (ENHANCE) Hobart et al 2019	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	316	319	PR fampridine: 21 (7) Placebo: 23 (7)	Important	LOW
Any AE leading to study withdrawal, (n, %) at 24 weeks follow-up [lower percentages indicate benefit]									
1 RCT (ENHANCE) Hobart et al 2019	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	316	319	PR fampridine: 22 (7) Placebo: 24 (8)	Important	LOW
Most common treatment-emergent AEs by MedDRA® Preferred Term (≥ 5% in any treatment group), (n, %) at 24 weeks follow-up [lower percentages indicate benefit]									
1 RCT (ENHANCE) Hobart et al 2019	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	316	319	*Urinary tract infection:* PR fampridine: 41 (13) Placebo: 30 (9) *MS relapse:* PR fampridine: 34 (11) Placebo: 33 (10) *Fall:* PR fampridine: 24 (8) Placebo: 19 (6) *Back pain:* PR fampridine: 16 (5) Placebo: 11 (3) *Headache:* PR fampridine: 15 (5) Placebo: 15 (5) *Nasopharyngitis:*	Important	LOW

							PR fampridine: 15 (5) Placebo: 18 (6) *Upper respiratory tract infection:* PR fampridine: 15 (5) Placebo: 10 (3)		

Abbreviations

ADLs: activities of daily living; AE: adverse event; BBS: Berg balance scale; BSC: best supportive care; CI: confidence interval; EDSS: expanded disability status scale; EQ-5D; EuroQol 5-dimensions; HF: hip flexion; 9-HPT: 9-hole peg test; HRQoL: health related quality of life; LSM: least square means; MCID: minimally clinically important difference; MS: multiple sclerosis; MSIS-29 PHYS: multiple sclerosis impact scale-29 physical subscale; MSIS-29 PSYCH: multiple sclerosis impact scale-29 psychological subscale; MSWS-12: multiple sclerosis walking scale; MVC: maximal voluntary contraction; n: number; Nm: Newton meter; NS: not significant; OR: odds ratio; PGIC: patient global impression of change; PR: prolonged release; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; SR: slow release; SSST: six spot step test; 5-STS: 5 times sit to stand; T25FW: timed 25 foot walk; TUG: timed up and go; VAS: visual analogue scale.

1 Risk of bias: serious limitations due to unclear methods used to assess reliability of outcome measures, and a high proportion of patients lost to follow-up.
2 Risk of bias: very serious limitations due to selection bias (inclusion of treatment responders), unclear blinding of outcome assessors, lack of information about whether the groups were treated similarly, and low statistical power.
3 Indirectness: very serious indirectness as the population included only patients who had previously responded to treatment with SR fampridine.
4 Risk of bias: very serious limitations due to the post hoc integrated analysis not meeting JBI SRMA checklist criteria in terms of not following standard systematic review methods and procedures such as duplicate and independent critical appraisal of included studies. Despite the high risk of bias, it was agreed that the certainty of the evidence would only be partially downgraded because the searches for this evidence review did not identify any other RCTs that met the PICO eligibility criteria and our own risk of bias assessment/critical appraisal of the two RCTs found serious (but not very serious) risk of bias due to unclear methods used to assess reliability of the outcomes reported in the integrated post hoc analysis.
5 Risk of bias: very serious limitations due to unclear methods used to assess reliability of outcome measures, a high proportion of patients lost to follow-up and no reporting of statistical measures
6 Risk of bias: very serious limitations due to unclear methods used to assess reliability of outcome measures, high proportion of patients lost to follow-up, post hoc analysis and no reporting of statistical measures for some outcomes.

