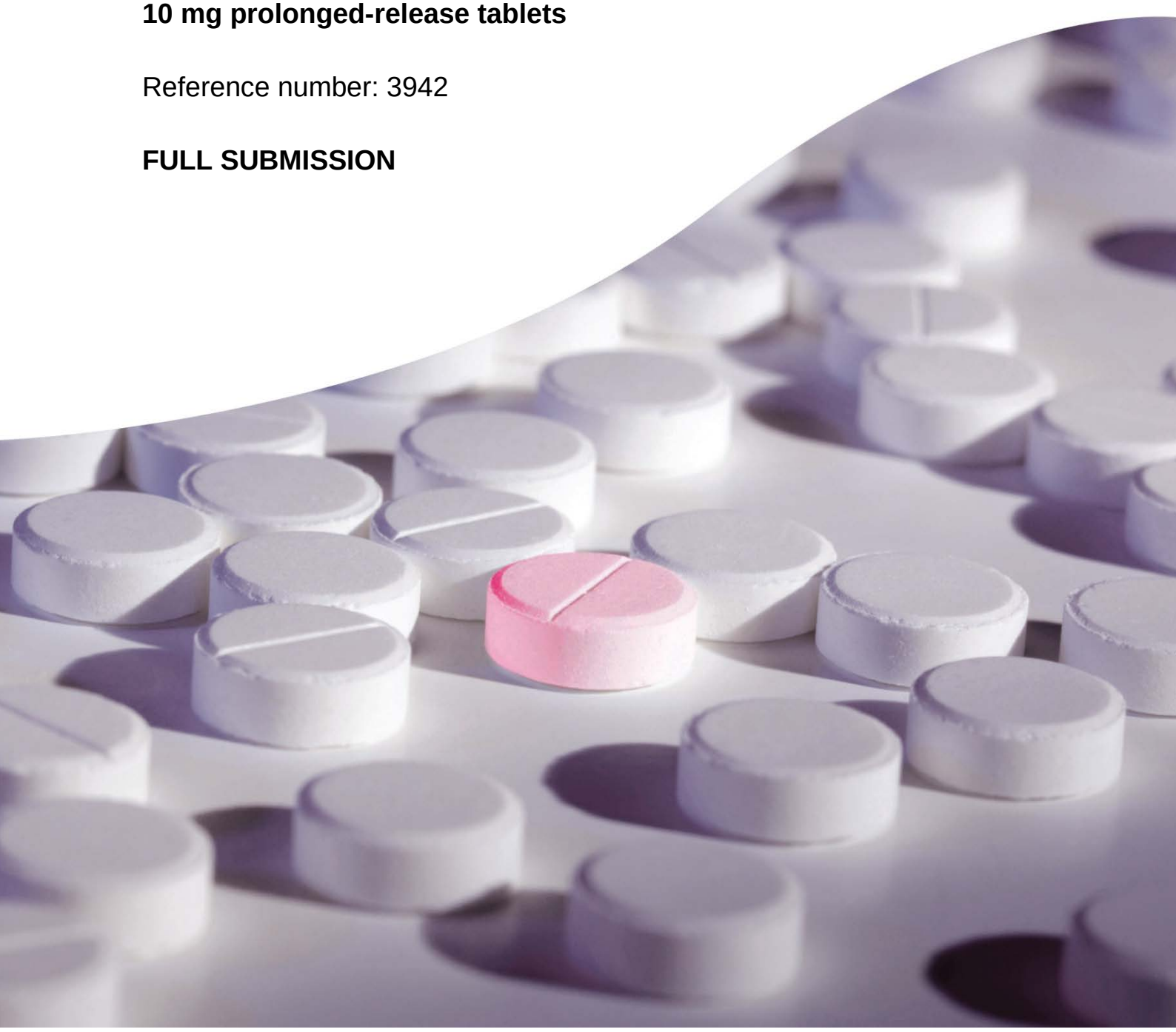
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Fampridine (Fampyra®)
10 mg prolonged-release tablets

Reference number: 3942

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Fampridine (Fampyra®) 10 mg prolonged-release tablets

1.0 KEY FACTS

Assessment details	Prolonged-release fampridine (Fampyra®) for the improvement of walking in adult patients with multiple sclerosis with walking disability (Expanded Disability Status Scale 4 to 7). Following a Welsh Government directed appraisal in September 2014, prolonged-release fampridine was not recommended for use in NHS Wales. This current appraisal is based on a full submission and includes new clinical evidence and a Wales Patient Access Scheme.
Current clinical practice	Prolonged-release fampridine is the first medicine licensed to improve walking in adults with multiple sclerosis related walking disability. The comparator included in the company's submission is best supportive care, including walking aids, exercise regimens, physiotherapy and a range of treatments that reduce muscle spasticity.
Clinical effectiveness	Evidence to support this submission includes the pivotal phase III, randomised, placebo-controlled study (ENHANCE). The primary outcome was the proportion of patients who achieved a mean improvement from baseline of at least eight points on the twelve-item multiple sclerosis walking scale score. There was a statistically significant, but modest, improvement for patients treated with prolonged-release fampridine compared with placebo over 24 weeks. Supporting evidence is provided by two phase III studies (MS-F203 and MS-F204) and a phase II study (MOBILE). In the MS-F203 and MS-F204 studies the primary endpoint, walking speed, was measured using the Timed 25-Foot Walk test. The proportion of responders was statistically significant in favour of prolonged-release fampridine. Both studies had open-label extension phases. At the end of the extension phases, the mean walking speed was similar to baseline levels. Quality of life measures, using the EQ-5D tool, were not significantly different between treatment groups in ENHANCE or MOBILE studies.
Cost-effectiveness	The submission includes a cost-utility analysis comparing prolonged-release fampridine and best supportive care to placebo and best supportive care. The company base case suggests an incremental cost-effectiveness ratio of **[commercial in confidence figure removed]** per quality-adjusted life-year gained.

