PUBLIC SUMMARY DOCUMENT
Product: Fampridine, modified release tablet, 10 mg, Fampyra®
Sponsor: Biogen Idec Australia Pty Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application

The submission sought an Authority Required listing for initial and continuing treatment for the symptomatic improvement of walking ability of an ambulatory patient with clinically definite multiple sclerosis who meets certain criteria.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Fampridine was approved by the TGA on 13 May 2011 for the symptomatic improvement of walking ability in adult patients with multiple sclerosis (MS).

4. Listing Requested and PBAC's View

Authority required

Initial treatment for the symptomatic improvement of walking ability of an ambulatory patient with clinically definite multiple sclerosis.

(a) The diagnosis of clinically definite multiple sclerosis must be confirmed by magnetic resonance imaging of the brain and/or spinal cord and the date of the scan included in the authority application, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient.

AND

(b) The patient must be able to complete two trials of the Timed 25 Foot Walk within 5 minutes of one another

AND

(c) The patient has impaired walking ability. The average time taken to complete the two Timed 25 Foot Walks is within the range of 8 to 45 seconds

A maximum of 8 weeks of treatment will be authorised under this restriction

Continued treatment

Continuing PBS subsidised treatment by a neurologist of a patient who has demonstrated an adequate response.

An adequate response is defined as at least a 20% improvement in time taken to complete the T25FW tests during the 8 week initiation trial.

Continued treatment ('grandfather patients')

Continuing PBS subsidised treatment by a neurologist of a patient who is receiving treatment with, and demonstrated adequate response to fampridine at the time of application.

Note:

Individuals who become dependent on a wheelchair for mobility are no longer eligible for continued treatment

The pre-treatment and on treatment T25FW assessments must be completed under the following conditions:

- Patient is not suffering from side effects of recently administered concomitant MS medications
- Patient is not suffering from or recovering from a recent relapse or exacerbation
- Patient is not suffering from acute illness likely to impact on walking speed assessment
- Patient is not suffering from greater fatigue or mobility dysfunction than is usual

The PBAC considered that the proposed restriction would not adequately limit access to patients with a genuine response to treatment. *See Recommendation and Reasons.*

5. Clinical Place for the Proposed Therapy

MS is a progressive, chronic disease of the central nervous system; characterised by demyelination and axonal loss. MS results in a variable and complex range of symptoms, including visual disturbance, fatigue, pain, reduced mobility and co-ordination, cognitive impairment, and mood changes. Most patients present with relapsing-remitting MS, characterised by acute clinical attacks (relapses) followed by variable recovery and periods of clinical stability. After about 10 years, the majority of these patients develop secondary progressive MS, which is characterised by sustained deterioration with or without relapses. A smaller proportion of patients develop sustained deterioration from the start (primary progressive MS). Some patients who begin with progressive deterioration may experience relapses with time (progressive relapsing MS).

Fampridine was proposed to be used in addition to current management of MS patients.

6. Comparator

The submission nominated placebo as the comparator. The PBAC accepted that placebo was an appropriate comparator but considered that as the sponsor's survey indicated that 84% of treating neurologists refer patients for physiotherapy, a comparison with physiotherapy as a non-pharmacological treatment may be appropriate.

7. Clinical Trials

The submission presented three randomised trials comparing fampridine 10 mg twice daily (bd) with placebo in 638 patients with MS: Trials MS-F203, MS-F204 (pivotal trials) and MS-F202 (dose-finding study, supportive evidence). Meta-analyses of the results of these three trials were presented in the submission.

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
MS-F203 Goodman AF et al.	Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial.	*Lancet* (2009); 373: 732–38
MS-F204 Goodman AD et al.	A Phase 3 Trial of Extended Release Oral Dalfampridine in Multiple Sclerosis.	*Ann Neurol* 2010;68:494–502

Trial ID/ First author	Protocol title/ Publication title	Publication citation
MS-F202 Goodman AD et al.	Dose comparison trial of sustained-release fampridine in multiple sclerosis.	*Neurology* 2008;71:1134-41

Note: The MS-F202 trial included 3 fampridine dose groups (10, 15 and 20 mg twice daily). The submission presented efficacy data only for the 10 mg twice daily fampridine dose group as this dose is consistent with that recommended in the Australian Product Information.

8. Results of Trials

The primary outcome was any improvement in walking speed in at least three out of four measurements during the trial. Secondary outcomes were proportional improvement in walking speed, change from baseline in walking speed, in 12 item MS Walking scale, in Lower Extremity Manual Muscle Test (LEMMT), in Ashworth score and average Subject Global Impression (SGI) and Clinician Global Impression (CGI). Quality of Life measures were included from the supportive trial, MS-F202 via the MS Quality of Life Inventory (MSQLI).

