Modeling the cost-effectiveness of prolonged-release fampridine for the treatment of walking impairment in patients with multiple sclerosis in Sweden

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\textbf{ABSTRACT}

\textbf{Aims:} To evaluate the cost-effectiveness of adding prolonged-release (PR)-fampridine to best supportive care (BSC) alone for the improvement of walking ability in patients with MS.

\textbf{Methods:} A cost-utility analysis based on a Markov model was developed to model responders and timetimed 25-foot walk (T25FW) scores, accumulated costs, and quality-adjusted life-years (QALY) in adults with MS and Expanded Disability Status Scale (EDSS) scores between 4 and 7. The analysis was conducted from a Swedish societal perspective.

\textbf{Results:} In the base-case analysis, PR-fampridine plus BSC led to a higher QALY gain than BSC alone. The largest direct cost was professional care provision followed by hospital inpatient stays while the indirect cost was the loss of earnings due to days off work. The incremental cost-effectiveness ratio (ICER) for PR-fampridine plus BSC compared with BSC alone was 57,109 Swedish Kronor (kr)/QALY (€5,607/QALY [1 kr = €0.0981762 on 8 April 2021] and $6,675/QALY [1 kr = $0.116890 on 8 April 2021]). All sensitivity analyses performed resulted in ICERs below 500,000 kr ($49,088 and $58,445).

\textbf{Limitations:} Resource use data were not specific to the Swedish market.

\textbf{Conclusions:} PR-fampridine represents a cost-effective treatment for MS-related walking impairment in Sweden, due to improvements in patients’ quality of life and reduced healthcare resource utilization.

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\textbf{INTRODUCTION}

Walking impairment is common among patients with multiple sclerosis (MS)\textsuperscript{1,2,6}, with the risk increasing as the disease progresses\textsuperscript{3}, contributing to its considerable humanistic\textsuperscript{4,7} and economic burden\textsuperscript{8–11}. There are currently limited options for the treatment of walking impairment in MS, with prolonged-release (PR)-fampridine (Fampry\textsuperscript{a}) being the only pharmacological therapy approved for this indication\textsuperscript{12}. Standard care for MS walking impairment may constitute any therapy that could potentially impact or assist with walking impairment, such as walking aids, exercise regimes, physiotherapy and/or spasticity treatments, which together may be regarded as best supportive care (BSC)\textsuperscript{13}. BSC may have some limited effect in reducing walking impairment\textsuperscript{14}.

Given the limited effect of BSC, two phase III, randomized, double-blind, placebo-controlled trials, MS-F203 and MS-F204, were conducted to evaluate the clinical effectiveness of PR-fampridine in improving ambulation in patients with relapsing-remitting, secondary-progressive and primary progressive MS. Both trials met their primary efficacy endpoints of improved timed walk response\textsuperscript{15,16}. Efficacy and safety of PR-fampridine were also assessed in phase II, randomized, double-blind, placebo-controlled, MOBILE study\textsuperscript{17} and the phase III, randomized, double-blind, placebo-controlled ENHANCE study\textsuperscript{18}, both of which investigated the broader primary endpoint of clinically meaningful (at least eight-point) improvement in walking ability on the MSWS-12. In both trials, a higher proportion of PR-fampridine-treated patients demonstrated a clinically meaningful improvement in MSWS-12 scores from baseline over a 24-week period than those in the placebo group\textsuperscript{17,18}.

Previous MS economic analyses assessed the cost-effectiveness of disease-modifying therapies (DMTs), associated with Expanded Disability Status Scale (EDSS) levels and/or relapse\textsuperscript{19}. Since PR-fampridine is not a DMT and has shown an effect on walking, EDSS models are inappropriate. No published economic analyses have previously been designed to specifically assess the cost-effectiveness of treatments for MS-related walking impairment.
The objective of this economic analysis was to evaluate the cost-effectiveness of PR-fampridine plus BSC versus BSC alone for the improvement of walking ability in adult MS patients in Sweden.

A prior version of the economic model presented here, using the same structure and methods, has been used in various national reimbursement submissions. The model was submitted to the Swedish Dental and Pharmaceutical Benefits Agency (Tandvårds-Läkemedelsförmånsverket [TLV]) who reviewed the analysis and granted reimbursement to PR-fampridine in October 2018. The model described here underwent a thorough independent quality check that led to improvements with regards to the data used for long-term extrapolation of clinical trial data.