	Should it be clinically reasonable to accept different health state utility estimates for responders in each treatment arm, AWTTC considers the lowest plausible incremental cost-effectiveness ratio to be **[commercial in confidence figure removed]**; this increases to between **[commercial in confidence figures removed]**, should the use of single health state utility estimates be more appropriate. The difference in incremental cost-effectiveness ratio estimates are driven by the utility data used.
Budget impact	The company estimates that 3,634 patients are eligible to receive treatment with prolonged-release fampridine in Wales in Year 1, increasing to 3,691 patients in Year 5. The company base case suggests an additional cost of **[commercial in confidence figure removed]** in Year 1, increasing to **[commercial in confidence figure removed**] in Year 5.

This assessment report is based on evidence submitted by Biogen Idec Ltd[1] and an evidence search conducted by AWTTC on 22 August 2019.

2.0 BACKGROUND

2.1 Condition and clinical practice

Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory condition of the central nervous system[2], characterised by inflammation, demyelination and damage to nerves[3]. MS is a potentially highly debilitating disorder, with considerable personal, social and economic consequences, and it is the most common cause of serious physical disability in adults of working age[2].

People with MS typically develop symptoms in their late 20s[2]. Most people present with relapsing-remitting MS, characterised by unpredictable acute episodes of neurological dysfunction or relapse, followed by variable recovery and periods of clinical stability[4]. Other less common types of MS are secondary progressive, primary progressive and progressive-relapsing[4,5]. The symptoms of MS are variable; people with MS typically develop multiple neurological dysfunctions, such as visual and sensory disturbances, limb weakness, gait problems, and bladder and bowel symptoms, which are followed by recovery or functional disability over time. Balance or coordination problems, dizziness, numbness and muscle stiffness or weakness can lead to walking difficulties[6]. Walking impairment affects more than 90% of individuals over time, and is consistently reported as one of the most distressing impairments by individuals with MS[7].

Current National Institute for Health and Care Excellence (NICE) clinical guidelines recommend non-pharmacological interventions, such as exercise programmes, for the management of people with MS and mobility problems[2]. NICE clinical guidelines do not recommend using fampridine to treat lack of mobility in people with MS because it is not considered a cost-effective treatment[2].

2.2 Medicine

Fampridine, also known as 4-aminopyridine, is a selective potassium channel blocker that acts on damaged nerves, preventing charged potassium particles from leaving the nerve cells and allowing electrical impulses to continue travelling along the nerves to stimulate the muscles[5].

Fampridine is a 10 mg prolonged-release (PR) tablet, which is recommended to be taken twice daily, 12 hours apart[8]. It is licensed for the improvement of walking in adult patients with MS with walking disability (Expanded Disability Status Scale [EDSS] 4 to 7: see Glossary)[8]. PR fampridine is the first licensed treatment for the improvement of walking in people with MS[5]. The company states that PR fampridine can be used first-line as monotherapy or concomitantly with disease-modifying therapies[1]. The initial prescription of PR fampridine should be limited to two to four weeks of therapy, after which response to treatment should be assessed[8]. If no improvement is observed, PR fampridine should be discontinued. In addition, the benefits of PR fampridine should be re-evaluated if a decline in walking ability is observed and treatment discontinued if patients no longer receive walking benefit[8].

Following a directive from Welsh Government in 2014, PR fampridine (Fampyra®) was not recommended by the All Wales Medicines Strategy Group (AWMSG) [9]. In September 2014, AWMSG stated that the case for cost-effectiveness has not been proven[9]. In this current appraisal, the company has provided a full submission to reflect new clinical evidence in the form of the ENHANCE study, which resulted in a switch from a conditional marketing authorisation to a full marketing authorisation, as well as an approved Wales Patient Access Scheme[1].

2.3 Comparators

The comparator included in the company's submission is best supportive care (BSC), which may constitute any therapy that could potentially impact or assist with walking impairment, such as walking aids, exercise regimens, physiotherapy or treatments that reduce muscle spasticity[1].