a. The PGIC is a global assessment of the patient's impression of how the study drug affected their overall walking during the preceding seven days. The PGIC was scored on a seven-point scale (from 1 = very much worse to 7 = very much improved).
b. The T25FW is a test that objectively measures functional capacity of the lower extremities in patients using a timed 25 foot walk.
c. The SSST assesses functional capacity of the lower extremities in terms of walking speed, but also co-ordination and balance by kicking blocks out of five circles on the floor.
d. The MSWS-12 score includes 12 questions that ask about different aspects of walking: ability and speed of walk; ability to run; ability to climb and descend stairs; balance and smoothness of gait; and support, effort, and concentration required. Patients rate limitations of their mobility due to MS on a Likert 5-point scale (from 1 = not at all to 5 = extremely). Total score ranges from 1 to 60 and is transformed to a scale of 0–100. A higher MSWS-12 score represents poorer walking ability.
e. The proportion of patients with MS with a mean improvement in MSWS-12 score exceeding the predetermined threshold (⩾8 points) from baseline over 24 weeks (i.e. people with MS who met the definition of PR-fampridine responders for this analysis), analysed using a logistic regression model with treatment group as the classification variable and study, baseline MSWS-12 score, baseline TUG speed, age, and screening EDSS score as covariates. Findings on the MSWS-12 score for mean improvement of ≥8 points are also reported for the important outcome 'proportion of treatment responders' as this was how treatment responders were defined in the two RCTs and post hoc integrated analysis of the two RCTs.
f. TUG speed is an objective measure of dynamic balance and mobility. TUG measures the speed of individuals to move from a seated position to stand up, walk 3 m, turn, walk 3 m. In ENHANCE, TUG (feet/second) was performed at the same time (± 3 h) and with the same footwear and walking aids (if required) during each visit to avoid variation.
g. The MSIS-29 PHYS score is a self-reported measure of the physical impact of MS. The MSIS-29 PHYS score is calculated by summing the 20 items and transforming the score to a scale of 0 (no impact of MS) to 100 (extreme impact of MS).
h For each visit, MSIS-29 PSYCH scores were calculated by totalling the nine individual items and transforming to a scale with a range of 0 (no impact of MS) to 100 (extreme impact of MS).
i. The 5-STS assesses functional capacity of the lower extremities in terms of time taken to stand up and sit down on a chair five times.
j. The 9-HPT measures finger dexterity in terms of the time taken to place nine pegs into a square board with holes for the pegs.

k. ABILHAND measures manual ability to manage daily activities among chronic stroke patients. Patients estimate the ease or difficulty of performing each upper limb activity using a 3-level response scale: impossible (0), difficult (1), and easy (2). A higher ABILHAND score represents better manual ability.
l. The BBS score measures static and dynamic balance. Each task is scored from 0 (unable to perform) to 4 (able to perform independently). A higher BBS score represents better balance; recommended to predict multiple falls once a fall has occurred.
m. Outcomes were reported as clinically meaningful ≥8 improvement in MSWS-12 score from baseline, but these patients were also defined as treatment responders.
n. Severe AEs were defined as symptoms causing severe discomfort, incapacitation, or significant impact on daily life.
o. A serious AE was any untoward medical occurrence that resulted in death/risk of death, hospitalisation/prolonged hospitalisation, persistent or significant disability/incapacity, or resulted in a congenital anomaly/birth defect. There were two deaths, both of which were considered unrelated to study treatment (coronary artery stenosis and acute myocardial infarction), and occurred after the participant had completed study treatment but before completing the 2-week post-treatment follow-up.