Methods

Model overview

A cost-utility analysis based on a Markov model was developed to model PR-fampridine treatment responders defined in the model using the 12-item Multiple Sclerosis Walking Scale (MSWS-12), timed 25-foot walk (T25FW) scores, accumulated costs and quality-adjusted life-years (QALYs) in Swedish patients with MS-related walking impairment. A 20-year time horizon was used in the base-case scenario as agreed with the TLV (Swedish Dental and Pharmaceutical Benefits Agency). However, an alternative scenario looked at a 10-year time horizon and a lifetime time horizon to capture all short- and long-term costs and benefits resulting from PR-fampridine treatment. As recommended by Swedish guidelines, both effects and costs were discounted at a rate of 3.0%. The analysis was conducted from a societal perspective, which is recommended and considered appropriate to capture all direct and indirect costs associated with MS-related walking impairment. Furthermore, utility decrements were applied to the model to reflect the incidence of adverse events (AEs) and an alternative weighting approach to BSC utilities was explored in a scenario analysis.

Treatment effect in terms of response to treatment and time on treatment was derived from the PR-fampridine clinical trial program.

The modelled patient population matches the ENHANCE phase III study population, which consisted of adult MS patients with EDSS scores between 4 and 7, corresponding to the approved European Medicines Agency (EMA) indication of PR-fampridine. Accordingly, patients had a mean starting age of 48.9 years, a mean 137 months since diagnosis and 42% were males. Because the model also includes T25FW, which was not measured in the ENHANCE (or MOBILE) trials, this was assumed to be on average 2.1 feet per second, to match the baseline values observed in the MS-F203 and MS-F204 trials. Although the studies were comparable in terms of patient age, disease duration and EDSS, there were slight differences in the proportions of patients with relapsing-remitting MS (MS-F203: 29% placebo, 27% PR-fampridine; MS-F204: 34% placebo, 36% PR-fampridine; ENHANCE: 49% placebo, 53% PR-fampridine) and secondary-progressive MS (MS-F203: 49% placebo, 55% PR-fampridine; MS-F204: 47% placebo, 52% PR-fampridine; ENHANCE: 31% placebo, 30% PR-fampridine). However, the differences were not considered significant enough to preclude their use in the model.

The two-arm Markov model includes two treatment strategies: PR-fampridine and BSC (herein referred to as the PR-fampridine arm), and BSC alone. In this analysis, BSC was used to denote all background supportive care that could be used concomitantly to manage MS symptoms. Because PR-fampridine is added to BSC, BSC is present in both arms of the model, reflecting current treatment practice. The recommended dose of PR-fampridine is one 10 mg prolonged-release tablet, twice daily. Patients receiving PR-fampridine start in the “response evaluation” health state until the end of the responder-identification period, which is set at 4 weeks (one cycle) post-treatment initiation, in line with the summary of product characteristics. Depending on their response to treatment, patients either “continue treatment with PR-fampridine and BSC”, enter the “withdrawal from treatment” health state, or die, reflecting the patient journey experienced by MS patients. Patients treated with BSC alone can either remain in the “continue treatment with BSC” health state or transition to “death”. Death is an absorbing state in the model, and patients can transition from any health state to the death state at any cycle in the model (Figure 1).

PR-fampridine responders incur the improved health outcomes associated with treatment response, as reported in the MS-F203, MS-F204, ENHANCE and MOBILE clinical studies, related to increased utility and improved walking ability, and thus, reduced need for care, compared with patients in the “withdrawal from treatment” health state. Once patients withdraw from treatment with PR-fampridine – due to any reason including lack of response to treatment, AEs or other reasons – costs and QALYs are assumed to equal those in the “continue treatment with BSC” health state, reflecting clinical practice. Even though walking speed improvements have been observed upon re-initiation of PR-fampridine, it was conservatively assumed that once patients withdraw from PR-fampridine treatment they cannot transition back to the “continue treatment with PR-fampridine and BSC” health state and all treatment effects is lost.