2.4 Guidance and related advice

- NICE Clinical Guideline 186. Multiple sclerosis in adults: management (October 2014, last updated July 2019)[2].
- AWMSG Advice. Fampridine (Fampyra®) for the improvement of walking in adult patients with MS with walking disability (EDSS 4–7) (Not recommended: September 2014, last reviewed December 2017)[9].
- AWMSG Advice. Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®) for symptom improvement in adult patients with moderate to severe spasticity due to MS (Recommended: August 2014, last reviewed October 2017)[10].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, fampridine (Fampyra®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

3.0 CLINICAL EFFECTIVENESS

The company submission included results from a pivotal phase III study (ENHANCE), which compared the efficacy and safety of PR fampridine with placebo on walking ability in people with MS who have walking impairment[1,7]. The ENHANCE study was conducted on recommendation of the European Medicines Agency (EMA) to re-affirm the clinical meaningfulness of PR fampridine, and resulted in conversion from a conditional to full marketing authorisation in May 2017[4]. The company also included results from two earlier phase III studies (MS-F203 and MS-F204) that supported the conditional marketing authorisation, and their corresponding open-label extension studies (MS-F203EXT and MS-F204EXT), analysing the effect of PR fampridine on walking speed in people with MS[1,11-13]. The company submitted details describing a phase II study (MOBILE), which was a double-blind study assessing walking ability and balance, and informed the endpoints in the ENHANCE study[1,14].

The company also provided evidence from an open-label study (ENABLE) and two single-arm observational studies[15-17]. The patient population (EDSS 1 to 8.5) in the ENABLE study does not match the population covered by the licensed indication, and the observational studies do not provide any comparative efficacy data[15-17]. These studies do not inform the health economic model and will not be discussed further.

3.1. ENHANCE study

ENHANCE was a multicentre, randomised, double-blind, placebo-controlled phase III study (n = 636)[7]. This study recruited adults aged 18 to 70 years with any subtype of MS, an EDSS score of 4 to 7, and investigator-assessed walking impairment. Patients were randomised 1:1 to receive PR fampridine 10 mg orally twice daily for 24 weeks or placebo. Randomisation was stratified by baseline EDSS score (≤ 6.0 or 6.5 to 7.0) and by prior 4-aminopyridine use. The double-blind phase was followed by a two-week post-treatment follow-up. Concomitant use of approved disease-modifying therapies and medications for fatigue or spasticity were allowed if the medicine and dose remained stable throughout the study; physiotherapy and rehabilitation therapy were also allowed[7].

The primary endpoint was the proportion of patients who achieved a mean improvement from baseline of at least eight points on the twelve-item MS walking scale (MSWS-12: see Glossary) score over 24 weeks[7]. The primary outcome was assessed in the intention-to-treat population, defined as all randomised patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment. There was a statistically significant difference in the percentage of patients achieving the primary endpoint: a higher percentage of PR fampridine-treated participants had a clinically meaningful improvement in MSWS-12 score over 24 weeks versus placebo (PR fampridine-treated patients: 136/315 [43.2%]; placebo patients: 107/318 [33.6%]; odds ratio 1.61 [95% confidence interval [CI] 1.15–2.26]; p=0.006)[7].

Results for the secondary endpoints were supportive of the primary endpoint. For PR fampridine versus placebo, more participants had a ≥ 15% improvement in timed up and go (TUG: see Glossary) speed, and there was greater mean improvement in the MS Impact Scale physical score (MSIS-29 PHYS score: see Glossary); these results were statistically significant. Numerical improvements that were not statistically significant were observed in the Berg Balance Scale (BBS: see Glossary) and ABILHAND (see Glossary)[7]. Quality of life measures, including EQ-5D-3L (see Glossary), showed little change from baseline and minimal differences between the groups[4].

3.2 MS-F203 and MS-F204 studies

MS-F203 and MS-F204 were multicentre, randomised, double-blind, placebo-controlled phase III studies conducted to evaluate the effect of PR fampridine on patients aged 18 to 70 years with MS[11,12]. Patients were eligible for the studies if they were able to complete two trials of the Timed 25-Foot Walk (T25FW) test in an average time of 8 to 45 seconds at screening. Concomitant treatment with immunomodulators was allowed. Patients were randomised to receive treatment in the double-blind phase with either fampridine 10 mg PR twice-daily or placebo, followed by a follow-up period without treatment. The two studies differed in the duration of the double-blind phase (14 weeks for MS-F203; nine weeks for MS-F204), the randomisation scheme (3:1 for MS-F203 and 1:1 for MS-F204) and the duration of the follow-up period (four weeks for MS-F203 and two weeks for MS-F204)[11,12].

The primary outcome in both studies was the proportion of T25FW responders, where response was defined as a faster walking speed on at least three of four on-treatment visits compared with the maximum speed for any of first five off-treatment visits[11,12]. In both studies, there were statistically more responders in the PR fampridine group compared with placebo. In study MS-F203, the number of responders in the PR fampridine group was 78/224 (34.8%) compared to 6/72 (8.3%) in the placebo group (odds ratio 4.75 [95% CI 2.08–10.86]; $p < 0.0001$). In study MS-F204, the number of responders in the PR fampridine group was 51/119 (42.9%) compared to 11/118 (9.3%) in the placebo group (odds ratio 8.14 [95% CI 3.73–17.74]; $p < 0.0001$).

The primary endpoint was supported by two of the secondary endpoints: average change in walking speed and average change in Ashworth spasticity score (see Glossary)[11,12]. The lower extremity manual muscle test (LEMMT: see Glossary) results were favourable to PR fampridine-treated versus placebo-treated patients; however, statistical superiority was only achieved in MS-F203[11,12].