The following table summarises the proportions of "consistent responders" in the trials.

Proportion of consistent responders (> 0% improvement for at least 3 of 4 on-treatment visits)

Trial ID	F	PBO	OR [95% CI]	RR [95% CI]	RD [95% CI]	NNT [95% CI]
	n/N (%)	n/N (%)				
MS-F202 *Post hoc*	18/51 (35.3)	4/47 (8.5)	**5.86** **[1.81, 18.98]**	**4.15** **[1.51, 11.37]**	**0.27** **[0.11, 0.42]**	**4** **[3, 9]**
MS-F203	78/224 (34.8)	6/72 (8.3)	**5.88** **[2.44, 14.17]**	**4.18** **[1.90, 9.18]**	**0.26** **[0.18, 0.35]**	**4** **[3, 6]**
MS-F204	51/119 (42.9)	11/118 (9.3)	**7.30** **[3.55, 14.97]**	**4.60** **[2.52, 8.37]**	**0.34** **[0.23, 0.44]**	**3** **[3, 5]**
Pooled results	148/394 (37.6)	21/237 (8.9)	**6.53** **[3.95, 10.80]**	**4.38** **[2.85, 6.75]**	**0.29** **[0.23, 0.35]**	**4** **[3, 5]**
Chi-square for heterogeneity			P=0.91	P=0.98	*P=0.56*	-
I^2 statistic			0%	0%	*0%*	-

NNT are calculated using a sampling method (sample size 1,000,000).
Abbreviations: CI, confidence interval; F, fampridine; NNT, number needed to treat; OR, odds ratio; PBO, placebo; RR, relative risk; RD, risk difference
Note: Bolded results are statistically significantly different between arms.

For the primary outcome of any improvement in walking speed 37.6% of patients responded compared to 8.9% of patients in the placebo arm. For the patient subgroup identified by the proposed PBS restriction (improvement in walking speed of 20% or more) 31.5% of patients in the treatment arm demonstrated a response. This compared with 13.1% of patients in the placebo arm who, under the proposed restriction would qualify for continuing access to fampridine. The PBAC noted the assertion in the sponsor's pre-PBAC response that it would be misleading to apply these response rates across the MS population to determine treatment effect, as this discounts the effect of the restriction in identifying patients who are most likely to respond to treatment.

The following table presents the proportion of responders (20% improvement in average walking speed).

Proportion of responders (≥20% improvement in average walking speed) across the double-blind treatment period

Trial ID	F	PBO	OR [95% CI]	RR [95% CI]	RD [95% CI]	NNT [95% CI]
	n/N (%)	n/N (%)				
MS-F202 Post hoc[a]	12/51 (23.5)	5/47 (10.6)	2.58 [0.83, 8.01]	2.21 [0.84, 5.81]	0.13 [-0.02, 0.27]	8 [-32, 57]
MS-F203 Post hoc	71/224 (31.7)	8/72 (11.1)	**3.71 [1.69, 8.16]**	**2.85 [1.44, 5.64]**	**0.21 [0.11, 0.30]**	**5 [4, 9]**
MS-F204 Post hoc	41/119 (34.5)	18/118 (15.3)	**2.92 [1.56, 5.47]**	**2.26 [1.38, 3.69]**	**0.19 [0.08, 0.30]**	**6 [4, 13]**
Pooled results	124/394 (31.5)	31/237 (13.1)	**3.10 [1.97, 4.86]**	**2.41 [1.67, 3.49]**	**0.19 [0.12, 0.25]**	**6 [4, 8]**
Chi-square for heterogeneity			P=0.84	P=0.84	P=0.77	-
I^2 statistic			0%	0%	0%	-

data in italics calculated during the evaluation. NNT are calculated using a sampling method (sample size 1,000,000).

Abbreviations: CI, confidence interval; F, fampridine; NNT, number needed to treat; OR, odds ratio; PBO, placebo; RR, relative risk; RD, risk difference

[a] Definition of responders in the CSR was ≥ 20% average improvement over 12 weeks of stable treatment. The data presented is based on a definition of ≥ 20% average improvement over 14 weeks of double-blind treatment.

Note: Bolded results are statistically significantly different between arms.

Post hoc analysis identified a patient group with improvement in walking speed of at least 20%. This translates to an improvement in the time to walk the 25-foot walk test of at least 16.7%. Treatment of this patient group was used to define the proposed restriction and to generate the base case ICER.