Model parameters

Transition probabilities

The treatment response rate was obtained from the ENHANCE clinical trial program (Table 1), where the response was defined as a mean improvement on the MSWS-12 score of ≥8 points from baseline over a 24-week treatment period. A 5-year retention probability was estimated from pooled MS-F203 EXT and MS-F204 EXT studies for patients responding to PR-fampridine and used to estimate the withdrawal probability (for any reason including patients’ perceived lack of treatment effect, the decline in T25FW, and AEs) for each 4-week cycle (Table 1).
Natural history and treatment effect

There are no long-term clinical trial or resource use data from MSWS-12. Therefore, disease evolution and PR-fampridine treatment effect were defined according to T25FW. The rate of long-term natural progression of MS with regards to walking speed was obtained from T25FW scores over 24 months that were reported for the placebo arm of the IMPACT trial of interferon beta-1a intramuscular versus placebo. The IMPACT trial was chosen because it captured T25FW in a population with advanced MS, which closely matches the PR-fampridine population. Choice of this trial can be considered conservative because the placebo arm experienced the slowest published rate of T25FW decline, and therefore likely underestimates the true impact of PR-fampridine. Progression with regards to T25FW for BSC-treated or PR-fampridine treatment withdrawn patients was based on this dataset and then extrapolated beyond the trial’s time horizon using a weighted linear regression (Figure 2).

For patients who respond to PR-fampridine, results from the two extension studies (MS-F203EXT and MS-F204EXT) were used to model the corresponding progression of T25FW over time, with a weighted linear regression fitted to the pooled data to allow extrapolation beyond the 60-months trial duration. As no data were available regarding the potential sustained treatment effect of PR-fampridine in patients who withdrew from treatment, it was conservatively assumed that these patients lose all treatment effect.

Mortality
PR-fampridine is not associated with a reduced or increased risk of death, therefore the same mortality rate was applied to both arms. A relative risk of 1.44 for patients with MS compared with the general population was applied to the general mortality probabilities, obtained from 2017 Swedish lifetables.

Adverse events
AE rates and the costs of non-serious AEs associated with PR-fampridine were taken from the ENHANCE study (Table 2). Given that the majority of AEs were mild to moderate (serious urinary tract infection or fall each occurred in <1% of PR-fampridine or placebo patients), all AEs were modelled as non-serious. MS relapses were assumed to be unrelated to PR-fampridine treatment and associated with inflammatory disease activity and were therefore excluded from the model. The probability of AEs was incorporated into the model as a per-cycle probability of any AE by first calculating the 26-week risk, then converting it into a 4-week risk by assuming a constant rate.

Utility data
In the base-case analysis, health state utilities were derived from EuroQol-5 Dimensions-3 Level (EQ-5D-3L) values from the ENHANCE study (Table 3), given that ENHANCE was the largest and longest phase III randomized trial of PR-fampridine.

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**Table 1. Transition probabilities.**

| Item                                                      | Value | Source          |
|-----------------------------------------------------------|-------|-----------------|
| PR-fampridine treatment response rates                    | 0.432 | ENHANCE<sup>18</sup> |
|                                                          | 0.485 | MOBILE<sup>17</sup> |
| 4-weekly probability of treatment withdrawal             | 0.007 | Long-term extension studies of MS-F203 and MS-F204<sup>23</sup> |
| MS adjusted mortality rate                                | Variable* | Kingwell<sup>24</sup> |

* A relative risk increase of 1.44 for patients with MS (compared with the general population) was applied to the 2017 Swedish mortality probabilities<sup>25</sup>. Abbreviations. MS, multiple sclerosis; PR, prolonged-release.
The 3-level version of EQ-5D (no problems, some problems, or unable to/extreme problems) might not be sensitive enough to detect the impact of walking changes on utility given that PR-fampridine is restricted to patients with baseline mobility impairment. In ENHANCE, 82% of PR-fampridine responders reported no change in mobility as measured by EQ-5D-3L from baseline to Week 24. A greater improvement was observed in MOBILE, likely due to the more sensitive 5-level questionnaire (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems). Therefore, utility values from MOBILE (EQ-5D-5L; Table 4) and from a pooled analysis of ENHANCE and MOBILE (Table 5) were used in alternative scenarios to investigate their impact on cost-effectiveness results. Furthermore, a conservative scenario analysis was conducted in which the utility gains observed in the BSC group were applied to the Responder baseline utility to derive utilities used in the scenario analysis. 