3.3 MS-F203EXT and MS-F204EXT studies

MS-F203EXT and MS-F204EXT were open-label extension studies evaluating the long-term effect of PR fampridine on walking speed in patients who had been participants in MS-F203 and MS-F204, respectively (MS-F203EXT: n = 269 patients enrolled; MS-F204EXT: n = 214 patients enrolled)[13]. All patients received 10 mg PR fampridine twice-daily with assessments at two weeks, 14 weeks, 26 weeks and then at six month intervals over a period of up to 3.8 years (MS-F204EXT) or up to 5.3 years (MS-F203EXT). Results for both studies showed that walking speed of responders remained greater than that of non-responders; however, mean walking speed decreased continuously for both responders and non-responders, and was similar to the baseline levels by the end of the study[13].

3.4 MOBILE study

MOBILE was a multicentre, randomised, placebo-controlled, exploratory, phase II study, which recruited patients similar to the ENHANCE study[14]. Patients were randomised to receive either 10 mg PR fampridine twice-daily (n = 68) or placebo (n = 64) for a 24 week double-blind treatment period. Over the study period, a higher proportion of PR fampridine-treated patients experienced a clinically meaningful improvement (≥ 8 point mean improvement) in MSWS-12 score (48.5% of PR fampridine-treated patients compared to 28.1% of placebo patients, $p = 0.015$). Secondary endpoints assessed mobility and balance using the TUG test and the BBS. A higher proportion of patients in the PR fampridine arm than in the placebo arm showed a clinically meaningful improvement (defined as ≥ 15% mean improvement in TUG speed; 47.1% in the PR fampridine group compared to 30.2% in the placebo

group, p = 0.026). PR fampridine-treated patients showed greater improvements from baseline in BBS compared with placebo-treated patients[14].

Quality of life measurements were measured using the MSIS-29 PHYS and the EQ-5D-5L tool (see Glossary). MSIS-29 PHYS scores, which assessed the impact of MS on physical and psychological functioning, showed greater improvement in the PR fampridine arm versus the placebo arm[14]. No clear differences in the change between baseline and on-treatment EQ-5D visual analogue scale and utility scores were observed between PR fampridine- and placebo-treated patients[14].

3.5 Safety information

The EMA concluded that the safety findings in the ENHANCE study were consistent with the known safety profile of PR fampridine in previous clinical studies and post-marketing experience[4]. The incidence of adverse events related to study treatment was higher in the PR fampridine-treated group than the placebo treatment group: 18% and 13%, respectively. Most subjects had adverse events that were considered mild or moderate in severity, and the incidence of adverse events that were considered severe was the same (3%). Adverse events that were more common in the PR fampridine-treated participants were urinary tract infections and insomnia[7]. The most common reason for discontinuation in both groups was adverse events (7% in both treatment groups). There were no new safety findings with respect to the important risks of seizures, hypersensitivity, urinary tract infections and interactions with organic cation transporter 2 inhibitors[4].

As in the ENHANCE study, treatment-related adverse events in the MS-F203 and MS-F204 studies were reported at a higher rate in the PR fampridine arms than in the placebo arms[11,12]. Treatment discontinuation due to treatment-emergent events occurred for eight patients in the PR fampridine arm of MS-F203, two of which were regarded by the investigator as possibly related to treatment: a focal seizure in a patient with sepsis and an episode of severe anxiety[11,12]. Seizure risk is highlighted in the Summary of Product Characteristics. The overall safety profile of the MS-F203EXT and MS-F204EXT studies was consistent with that observed in the parent trials[13].

3.6 Ongoing studies

The applicant company highlighted one ongoing study:

- LIBERATE is an ongoing study, with a primary objective to collect real-world data on safety, and a secondary objective to collect patient-reported data on wellbeing and physician-reported data on walking ability in fampridine-treated patients with MS in routine clinical practice.

3.7 AWTTC critique

- Fampridine is the first medicine licensed for the treatment of walking impairment in patients with all subtypes of MS and addresses an unmet need. MS has adverse and often highly debilitating effects on a person's quality of life and that of their families. Although disease-modifying therapies have been shown to be effective in reducing relapse rates and disease progression in people with the relapsing-remitting form of MS, disease-modifying therapies do not specifically target the symptoms of MS.
- The primary endpoint used in the ENHANCE study is accepted by the EMA as clinically meaningful[4]. It uses the MSWS-12 scale which assesses multiple aspects of walking ability, as reported by patients, rather than speed which was assessed in the earlier phase III studies[7,11,12].

- The results of the ENHANCE study confirmed that treatment with PR fampridine results in a clinically meaningful improvement in walking in a proportion of patients with MS with walking disability, though the effect size is considered as modest by the Committee for Medicinal Products for Human Use[4], and the maintenance of effect is unclear[5]. The decline in walking speed over time in the extension studies MS-F203EXT and MS-F204EXT could be due to progression of disease or lack of maintenance of effect[5].
- Overall, approximately one third of patients treated might get a relevant benefit from treatment with PR fampridine[4]. Analyses from the ENHANCE study demonstrated that early detection of non-responders facilitates the decision to discontinue treatment, avoiding unnecessary exposure[4]. This is reflected in the Summary of Product Characteristics, which recommends that patients discontinue treatment if no improvement is observed within two to four weeks[8].
- The higher response rate for the primary analysis in the placebo group of ENHANCE compared with the placebo groups in MS-F203 and MS-F204 might be due to the subjective nature of the MSWS-12 questionnaire compared with the objective T25FW test[4].
- Quality of life data collected using the EQ-5D-3L in the ENHANCE study showed little change from baseline and minimal differences between the groups. The company suggests that EQ-5D-3L is insensitive to measuring changes in quality of life in people with MS.
- Determining renal function before treatment with PR fampridine and its regular monitoring during treatment is recommended in all patients (particularly in older people in whom renal function might be reduced)[8].