Table 3: PR fampridine vs no comparator

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	PR fampridine	No comparator	Result		
ADLs – 3 prospective case series									
EDSS[a] in all patients, mean (±SD) at baseline and two weeks follow-up [lower values indicate benefit]									
1 prospective case series Marzal-Alfaro et al 2018	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	27	None	Pre-treatment score: 5.8 (0.9) Post-treatment score: 5.8 (NR)	Important	VERY LOW
EDSS[a] in all patients, mean (±SD) at baseline and one month follow-up [lower values indicate benefit]									
1 prospective case series Fragoso et al 2016	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	NR[b]	None	Pre-treatment score: 5.2 (1.1) Post-treatment score: 5.0 (1.4) *Difference between pre- and post-treatment scores: p=0.29* Improvements were observed in 14 patients (17.5%)	Important	VERY LOW
EDSS[a] in all patients, mean (±SD) at baseline and three months follow-up [lower values indicate benefit]									
1 prospective case series Marzal-Alfaro et al 2018	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	26	None	Pre-treatment score: 5.8 (0.9) Post-treatment score: 5.8 (NR)	Important	VERY LOW
EDSS[a] in all patients, mean (±SD) at baseline and six months follow-up [lower values indicate benefit]									
1 prospective case series Marzal-Alfaro et al 2018	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	18	None	Pre-treatment score: 5.8 (0.9) Post-treatment score: 5.7 (NR)	Important	VERY LOW
EDSS[c] in treatment responders,[d] mean (±SD) at baseline and six months follow-up [lower values indicate benefit]									
1 prospective case series Alvarez-Payero et al 2017	Very serious limitations[4]	Very serious indirectness[5]	Not applicable	Not calculable	25	None	Pre-treatment score: 6.1 (0.9) Post-treatment score: 5.6 (0.1) *Difference between pre- and post-treatment scores: p<0.05*	Important	VERY LOW

EDSS[c] in all patients, % improvements from baseline to six months [lower values indicate benefit]									
1 prospective case series Alvarez-Payero et al 2017	Very serious limitations[4]	Very serious indirectness[5]	Not applicable	Not calculable	30	None	Improvements in EDSS resulted in 9.1% of all patients (treatment responders and non-responders) reducing the number of supports needed for walking	Important	VERY LOW
Abbreviations ADLs: activities of daily living; EDSS: expanded disability scale score; NR: not reported); PR: prolonged release; SD: standard deviation.									

1 Risk of bias: serious limitations due to uncertainty around the methods used to identify and measure the condition in patients.
2 Indirectness: serious indirectness due to lack of a comparator group.
3 Risk of bias: very serious limitations due to unclear study methods and potential for selection bias, and limited details of clinical and demographics for patients.
4 Risk of bias: very serious limitations due to unclear study methods, and incomplete reporting of follow up results for all patients.
5 Indirectness: very serious indirectness due to lack of a comparator group and reporting outcomes for treatment responders only.

a General neurological disability before and after treatment with fampridine was assessed by means of the expanded EDSS which assesses neurological disability from zero (normal) to ten (death) in increments of 0.5 points, with particular focus on gait. Fampridine was considered efficacious for improvement of disability if the EDSS score decreased by at least 1.0 point after one month of treatment.
b The number of patients assessed by EDSS was not reported; although 89 patients were included in the study, the observed improvements in 14 (17.5%) patients suggests that not all patients were assessed.
c Variations of 0.5 points, between EDSS 4 and 7, were considered of clinical impact because this range on the scale reflects important changes in walking ability, corresponding EDSS 4 to a restricted walking up to 500 m and EDSS 7.0 to a severely affected deambulation, no more than 5 m without a walking aid.
d Response was defined as increased gait speed (≥20%) using the T25FW test and decreased MSWS-12 score (≥4 points).

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
Cost-effectiveness analysis	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER), is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Life years gained (LYG)	Average years of life gained per person as a result of an intervention.
Odds ratio (OR)	Compares the odds (probability) of something happening in 1 group with the odds of it happening in another. An odds ratio of 1 shows that the odds of the event happening (for example, a person developing a disease or a treatment working) is the same for both groups. An odds ratio of greater than 1 means that the event is more likely in the first group than the second. An odds ratio of less than 1 means that the event is less likely in the first group than in the second group.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).

P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Reliability	The ability to get the same or similar result each time a study is repeated with a different population or group.
Sensitivity analysis	A means of exploring uncertainty in the results of economic evaluations. There may be uncertainty because data are missing, estimates are imprecise or there is controversy about methodology. Sensitivity analysis can also be used to see how applicable results are to other settings. The analysis is repeated using different assumptions to examine the effect of these assumptions on the results.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical power	The ability of a study to demonstrate an association or causal relationship between 2 variables (if an association exists) means that the study is statistically significant. The statistical power of a study is primarily related to the number of people included. If too few people are included, any differences in the outcomes will not be statistically significant.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.
Subgroup analysis	A way to find out from a study if a treatment is more effective in one group of people (for example, who are a particular age or have particular symptoms) than another. It uses evidence from a defined subgroup within the whole analysis set.
Validity	Whether a test or study actually measures what it aims to measure. Internal validity shows whether a study or test is appropriate for the question, for example, whether a study of exercise among gym members measures the amount of exercise people do at the gym, not simply whether people join. External validity is the degree to which the results of a study hold true in non-study situations, for example, in routine NHS

	practice. It may also be referred to as the generalisability of study results to non-study populations.