### Table 2. AE excluding MS relapse observed in the ENHANCE study included in the cost-utility model.

| AE, n (%) | PR-fampridine (n = 316) | Placebo (n = 319) |
|-----------|--------------------------|-------------------|
| Most common treatment-emergent AEs by MedDRA preferred term (≥5% in any treatment group) | | |
| Urinary tract infection | 41 (13) | 30 (9) |
| Fall | 24 (8) | 19 (6) |
| Back pain | 16 (5) | 11 (3) |
| Headache | 15 (5) | 15 (5) |
| Nasopharyngitis | 15 (5) | 18 (6) |
| Upper respiratory tract infection | 15 (5) | 10 (3) |
| Treatment-emergent AEs of special interest by MedDRA preferred term (≥1% in any treatment group) | | |
| Cardiovascular disorder (palpitations, tachycardia, arrhythmia) | 6 (2) | 2 (<1) |
| Rash | 8 (3) | 4 (1) |

### Table 3. Utilities based on EQ-5D-3L values from the ENHANCE study.

| Time Point | Adjusted EQ-5D-3L Values from ENHANCE | Scenario analysis: adjusted BSC utilities |
|------------|----------------------------------------|-----------------------------------------|
| Baseline | 0.6350 | 0.605 | 0.6350 |
| Week 2 | 0.6730 | 0.649 | 0.6790 |
| Week 4 | 0.6890 | 0.626 | 0.6560 |
| Week 24 | 0.6770 | 0.634 | 0.6640 |

Note: utility gains observed in the Withdrawal from treatment, non-responder and BSC group were applied to the Responder baseline utility to derive utilities used in the scenario analysis “Adjusted BSC utilities”. 

### Table 2. AEs excluding MS relapse observed in the ENHANCE study included in the cost-utility model.

![Figure 2. Long-term T25FW extrapolated using a linear regression.](image)

Data points represent time off treatment between the end of the parent trial and the beginning of the extension studies.

Abbreviations. BSC, best supportive care; T25FW, timed 25-foot walk.

Abbreviations. AE, adverse event; MS, multiple sclerosis.

Abbreviations. BSC, best supportive care; EQ-5D-3L, EuroQoL-5 Dimensions-3 Level.
The PR-fampridine drug was estimated in the base-case analysis, reflecting the societal perspective in Sweden (Table 6). The direct (PR-fampridine drug cost, healthcare professional visits) and indirect (work productivity losses) costs were estimated in the base-case analysis, with an incremental QALY gain of 0.12 for PR-fampridine compared with BSC, and an ICER of 53,060 kr/QALY. PR-fampridine domination BSC when resource use costs were increased by 25%. A lifetime horizon produced an ICER of 57,109 kr/QALY which is equal to the result in the base case as in the model all patients discontinue treatment before year 20. A 10-year time horizon produced an ICER of 77,605 kr/QALY showing that PR-fampridine remains cost-effective with a shorter time horizon.

Cost data and resource use
Both direct (PR-fampridine drug cost, healthcare professionals, hospitalizations, treatment of AEs, cost of care and modifications/ aids) and indirect (absence from work) costs were estimated in the base-case analysis, reflecting the societal perspective in Sweden (Table 6). The PR-fampridine drug cost (1,402.85 Swedish Kronor (kr) every 4 weeks (€138 [1 kr = €0.0981762 on 8 April 2021] and $164 [1 kr = $0.116890 on 8 April 2021]), the same rates have been used in all currency conversions presented) was assigned to all PR-fampridine-treated patients, regardless of response status. Similarly, it was assumed that both responders and non-responders will visit their neurologist in the first cycle of the model (4 weeks) after starting treatment with PR-fampridine to assess response to treatment. It was assumed that no additional administration cost is associated with PR-fampridine, and BSC does not incur drug, administration cost or neurologist visits. Resource use in the base-case analysis was informed by the relationship between medical resource consumption and walking speed, as measured by the T25FW, collected in the Adelphi MS disease-specific program. Univariate analyses were conducted with the T25FW as the independent variable. Multivariate analyses were also conducted with the following covariates: age, gender, body mass index, months since diagnosis, and relevant comorbidities such as hypertension, diabetes, arthritis, and osteoporosis. Backward stepwise variable elimination based on individual statistical significance (at 5%) and overall goodness-of-fit measures were applied to optimize the regression model. The final univariate and multivariate equations are available in Supplementary Appendix A. The base-case analysis in the model used the univariate analysis for all resource use items. All direct costs were from the Southern Healthcare Region prices and reimbursements list and were inflated to 2018.