4.0 COST-EFFECTIVENESS

4.1 Context

The company's submission includes a cost-utility analysis (CUA) and considers oral fampridine (Fampyra®) 10 mg PR tablets in addition to BSC, compared to placebo in addition to BSC, in adult patients with MS and walking disability (EDSS 4 to 7)[1].

The CUA takes the form of a decision tree for response assessment followed by a Markov cohort model, comprising 28–day cycles. The decision tree allows for categorisation of treatment effect into responders and non-responders, with patients then transitioning into a Markov model comprising of three health states: responder, non-responder, and death. Patients may transition to death from any health state[1]. The model adopts a 5-year time horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are discounted at 3.5% and a simple Wales Patient Access Scheme (WPAS) discount is incorporated[1].

The efficacy data used to inform the PR fampridine and placebo response rates and responder health state are derived from the ENHANCE study, with response defined as an improvement in MSWS-12 by eight points or more from baseline[7]. The non-responder health state is informed by withdrawal associated with a loss of efficacy and is based on a study which reported the 5-year probability of patients remaining on treatment following a response of 62.1%[18]. This 5-year probability is used to estimate the probability of withdrawal each 4-week cycle. Withdrawal due to mortality is considered separately.

The model estimates the number of patients with treatment-related adverse events by calculating the proportion of patients who experienced adverse events as reported in the ENHANCE study: 18% of patients in the PR fampridine treatment group and 13% in the placebo group[7]. Adverse event data were reported for the 26-week duration of the study from which the risk of a patient experiencing an adverse event was converted into a 4-week risk, assuming a constant rate, to align with the 4-week cycle length used in the model. Only adverse events occurring in ≥ 5% of patients are included in the analysis and, thus, only non-serious adverse events occurring in ≥ 5% of patients are considered. No serious adverse events are included in the analysis as no adverse event occurred in ≥ 5% of patients. In addition, no medicine-related serious adverse events were recorded in the PR fampridine arm[1,7].

The model includes the cost of treatment associated with PR fampridine, including medicine acquisition costs and a hospital-based response assessment occurring at Week 4. Dosing is based on patients receiving PR fampridine 10 mg every 12 hours, in accordance with the Summary of Product Characteristics[8], with patients who respond to treatment in the initial four weeks following initiation of treatment then continuing on treatment, until withdrawal due to either a loss of response or death. Medicine costs are not included for BSC as this is received in both arms and therefore would have no net effect in the analysis.

GP surgery visits associated with each adverse event experienced during treatment are derived from the Unit Costs of Health & Social Care[19], and medicine costs from the British National Formulary[20]. Remaining unit costs for outpatient and inpatient visits are sourced from NHS reference costs[21].

Health outcomes are accrued in both the responder and non-responder health states, using treatment specific and state-specific utility weights. The model includes EQ-5D utilities for the responder and non-responder health states for the PR fampridine and placebo arms at time points up to 24 weeks, with the last values carried forward over the remainder of the 5-year time horizon. The company has supported the use of separate responder and non-responder utility values based on trial-reported MSWS-12 mean change from baseline data from the MOBILE and ENHANCE studies. This shows a higher proportion of PR fampridine patients achieving a ≥ 8-point mean reduction (improvement) from baseline over the study period (24 weeks).

In the company base case, EQ-5D-5L data collected in the MOBILE phase II study have been mapped to the EQ-5D-3L using the Van Hout algorithm[14,22]. Age-related utility decrements are included in the analysis. Utility decrements for adverse events were selected as the closest available matches from a catalogue[23] and applied in responder and non-responder health states, in each cycle, for PR fampridine and placebo arms.

Deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model. The parameters tested, among others, include: discount rates for costs and benefits, utility, response and withdrawal rates, unit costs and resource use. Scenario analyses explore the impact of alternative utility values using the EQ-5D-5L valuation set from the MOBILE study[14] and EQ-5D-3L data from the ENHANCE study[7]. The impact of alternative response rates are considered using data from the MOBILE[14], MS-F203[11] and MS-204[12] studies, as well as alternative discontinuation rates and time horizons.

4.2 Results

The results of the base case are detailed in Table 1. When compared with placebo, the incremental cost-effectiveness ratio (ICER) generated is **[commercial in confidence figure removed]** per quality-adjusted life-year (QALY) gained. The main cost differences can be attributed to the medicine acquisition cost of PR fampridine. The incremental QALY gains are predominantly driven by the difference in utility values for responders and non-responders in the PR fampridine and placebo arms.