References

Included studies

- Acosta C, Gianinazzi M, Dort T, Armstrong N, Ryder S, Lundqvist T, et al. Modeling the cost-effectiveness of prolonged-release fampridine for the treatment of walking impairment in patients with multiple sclerosis in Sweden. Journal of Medical Economics. 2021;24(1):770-80.
- Alvarez-Payero M, Valeiras-Munoz C, Lion-Vazquez S, Pineiro-Corrales G, Munoz-Garcia D, Midaglia L. Experience with fampridine in clinical practice: analysis of a possible marker of clinical response. International Journal of Neuroscience. 2017;127(10):915-22.
- Fragoso YD, Adoni T, Alves-Leon SV, Apostolos-Pereira SL, Barreira AA, Brooks JB, et al. Real-life experience with fampridine (Fampyra R) for patients with multiple sclerosis and gait disorders. Neurorehabilitation. 2016;39(2):301-4.
- Gasperini C, Hupperts R, Lycke J, Short C, McNeill M, Zhong J, Mehta LR. Prolonged-release fampridine treatment improved subject-reported impact of multiple sclerosis: Item-level analysis of the MSIS-29. Journal of the Neurological Sciences. 2016;370:123-31.
- Hobart J, Ziemssen T, Feys P, Linnebank M, Goodman AD, Farrell R, et al. Assessment of Clinically Meaningful Improvements in Self-Reported Walking Ability in Participants with Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III ENHANCE Trial of Prolonged-Release Fampridine. CNS Drugs. 2019;33(1):61-79.
- Hupperts R, Lycke J, Short C, Gasperini C, McNeill M, Medori R, et al. Prolonged-release fampridine and walking and balance in MS: randomised controlled MOBILE trial. Multiple Sclerosis. 2016;22(2):212-21.
- Hupperts R, Gasperini C, Lycke J, Ziemssen T, Feys P, Xiao S, et al. Efficacy of prolonged-release fampridine versus placebo on walking ability, dynamic and static balance, physical impact of multiple sclerosis, and quality of life: an integrated analysis of MOBILE and ENHANCE. Therapeutic Advances in Neurological Disorders. 2022;15:17562864221090398.
- Jensen HB, Nielsen JL, Ravnborg M, Dalgas U, Aagaard P, Stenager E. Effect of slow release-Fampridine on muscle strength, rate of force development, functional capacity and cognitive function in an enriched population of MS patients. A randomized, double blind, placebo controlled study. Multiple Sclerosis and Related Disorders. 2016;10:137-44.
- Marzal-Alfaro MB, Martin Barbero ML, Garcia Dominguez J, Romero-Delgado F, Martinez Gines ML, Herranz A, Sanjurjo-Saez M. Impact of fampridine on quality of life: clinical benefit in real-world practice. European Journal of Hospital Pharmacy Science & Practice. 2018;25(3):138-43.
- Zhao X, Yang H, Wei T, Zhao J, Liu J, Huang Z, et al. Cost-effectiveness analysis of prolonged-release fampridine to treat walking disability of multiple sclerosis in China. Journal of Comparative Effectiveness Research. 2022;11(14):1057-69.

Other references

- Goodman AD, Brown TR, Krupp LB, et al. Sustained-release oral fampridine in

multiple sclerosis: a randomised, double-blind, controlled trial. Lancet. 2009 Feb 28;373(9665):732-8.

- Goodman AD, Brown TR, Edwards KR, et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. Ann Neurol. 2010 Oct;68(4):494-502.

NHS England
Wellington House
133-155 Waterloo Road
London
SE1 8UG