Clinical Priorities Advisory Group Summary Report

Agenda item	5.2
Date of Meeting	11.05.2026-13.05.2026
Title of the Proposition	Prolonged-released (PR) fampridine as a treatment of adults with Multiple Sclerosis and associated walking impairment
Unique Reference Number	2341
Programme of Care	Trauma
Clinical Reference Group	Neurology
Service/treatment status	delegated

Action requested

Support the adoption of the policy proposition

Recommend its relative prioritisation.

Summary of the proposition:

PR fampridine is recommended to be available as a routine commissioning treatment option for adults with MS and associated walking impairment, as defined by Expanded Disability Status Scale - EDSS score of 4-7, within the criteria set out in the policy proposition. The proposition is restricted to adults in line with the licence authorisation.

Clinical Panel recommendation:

The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

Assurances

The committee is asked to receive the following assurance:		
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of developmental and governance steps.	
2.	The Deputy Director of Acute Programmes confirms the proposition is supported by the following documentation (please tick the box where applicable)	
	Draft Clinical Commissioning policy proposition	☒
	Evidence Review	☒
	Public Health Evidence Report	☐
	Evidence to Decision Making (EtD) Summary	☒
	Equalities and Heath Inequalities Assessment (EHIA)	☒
	Prior Approval Form	☒
	Engagement Report	☒
	13Q Assessment and Patient & Public Voice Assurance	☒
	Clinical Panel Report	☒
	Policy Working Group membership	☒
	Other (please state if required)	☐
3.	The Deputy Director of Finance (Specialised Commissioning) confirms that the Impact Assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.	
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the Service and Operational Impact Assessments have been completed.	
5.	The Deputy Director of Quality and Nursing (Specialised Commissioning) confirms that the proposed quality indicators have been adequately defined (where applicable).	

Evidence Review Summary

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[1] *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[2] *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)**

[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 in the lower extremities in patients using a timed 25 foot walk.

	SSST[3] *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)** MSWS-12 score[4] *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)**

[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.

	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)** 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)[5,6] *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

[5] 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.

[6] 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.

	(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)** <u>MSWS-12 score</u> *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[7] *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 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)** TUG speed (MCID ≥15% improvement in TUG speed [metres/second]) *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)** MSIS-29 PHYS score (physical impact of MS in patients)[8] *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	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.

[7] 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.
[8] 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).

Certainty of evidence: Low to Moderate	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. EQ-5D-3L utility index 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 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)[9] *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)**

[9] 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).

	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 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)[10] *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)[11] *SR fampridine vs placebo* **At four weeks follow-up**

[10] 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.
[11] 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.

	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** 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 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[12] *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[13] *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

[12] 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.
[13] 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.

	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 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[14] *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[15]) 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)**

[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.

[15] 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.

	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)** **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	
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>[16] *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>[17] *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)**

[16] Severe AEs were defined as symptoms causing severe discomfort, incapacitation, or significant impact on daily life.
[17] 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.

	Any treatment-related serious AE *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)** 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)[18] *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**

[18] 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.

	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.

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[19] kronor per QALY gained. PR fampridine plus BSC dominated BSC alone when resource

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

	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 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.[20] **Critical Outcomes** **Walking ability**

[20] 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).

	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).[21] **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 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?

[21] 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.

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 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.

Outcome	Evidence statement
	• 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?

<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[22]</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[23]</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.
</td></tr>
</table>

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

Outcome	Evidence statement
	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.
Abbreviations DMT: disease-modifying therapy; MS: multiple sclerosis; PR: prolonged release; RCT: randomised controlled trial.	

Patient Impact assessment

This intervention will provide patients with an opportunity to maintain their walking for an extended period, allowing them to be physically mobile for longer than would be expected and so will have a positive impact on people living with a walking impairment as a result of MS.

The condition has the following impact on the patient's everyday life:

- **Mobility:** patients may have moderate to severe problems in walking about or are unable to walk about
- **Ability to provide self-care:** Patients may have moderate/severe problems in washing or dressing or are unable to wash or dress
- **Undertaking usual activities:** Patients may have moderate/severe problems in doing their usual activities or are unable to do their daily activities
- **Experience of pain/discomfort:** Patients may have moderate/severe/extreme pain or discomfort
- **Experience of anxiety/depression:** Patients may experience slightly/moderately/severely/extremely anxious or depressed

There are no commissioned or licensed pharmacological treatments which impact the ability to walk and all management strategies for MS-related walking impairment are physical. Access to physical therapy and rehabilitation specialists is inconsistent nationally and it is generally accepted that multidimensional approach to disability management contributes to improved outcomes.

Multiple sclerosis (MS) is an acquired disabling neurological disease of young adults that comprises of inflammation and neurodegeneration. The condition manifests as episodes of inflammation in the brain and / or spinal cord damaging the nerves and leading to a variety of symptoms. These may include weakness, pins and needles or sensory loss, loss of vision, impaired balance and coordination, difficulty walking, stiffness / spasms, bladder/bowel dysfunction and fatigue amongst others. People 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. Fifty percent of

people with MS need a walking aid and 25 percent are wheelchair users after 15 years of the illness.

Considerations

Equality and Health Inequalities Impact Assessment (EHIA)	
Summary of any potential impacts of the proposal	This policy proposition aims to make fampridine available for a specific proposed population, specifically people with MS associated walking impairment as defined by Expanded disability status Scale (EDSS) score of 4 to 7, where 4 is defined as ambulatory without rest for >500 meters and 7 is defined as unable to walk 5 meters even with aid, essentially restricted to wheelchair for around 12 hours a day. MS affects women 2-3 times more than men and therefore will have a greater benefit for this characteristic. Research suggests that the provision of fampridine can improve walking ability, quality of life and associated indicators such as independence and improvement in daily activities. There are also wider benefits including increased access to employment as well as benefits to carers and the wider family network. Patients can self-administer the oral treatment, which is one tablet twice daily. No adverse impacts have been identified.
13Q Assessment	
PPVAG outcome	No consultation required
Were PPVAG assured of the level of stakeholder testing?	Yes
Rare Disease Advisory Group	
Not Applicable	
Pharmaceutical	
Yes	

The Clinical Commissioning Policy Proposition recommends the use of fampridine to improve walking in adult patients with multiple sclerosis who have a walking disability as defined by an Expanded Disability Status Scale (EDSS) score of 4-7. This recommendation is aligned to the marketing authorisation for fampridine. Fampridine may be used in post-pubescent children by application of the NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children). Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined, using separate prior approval forms for registration of adults and children.

Fampridine is included on the NHS Payment Scheme Annex A, so is a high-cost drug.

National Programme of Care

The proposal received the full support of the Trauma National Programme of Care Assurance Group.