Table 1. Results of the base case analysis (WPAS medicine cost)

	PR fampridine	Placebo	Difference
Total drug and response assessment costs	¶¶	¶¶	¶¶
Total direct costs	¶¶	¶¶	¶¶
Total costs	¶¶	¶¶	¶¶
Total life-years	¶¶	¶¶	¶¶
Total QALYs	¶¶	¶¶	¶¶
ICER (£/QALY gained)	¶¶		
ICER: incremental cost-effectiveness ratio; PR: prolonged release; QALY: quality-adjusted life-year ¶¶ commercial in confidence figures removed			

The results of the univariate sensitivity analysis show that the ICER is most sensitive to the utility values for both PR fampridine and placebo, as well as response rates and the time horizon used. For each of these, except the EQ-5D-3L valuation set from the ENHANCE study, variations in parameter estimates produce ICERs within the usual accepted thresholds. The results of scenario analysis are assessed in order of plausibility in Table 2.

Probabilistic sensitivity analyses indicate that PR fampridine has a **[commercial in confidence figure removed]** and **[commercial in confidence figure removed]** probability of being cost-effective at a threshold of £20,000 and £30,000 per QALY gained, respectively.

Table 2. Results of scenario and sensitivity analyses

Scenarios	ICER	Plausibility
EQ-5D-5L valuation sets (MOBILE)	¶¶	This scenario provides a plausible alternative to the base case, given that these data are directly reported and uses the matching valuation set, demonstrating sensitivity to utility data selection
EQ-5D-3L valuation sets (ENHANCE)	¶¶	This scenario provides a plausible alternative to the base case, given that these data are directly reported and uses the matching valuation set, demonstrating sensitivity to utility data selection
Societal perspective using Adelphi	¶¶	A useful analysis which has plausibility as a scenario analysis
Response rate from MOBILE	¶¶	This scenario provides a plausible alternative to the base case, given that these data are from the same measure as the base case but from an alternative study
Higher cost of MS-related hospitalisation (£3,270)	¶¶	The rationale for this scenario is that this cost reflects the maximum cost for MS-related hospitalisation and is a plausible scenario
Discount rate 1.5% for costs and benefits	¶¶	This scenario is plausible and shows the possible effect on the ICER of alternative discount values.
4-weekly discontinuation rate BSC responders – doubled	¶¶	This scenario is plausible, given the uncertainty around the discontinuation rate which may be observed in clinical practice
4-weekly discontinuation rate PR fampridine & BSC responders doubled	¶¶	This scenario is plausible, given the uncertainty around the discontinuation rate which may be observed in clinical practice
4-weekly discontinuation rate PR fampridine & BSC responders halved	¶¶	This scenario is plausible, given the uncertainty around the discontinuation rate which may be observed in clinical practice
Response rate from MS-F203	¶¶	Responder rate from MS-F203 based on an alternative measure of walking status (T25FW). It lacks plausibility as the MSWS-12 measure used in the base case was reported in the study and would have provided a more plausible scenario analysis
Response rate from MS-F204	¶¶	Responder rate from MS-F204 based on an alternative measure of walking status (T25FW). It lacks plausibility as the MSWS-12 measure used in the base case was reported in the study and would have provided a more plausible scenario analysis
Time horizon 2-year	¶¶	This scenario reflects the effect on the ICER of a shorter time horizon, which given the timing of costs and effects in the model, may be suitable to assess the impact of a shorter time horizon
Time horizon 10-year	¶¶	This time horizon is potentially informative; however, the company indicate the model time horizon is selected to ensure patients do not progress to EDSS > 7 during the analysis. It is not clear this assumption holds with the extended time horizon
Direct costs increase by 25%	¶¶	Not necessarily more plausible than the base case, but shows the impact of uncertainty in the robustness of the health state costs analysis on the ICER
Direct costs decrease by 25%	¶¶	
BSC: best supportive care; EDSS: Expanded Disability Status Scale; ICER: incremental cost-effectiveness ratio; MS: multiple sclerosis; MSWS-12: Twelve-Item Multiple Sclerosis Walking Scale; PR: prolonged release; T25FW: Timed 25-Foot Walk ¶¶ commercial in confidence figures removed		

Table 3 Results of AWTTC generated scenarios

AWTTC-generated scenarios	ICER	Description
Average utility values for responders and non-responders over the 4-24-Week period from the mobile EQ-5D-mapped values used in the analysis for all time points.		
Average of health state utility scores used for all time points	¶¶	To address uncertainty around the use of utility values by time-points and assumption of continued effect based on the Week 24 value. Separate values used for PR fampridine and placebo treated patients
Utility values for non-response set to PR fampridine-treated patients	¶¶	To address uncertainty around the use of different utility values between treatment arms and assumption of continued effect based on the Week 24 value. Separate values used for response in PR fampridine and placebo treated patients, non-response assumed equal to PR fampridine
Utility values for non-response set to placebo-treated patients	¶¶	To address uncertainty around the use of different utility values between treatment arms and assumption of continued effect based on the Week 24 value. Separate values used for response in PR fampridine and placebo treated patients, non-response assumed equal to BSC
Average health state scores from PR fampridine treated patients	¶¶	To address uncertainty around the use of different utility values between treatment arms and assumption of continued effect based on the Week 24 value. An average of the utility values from the PR fampridine treated patients is applied in both arms
Average health state scores from placebo treated patients	¶¶	To address uncertainty around the use of different utility values between treatment arms and assumption of continued effect based on the Week 24 value. An average of the utility values from the placebo treated patients is applied in both arms
BSC: best supportive care; EDSS: Expanded Disability Status Scale; ICER: incremental cost-effectiveness ratio; MS: multiple sclerosis; MSWS-12: Twelve-Item Multiple Sclerosis Walking Scale; PR: prolonged release; T25FW: Timed 25-Foot Walk ¶¶ commercial in confidence figures removed		

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Reasonable justifications are provided for most of the assumptions applied in the model.
- The inclusion of a selection option, allowing alternative utility values derived directly from the study data to be used in the analysis, allows for an assessment of the main source of uncertainty in the model.
- Extensive sensitivity and scenario analyses have been conducted.
- The mapping of utilities from the EQ-5D-5L to the EQ-5D-3L represents good practice.