Sensitivity analyses were performed to test the robustness of the model results with respect to the uncertainty around the base-case assumptions and specific parameter estimates. The discount rates of costs and benefits were tested through one-way sensitivity analysis (OWSA) while probabilistic sensitivity analysis (PSA) was used to test the impact of varying multiple input parameters simultaneously (5000 iterations were used). A total of 172 parameters were varied in the PSA, including baseline patient demographics, multiple disease-related parameters, comorbidity factors, healthcare resources and costs, adverse events, utilities and treatment effectiveness parameters. See Supplementary Appendix B for the variation and distributions used for the PSA. Additionally, several scenario analyses tested the impact of varying the perspective, costs, utility scores and time horizon.

Results
In the base-case analysis, use of PR-fampridine led to an incremental QALY gain of 0.12 over BSC (Table 7). PR-fampridine was also associated with an incremental cost of 6,982 kr (€685 and $816) compared with BSC, resulting in an incremental cost-effectiveness ratio (ICER) for PR-fampridine compared with BSC of 57,109 kr/QALY (€5,607/QALY and $6,675/QALY). A detailed cost breakdown is presented in Table 8.

PSA results were similar to the deterministic base-case analysis, with an incremental QALY gain of 0.12 for PR-fampridine compared with BSC, and an ICER of 53,060 kr/QALY (€5,209/QALY and $6,202/QALY) (Figure 4). Assuming a threshold of 500,000 kr/QALY (€49,088/QALY and $58,445/QALY), there was a 96.76% probability of cost-effectiveness at a 56-pack price of 1,402.85 kr (Figure 5).

The model was run to investigate the impact of different assumptions and data scenarios (Table 9). All scenario analyses resulted in ICERs below the threshold with the healthcare payer perspective scenario resulting in the highest ICER (400,936 kr/QALY). PR-fampridine dominated BSC when resource use costs were increased by 25%. A lifetime horizon produced an ICER of 57,109 kr/QALY which is equal to the result in the base case as in the model all patients discontinue treatment before year 20. A 10-year time horizon produced an ICER of 77,605 kr/QALY showing that PR-fampridine remains cost-effective with a shorter time horizon.