For the secondary outcomes, the 12 item MS walking scale (MSWS-12) had a defined Minimal Clinically Important Difference (MCID) of a change of 6.2 points or more. The trial results (-3.19, [-5.23, -1.15, p=0.002) were statistically significant but did not reach the MCID. Small, statistically significant improvements were measured in LEMMT (0.09, [0.04, 0.14] on a scale of 0.0 to 5.0), Ashworth scale (-0.09 [-.14, -.04] on a scale of 0 to 4) and CGI (-0.23 [-0.36, -0.11] on a 7 point scale) but these were not considered to be clinically relevant. No statistically significant improvements were observed in SGI (0.09 [-0.08, 0.25] on a 7 point scale). Quality of Life data were measured only in the supportive Phase II MS-F202 trial using the MS Quality of Life Inventory and no significant difference was found between treatment and placebo arms.

Overall, the PBAC considered that the absolute treatment effect was modest and subject to considerable uncertainty. The mean average double-blind walking speed in the pooled treatment arm (including non-responders) for the 25-foot test course was approximately 10.7 seconds, compared with a time for placebo patients (pooled results) of approximately 11.3 seconds (equating to an additional 2.3 metres over a distance of 40.5 metres walked in one minute). The clinical relevance of this treatment response was considered to be questionable.

The PBAC noted that more patients in the fampridine treated groups experienced at least one adverse event (AE) compared with patients on placebo. AEs identified included balance disturbances, dizziness, headache, paraesthesias, tremor, psychiatric disorders (e.g. insomnia, anxiety), urinary tract infection (UTI), asthenia, nausea, fatigue, back pain and MS relapse. The PBAC noted also a safety communication issued by the US Food and Drug

Administration (FDA) on 23 July 2012, and the requirement by the European Medicines Agency (EMA) for an ongoing post-market trial, both concerning the risk of seizures.

9. Clinical Claim

The submission described fampridine as superior in terms of comparative efficacy, but inferior in terms of comparative safety over placebo. The PBAC considered the claim with regard to relative safety was reasonable but that the claim with regard to comparative efficacy was not reasonable. The PBAC noted also that the absolute treatment effect of fampridine was of uncertain clinical relevance.

10. Economic Analysis

The submission presented a stepped economic evaluation, which included a cost utility analysis with an economic model based on the superiority claim over placebo for comparative benefit. The time horizon of the model was 5 years, with one month cycles with walking speed as the only baseline characteristic, extrapolated over time for all patients (responders, non-responders and placebo). Patients on treatment were assumed to receive eight weeks of treatment, with responding patients discontinuing with no retrial. Responding patients were assumed to have the same probability of discontinuing in each cycle. For responding patients the incremental benefit was assumed to be maintained over placebo but walking speed for all patients was assumed to decline over the course of the model.

A base case ICER in the range of $15,000 - $45,000 was presented in the submission and was most sensitive to the choice of utilities and that the application of an alternative relationship between walking speed and utility, using Cohen (2010) and AMSLS resulted in an ICER greater than $200,000.

The PBAC considered that there were numerous problems with the economic model. *For PBAC's view, see Recommendation and Reasons.*

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million in Year 5. The PBAC considered the true number of patients and costs to be highly uncertain.

12. Recommendation and Reasons

The submission proposed listing fampridine 10 mg modified release tablets on the PBS as an Authority Required benefit for symptomatic improvement of walking ability of an ambulatory patient with clinically definite multiple sclerosis on a cost-effectiveness basis with placebo.

The submission nominated placebo as the comparator. The PBAC accepted that placebo was an appropriate comparator but considered that as the sponsor's survey indicated that 84% of treating neurologists refer patients for physiotherapy, a comparison with physiotherapy as a non-pharmacological treatment may be appropriate.

The sponsor proposed a restriction specifying that patients would complete a timed 25-foot walk test (T25FW) at baseline and following eight weeks of treatment. At baseline, patients complete two tests, five minutes apart, in an average time between eight and 45 seconds. An

improvement in walking time of at least 20% following eight weeks of treatment would qualify a patient for continuing treatment.