Limitations:

- Utility values included in the analysis are those modelled separately for responders and non-responders in each treatment arm. A rationale has been provided for the inclusion of treatment specific utilities; however, this remains a source of uncertainty in the analysis.
- The model uses a last observation carried forward model for applying utility data from Week 24 to the remaining time in the selected model time horizon, despite variability in the utility scores reported at the preceding time points. No rationale is provided for this approach. A more appropriate method would have been to use single health-state specific utilities for responders and non-responders, unless there was a valid justification for a change in utility over time, and that Week 24 utility values continue to be representative for the duration of the time horizon.
- Resource use has been estimated through a survey. However, the variables included in the analysis are calculated based on the T25FW, while the base case response measure is the MSWS-12. The applicability of the data to the alternative response measure has not been provided.
- Despite providing a detailed account of the model, the submission also includes descriptions of evidence not included in the model. For example, the resource use data obtained from the High Risk Institutes in Germany.
- The rationale for the exclusion of serious adverse events from the model is not clearly justified. The reason provided for exclusion is that “no serious adverse events were considered PR fampridine-related[1]”. However, non-serious adverse events were included for both PR fampridine and placebo.
- The time horizon used by the company is clearly justified in the submission. However, the company has conducted a sensitivity analysis to explore how the ICER changes in response to a longer time horizon, which might conflict with the justification for the base case time horizon: that is, that patients will not progress to EDSS above 7. Therefore, the 10-year time horizon scenario analysis and other alternative time horizon scenarios have an uncertainty around progression to EDSS > 7, which cannot be addressed in the current analysis.
- A rationale for the selected starting age in the model is not provided.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC identified a number of economic evaluations which include PR fampridine. The review identified: a previous appraisal by AWTTC undertaken without a company submission[9]; an appraisal by the Canadian Agency for Drugs and Technologies in Health[24]; and NICE CG186, which provides guidelines for the management of MS in adults in the UK, where PR fampridine is one of the treatment options, but is not recommended for use in MS because it is not a cost-effective treatment[2]. NICE has not reviewed fampridine within the context of a technology appraisal. Finally, a re-submission to the Scottish Medicines Consortium was identified, which found that "the submitting company did not present a sufficiently robust economic analysis to gain acceptance by the Scottish Medicines Consortium"[25], the company advise that a final resubmission is in process. NICE CG186 does not report the results of the CUA[2]. The AWTTC analysis reported results for a CUA, limited to treatment costs using the fampridine list price and limited data undertaken by NICE using published clinical data from the MS-F204 study. The results were an ICER of £160,884 over 1-year, with a cost of treatment of £4,719 and an incremental QALY of 0.02933. The AWTTC appraisal considered two scenarios based on the same clinical and cost data used by NICE, examined the impact of changing utility assumptions by equating the baseline utility to that of the PR fampridine-treated patients, and equated the baseline utility to that of the placebo-treated patients. The results of these analyses were an incremental QALY in the first scenario of 0.1461 and an ICER of £322,913, and an incremental QALY of 0.01511 and an ICER of £312,270 in the second scenario. A third AWTTC analysis used clinical data from MS-F203, resulting in an incremental QALY of 0.03643 and an ICER of £115,498. Finally, the Canadian Agency for Drugs and Technologies in Health appraisal reported uncertainties in the company submission associated with the utility analysis; addressing these issues caused the plausible ICER to increase from the company value of Can$30,000 to between Can$54,000 and Can$500,000, with the probable estimate the upper end of that range. However, the Canadian analysis and the reported uncertainty may be due in part to the difference in health systems. The various appraisals identified all cited the utility data as the key uncertainty in the analysis.

5.0 BUDGET IMPACT

5.1 Context and methods

The company has estimated that there will be 5,291 people with MS in 2019. This estimate is based on Office for National Statistics population statistics[26,27] and Welsh specific incidence and prevalence data[28]. To calculate the number of people who need treatment in Wales, the company has based the analysis on prevalence estimates, assuming a constant prevalence rate with an 0.39% annual population growth rate[27], together with an MS-adjusted mortality rate[29]. The analysis assumes that of the prevalent MS population, **[commercial in confidence figure removed]**, will be eligible for treatment with PR fampridine[1]. It is assumed that incident patients would be ineligible for treatment as they would have an EDSS below 4. An assumed market share of **[commercial in confidence figure removed]** in Year 1, increasing to **[commercial in confidence figure removed]** in Year 5, is representative of a patient starting treatment with PR fampridine and achieving a response. As there are no comparator medicines to consider, the uptake rate for PR fampridine in the analysis is based on a simple additional medicine cost basis, without displacement of other medicines. Adverse events are not included in the analysis.