Discussion
It has previously been demonstrated in a cross-sectional, patient record-based study in five European countries, that patients with greater walking impairment used significantly
| Cost item                  | Unit cost (kr) | Notes                                           |
|---------------------------|----------------|-------------------------------------------------|
| **Treatment costs**       |                |                                                 |
| PR-fampridine (per year)  | 18,287.17      | Source: Biogen Sweden                            |
| Administration            | 0.00           | Not applicable                                  |
| Monitoring (PR-fampridine)| 2,986.00       | Re-visit at neurology clinic                    |
| **Direct costs**          |                |                                                 |
| GP                        | 1,594.00       |                                                 |
| Neurologist               | 2,986.00       | Re-visit at neurology clinic                    |
| MS specialist             | 2,986.00       | Re-visit at neurology clinic                    |
| MS nurse                  | 1,494.00       | Other HCP at neurology clinic                   |
| ER doctor                 | 3,672.00       | Other HCP at ER                                 |
| ER visit                  | 1,116.00       | Other HCP at ER                                 |
| Internist                 | 1,091.00       |                                                 |
| Physiotherapist           | 996.00         | Other HCP at rehabilitation unit                |
| Ophthalmologist           | 3,557.00       |                                                 |
| Urologist                 | 2,011.00       |                                                 |
| Gastroenterologist        | 1,765.00       | Re-visit at gastroenterology clinic; new visit 3,113 kr |
| Psychiatrist              | 3,997.00       | General psychiatrist                             |
| Other doctor              | 1,594.00       | Cost for GP (assumption)                        |
| MS-related hospitalization| 30,702.00      | Inpatient care for neurology disorder, university hospital, 6 days |
| Nonprofessional care (per year) | 57,821.00 | Annual cost of informal care*                   |
| Professional carer (per year) | 179,039.00 | Personal assistant (users = 16.8%), Nurse home visits (users = 5.9%), Home help (users = 11.8%), Transportation (28.8%) |
| **Modifications and aids**|                |                                                 |
| Walking aids (per year)   | 2,246.00       | Walking aids (users = 4.0%), wheelchair (users = 2.2%), Electric wheelchair/scooter (users = 4.2%)* |
| Home modifications (per year) | 4,972.00     | We considered as home modifications: stair lift/elevator (users = 2.2%); bed lift (users = 0.1%); ramps/rails (users = 3.3%); other home modifications (users = 9.0%)* |
| Car modifications (per year) | 4,504.00      |                                                 |
| Work modifications (per year) | 690.00        | Special utensils and devices (users = 3.0%), Glasses (users = 5.8%), Cooling vest (users = 4.1%), Recreational aid (users = 3.2%)* |
| **AE costs**              |                |                                                 |
| Urinary tract infection   | 2,025.97       | Urologist appointment 2,011.00 kr plus Ciprofloxacin generic 500mg. Once a day for 5 days 14.97 kr |
| Fall                      | 1,594.00       | GP appointment                                  |
| Back pain                 | 2,184.00       | Specialist appointment                          |
| Headache                  | 1,594.00       | GP appointment                                  |
| Nasopharyngitis           | 1,594.00       | GP appointment                                  |
| Upper respiratory tract infection | 1,622.29 | GP appointment plus Amoxicillin generic tabs 1000 mg. Once a day for 7 days 28.29 kr |
| Cardiovascular disorder   | 2,028.00       | Cardiologist appointment                        |
| Rash                      | 1,594.00       | GP appointment                                  |
| Indirect costs (loss of earnings) | 536,976.00 | Mean monthly salary (all sectors) = 32,800 kr (2016), 44,746 kr incl social fees and pension; 226 working days per year and 8 hours per day give hourly salary of 297 kr* |

**Note:** costs refer to unit costs unless otherwise specified.

*Costs are referenced from Berg33 and inflated from 2005 to January 2018, using inflation data from the following website: [https://www.scb.se/hitta-statistik/sverige-i-siffror/prisomraknaren/](https://www.scb.se/hitta-statistik/sverige-i-siffror/prisomraknaren/)

Abbreviations. AE, adverse event; ER, emergency department; GP, General Practitioner; HCP, health care professional; MS, multiple sclerosis; PR, prolonged-release.
Table 7. Results: QALYs, LYs, and costs per treatment, over 20 years.

| Item            | PR-fampridine | BSC | Incremental |
|-----------------|---------------|-----|-------------|
| Base Case       |               |     |             |
| QALYs           | 9.27          | 9.15| 0.12        |
| LYs             | 14.58         | 14.58| 0.00        |
| Total costs (kr): | 3,451,840.03 | 3,444,858.51| 6,981.52 |
| Total drug cost | (5,338,888.54; $403,485.58) | (5,338,203.12; $402,669.51) | (6,685.42; $816.07) |
| Direct costs    | 52,092.25     | 52,092.25| (-52,092.25) |
| (5,114.22; 6,089.06) | (5,114.22; 6,089.06) | (-52,092.25) |
| Indirect costs  | 2,084,141.07  | 2,120,181.45| -36,040.38 |
| (2,046,131.05; 2,436,615.25) | (2,080,151.36; 2,478,828.01) | (-4,037.95; -4,212.76) |
| ICER            | 57,108.51     | 57,108.51| (-57,108.51) |
|                | ($5,606.70; $6,675.41) | ($5,606.70; $6,675.41) | (-57,108.51) |

Note: 1 kr = $0.0981762 on 8 April 2021; 1 kr = $0.116890 on 8 April 2021.34
Abbreviations. BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; PR, prolonged-release; QALY, quality-adjusted life year.