5.2 Results

The budget impact is presented in Table 4. The company estimates that introducing PR fampridine would lead to a net medicine acquisition cost of **[commercial in confidence figure removed]** in Year 1, increasing to **[commercial in confidence figure removed]** in Year 5, and a resource use cost of **[commercial in confidence figure removed]** in Year 1, decreasing to **[commercial in confidence figure removed]** in Year 5. This is a consequence of the assessment of response at Week 4 following the initiation of treatment. These resource-type costs are included for potential planning purposes. The company carried out a scenario analysis, where decreasing uptake by 50% reduced the net acquisition cost to **[commercial in confidence figure removed]** in Year 1 and **[commercial in confidence figure removed]** in Year 5. Conversely, increasing uptake by 50% increased the net acquisition cost to **[commercial in confidence figure removed]** in Year 1 and **[commercial in confidence figure removed]** in Year 5.

Table 4. Company-reported costs associated with use of PR fampridine for the improvement of walking in adults with MS with walking disability (EDSS 4–7)

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	¶¶	¶¶	¶¶	¶¶	¶¶
Sub-population of eligible patients (indication under consideration)	¶¶	¶¶	¶¶	¶¶	¶¶
Uptake of new medicine (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving new medicine, allowing for discontinuations	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without new medicine	£0	£0	£0	£0	£0
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ commercial in confidence figures removed					

5.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact.
- The calculation of patient numbers with the introduction of PR fampridine fails to include the proportion of patients discontinuing from treatment correctly as these patients are simply removed and not accounted for as non-responders without treatment and assessment costs, or as receiving BSC only. This affects the patient counts in the analysis but not the results, as no cost is associated with BSC.
- The budget impact considerations are limited to acquisition costs: the cost of a response assessment at Week 4. Other cost associated with resource use are not included (e.g. costs associated with adverse events).
- It is uncertain how the estimates for treatment uptake for PR fampridine have been calculated.
- The company has included variability in market share as a scenario analysis. Since there is little information provided on the uptake assumptions, this provides a useful analysis of the potential range of uptake estimates, though further details would be desirable to establish the plausibility of the analysis.

GLOSSARY

ABILHAND
A subject-completed questionnaire that measures a subject's perceived difficulty in performing everyday manual activities during the preceding 3 months. Subjects rate a list of 56 activities as impossible (0), difficult (1), or easy (2). The transformed scale ranges from 0 to 100, where higher scores indicate greater manual ability.

Ashworth spasticity score
A rating given by an assessor testing passive resistance or level of stiffness in a patient to passive movement of a joint[30]. In studies MS-F203 and MS-F204 the Ashworth score was averaged across three muscle groups bilaterally: hip adductors, knee extensors and knee flexors[11,12].

Berg balance Scale (BBS)
A measure of patient's static and dynamic balance and is based on a score of 0 (unable to perform) to 4 (able to perform independently) for each of 14 balance-related tasks[31].

EQ-5D-3L health related quality of life (HRQoL) tool
A patient–reported instrument measuring HRQoL on five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression at three levels (1 = no problem, 2 = some problem and 3 = extreme problem). In addition the health state is evaluated using a visual analogue scale, where the patient records their current state from 0 (worst imaginable) to 100 (best imaginable)[32].

EQ-5D-5L health related quality of life (HRQoL) tool
A patient–reported instrument measuring HRQoL on five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression[33]. Each dimension has five levels (no problems, slight problems, moderate problems, severe problems and extreme problems). The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state[33].

Expanded Disability Status Scale (EDSS)
A method of quantifying MS disability and ranges from 0 to 10 in 0.5 unit increments[34]. A score of four corresponds to a patient with significant disability who is able to walk without aid or rest for 500 metres; a score of seven describes the status of a patient who is unable to walk beyond five metres even with aid[34].

Lower extremity manual muscle test (LEMMT)
In studies MS-F203 and MS-F204 the LEMMT measured strength in four muscle groups bilaterally (hip flexors, knee flexors and extensors and ankle dorsiflexors)[11,12].

Multiple Sclerosis Impact Scale (MSIS-29) physical score
A subject-completed questionnaire that comprises 29 questions to measure the physical (questions 1 to 20) and psychological (questions 21 to 29) impact of MS[4]. The physical score is calculated by summing across the 20 relevant items and transformed to a scale from 1 (no impact of MS) to 100 (extreme impact of MS)[4].

Multiple Sclerosis Walking Scale (MSWS-12)
The 12-item MSWS-12 is used by patients to record their opinions on their walking disability during the preceding two weeks[7]. The scale has 12 questions about different aspects of walking, such as ability and speed; ability to run; ability to climb and descend stairs; balance and smoothness of gait; support, effort and concentration required[7]. Patients rate limitations of their mobility due to MS on a Likert 5-point scale (from 1=not at all to 5= extremely). The total score across 12 questions (1-60) is transformed to a scale from 1 to 100, with a higher score representing poorer walking ability.

Timed walk responder
This was defined during studies MS-F203 and MS-F204 as a patient who had a faster walking speed in the T25FW for ≥ three visits out of four visits in the treatment phase of the studies, compared to the maximum walking speed achieved when not receiving treatment[11,12].

Timed up and go (TUG) test.
In the TUG test the time taken for patients to stand from a seated position, walk three metres, turn around, walk back and return to the seated position is recorded[35].

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