Table 8. Costs per patient per treatment (kr), over 20 years.

| Item                                      | PR-fampridine (responders and non-responders) | BSC | Incremental |
|-------------------------------------------|-----------------------------------------------|-----|-------------|
| Drug cost                                  |                                               |     |             |
| Cost of PR-fampridine                      | 49,106.25                                     | 0.00| 49,106.25 |
| Administration and monitoring costs        | 2,986.00                                      | 0.00| 2,986.00 |
| Total drug cost                            | 52,092.25                                     | 0.00| 52,092.25 |
| Direct cost                                |                                               |     |             |
| GP visits                                  | 67,094.56                                     | 68,366.62| -1,272.06 |
| (4,599.35; 4,586.35)                      | (5,459.35; 5,455.35)                          | 12.80|             |
| ER visit (includes ER visit and ER doctor)| 208,330.44                                    | 208,527.85| 155.40     |
| (208,330.44; 208,527.85)                 | (208,330.44; 208,527.85)                      |       |             |
| MS visits (includes MS specialist, neurologist and MS nurse) | 103,640.64                                    | 106,657.18| -3,016.54  |
| Physiotherapist outpatient visits          | 45,285.10                                     | 45,749.78| -464.68    |
| Other outpatient visits                    | 408,234.58                                    | 408,268.19| -33.61     |
| Hospital inpatient stays                   | 22,591.35                                     | 21,050.59| 1,540.76   |
| AE cost                                    | 1,164,334.67                                  | 1,196,446.54| -32,111.87|
| (4,599.35; 4,586.35)                      | (5,459.35; 5,455.35)                          |       |             |
| Work modifications                         | 13,457.03                                     | 13,677.07| -220.04    |
| MS visits (includes MS specialist, neurologist and MS nurse) | 28,296.38                                     | 28,651.91| -353.55    |
| Other outpatient visits                    | 15,754.50                                     | 16,020.23| -265.73    |
| Home modifications                         | 2,469.47                                      | 2,478.92| -9.45      |
| Total Direct Cost                          | 2,084,141.07                                  | 2,120,181.45| -36,040.38|
| (464.68; 464.68)                          | (464.68; 464.68)                              |       |             |
| Indirect cost                              |                                               |     |             |
| Loss of earnings                           | 1,315,606.71                                  | 1,324,677.06| -9,070.35 |
| Total indirect cost                        | 3,451,840.03                                  | 3,444,858.51| 6,981.52  |

Abbreviations. AE, adverse event; BSC, best supportive care; ER, emergency department; GP, general practitioner; MS, multiple sclerosis; PR, prolonged-release.

more healthcare resources (caregiver support and physician visits) than those with improved mobility. However, the cost-effectiveness of treatment for walking impairment in MS has not previously been assessed. This model compared the cost-effectiveness of PR-fampridine versus BSC alone for the improvement of walking ability from a societal perspective in Sweden. Assuming a willingness-to-pay threshold of 500,000 kr per QALY gained, PR-fampridine had over 96% probability of being cost-effective in Sweden. The ICER was estimated at 57,109 kr/QALY, due to improvements in patients’ quality of life through walking improvement and reduced healthcare resource utilization.

Uncertainty was further extensively explored in scenario analyses, which all showed ICERS falling below the willingness-to-pay threshold. As the model is very sensitive to the utility value assigned to responders at week 24 and carried forward, three scenario analyses were conducted with alternative sets of inputs. 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. When EQ-5D-3L values from the ENHANCE study were used in the base case, PR-fampridine use was associated with 0.12 incremental QALYs and an ICER of 57,109 kr/QALY; when the more sensitive EQ-5D-5L measure from MOBILE study was used, incremental QALYs increased to 0.44 and the ICER decreased to 15,668 kr/QALY. An integrated analysis combined the results from the ENHANCE and MOBILE trials.

The rate of long-term natural progression of walking impairment taken from the placebo arm of the IMPACT trial was deemed to be relatively conservative compared with other published trials. Similarly, lack of data demonstrating potential sustained treatment effect following withdrawal...
from PR-fampridine meant that conservatively, the whole treatment effect was assumed to be lost upon discontinuation of PR-fampridine.

The ability to easily identify treatment responders in clinical practice enables the discontinuation of ineffective treatment in non-responders from as early as 2 weeks after treatment initiation\textsuperscript{12}, reducing an unnecessary burden on both the patient and healthcare system. The model includes 4 weeks of treatment costs in all patients initiating PR-fampridine. In a real-life clinical setting, non-responders may be identified at any time between 2 and 4 weeks, offering the potential for further cost savings on unnecessary PR-fampridine treatment in these individuals that are not captured in the current model.

PR-fampridine is commonly used with DMTs and approximately 40\% of patients in the ENHANCE trial were taking
concomitant DMTs; most common DMTs were glatiramer acetate, fingolimod, interferon beta-1a\(^18\). Therefore, it is important to note that the effect of PR-fampridine seen in the clinical trials and represented in the model is incremental to any effect that DMTs can have on walking impairment. During clinical trials, concomitant DMT medication (except for daclizumab) was allowed, although no change in DMT was allowed for the duration of the trials.

Due to the clinical indication of PR-fampridine between EDSS 4 and 7, baseline patients on ENHANCE trial were older (mean age approximately 49 years) and had a longer time since diagnosis (approximately 14 years) compared to other trials for DMTs in MS. The OWSA and PSA tested the impact of variation in patients’ baseline characteristics and the results were generally insensitive to variations in those parameters.

### Limitations

There were some data limitations when developing this model. Data collected in extension studies\(^22\) were available for up to 5 years following the end of the original Phase III trials\(^{15,16}\), requiring extrapolation of T25FW data to model the long-term treatment effect.

Treatment response is defined in the model per the MSWS-12 whilst disease progression is defined according to T25FW, due to the lack of long-term data on this variable and data showing how MSWS-12 is related to resource use.

Resource use data were sourced from a study that was conducted in the five major European markets\(^7\), so these values were not specific to the Swedish market, although the associated costing analysis was. According to a large MS burden of illness study conducted in Sweden and 15 other

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**Table 9.** Cost-effectiveness scenario analysis results for PR-fampridine versus BSC.

| Scenario analysis                          | Incremental costs (kr) | Incremental QALYs | ICER (kr/QALY) |
|-------------------------------------------|------------------------|-------------------|----------------|
| Base case                                 | 6,981.52               | 0.12              | 57,108.51      |
| Time horizon                              |                        |                   |                |
| Lifetime (100 years)                      | 6,981.52               | 0.12              | 57,108.51      |
| 10 years                                  | 9,029.37               | 0.12              | 77,604.64      |
| Discounting rates for costs and health outcomes (default: 3% per year) |                        |                   |                |
| 0%                                        | 5,082.17               | 0.14              | 36,301.21      |
| 5%                                        | 7,930.27               | 0.11              | 72,093.33      |
| Perspective (default: societal)           |                        |                   |                |
| Healthcare payer                          | 16,051.87              | 0.12              | 131,303.57     |
| Clinical trial scenarios (default: ENHANCE) |                        |                   |                |
| 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                       |                        |                   |                |
| +25%                                      | −3,934.85              | 0.12              | PR-fampridine dominates |
| −25%                                      | 17,897.89              | 0.12              | 146,403.93     |

Abbreviations. BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PR, prolonged-release; QALY, Quality-adjusted Life Year.

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Figure 5. Cost-effectiveness acceptability curve.
European countries, the direct healthcare costs, informal care costs, and production losses were similar in Sweden compared to other European countries. This publication provides evidence that using data from other European countries might have some degree of applicability to the Swedish setting. The PSA did not account for the possible pairwise correlations between relevant inputs, and may therefore overestimate the variability of the probabilistic results displayed in the cost-effectiveness plane. Further research is required to address the current lack of evidence on possible correlations between inputs to provide more robust analyses.

Conclusions

PR-fampridine in combination with BSC improves walking ability compared with BSC alone as a treatment for patients with MS and EDSS 4-7. The addition of PR-fampridine to BSC resulted in an ICER of 57,109 kr/QALY (€5,607/QALY and $6,675/QALY), which is below an assumed willingness-to-pay threshold of 500,000 kr per QALY gained (€49,088/QALY and $58,445/QALY). PR-fampridine, therefore, represents a cost-effective treatment for MS-related walking impairment in Sweden, due to improvements in patients’ quality of life through walking improvement and reduced healthcare resource utilization.

Note

1. Marketed by Biogen Inc. outside of United States of America (USA) and by Acorda Therapeutics, Inc. in the USA.

Transparency

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Declaration of financial/other interests

AC, EM and GM are employees of and hold stock/stock options in Biogen.

DT and LT were employees of Biogen at the time the study was conducted and the manuscript drafted.

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Author contributions

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Previous presentations

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C. ACOSTA ET AL.

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