The PBAC considered that the T25FW would be extremely difficult to implement in reliably differentiating responders and non-responders. The PBAC noted that the T25FW is not routinely performed in clinical practice. The PBAC noted the following issues with the use of the T25FW:

- The absolute magnitude of performance improvement is subject to the performance in the baseline test. A patient intentionally underperforming in the baseline test would be more easily able to demonstrate a 20% improvement to access ongoing treatment;
- Motor symptoms of MS can vary on a daily basis, with greater or lesser amounts of fatigue rendering the use of walking speed as a measure of improvement unreliable;
- Background MS treatment used in conjunction with fampridine may have separate beneficial effects on motor symptoms of MS, including walking speed, concealing the true extent of effect of fampridine;
- Patients would be permitted multiple attempts at the test if certain factors (e.g. greater than usual fatigue, side effects of other MS medications, recent acute illness and recent exacerbation) are considered to have affected their performance.
- The proposed grandfather restriction contained no definition of "improvement".

The PBAC noted the sponsor's assertion in the pre-PBAC response that allowance for multiple attempts is consistent with other measures such as blood glucose tests, however considered that this would contribute to existing uncertainty about the test. The PBAC noted that the proposed continuation rule was not directly related to any a priori trial outcome. The PBAC considered that results of the T25FW were likely to be highly variable, affected by many extraneous factors and not sufficiently objective to be reliable and overall that implementation of the proposed restriction would be highly problematic and would not reliably separate responding from non-responding patients.

The submission presented 3 randomised controlled trials of fampridine compared to placebo in a total of 638 patients. MS-F202 was a dose-finding trial and the pivotal trials were MS-F203 and MS-F204. The primary outcome was any improvement in walking speed in at least three out of four measurements during the trial. Secondary outcomes were proportional improvement in walking speed, change from baseline in walking speed, in 12 item MS Walking scale, in Lower Extremity Manual Muscle Test (LEMMT), in Ashworth score and average Subject Global Impression (SGI) and Clinician Global Impression (CGI). Quality of Life measures were included from the supportive trial, MS-F202 via the MS Quality of Life Inventory (MSQLI).

Post hoc analysis identified a patient group with improvement in walking speed of at least 20%. This translates to an improvement in the time to walk the 25-foot walk test of at least 16.7%. Treatment of this patient group was used to define the proposed restriction and to generate the base case ICER.

For the primary outcome of any improvement in walking speed 37.6% of patients responded compared to 8.9% of patients in the placebo arm. For the patient subgroup identified by the proposed PBS restriction (improvement in walking speed of 20% or more) 31.5% of patients in the treatment arm demonstrated a response. This compared with 13.1% of patients in the placebo arm who, under the proposed restriction would qualify for continuing access to

fampridine. The PBAC noted the assertion in the sponsor's pre-PBAC response that it would be misleading to apply these response rates across the MS population to determine treatment effect, as this discounts the effect of the restriction in identifying patients who are most likely to respond to treatment.

For the secondary outcomes, the 12 item MS walking scale (MSWS-12) had a defined Minimal Clinically Important different (MCID) of a change of 6.2 points or more. The trial results (-3.19, [-5.23, -1.15, p=0.002) were statistically significant but did not reach the MCID. Small, statistically significant improvements were measured in LEMMT (0.09, [0.04, 0.14] on a scale of 0.0 to 5.0), Ashworth scale (-0.09 [-.14, -.04] on a scale of 0 to 4) and CGI (-0.23 [-0.36, -0.11] on a 7 point scale) but these were not considered to be clinically relevant. No statistically significant improvements were observed in SGI (0.09 [-0.08, 0.25] on a 7 point scale). Quality of Life data were measured only in the supportive Phase II MS-F202 trial using the MS Quality of Life Inventory and no significant difference was found between treatment and placebo arms.

Overall, the PBAC considered that the absolute treatment effect was modest and subject to considerable uncertainty. The mean average double-blind walking speed in the pooled treatment arm (including non-responders) for the 25-foot test course was approximately 10.7 seconds, compared with a time for placebo patients (pooled results) of approximately 11.3 seconds (equating to an additional 2.3 metres over a distance of 40.5 metres walked in one minute). The clinical relevance of this treatment response was considered to be questionable.

The PBAC noted that more patients in the fampridine treated groups experienced at least one adverse event (AE) compared with patients on placebo. AEs identified included balance disturbances, dizziness, headache, paraesthesias, tremor, psychiatric disorders (e.g. insomnia, anxiety), urinary tract infection (UTI), asthenia, nausea, fatigue, back pain and MS relapse. The PBAC noted also a safety communication issued by the US Food and Drug Administration (FDA) on 23 July 2012, and the requirement by the European Medicines Agency (EMA) for an ongoing post-market trial, both concerning the risk of seizures.

The submission claimed that fampridine is superior to placebo for comparative efficacy and inferior to placebo for comparative safety. The PBAC considered the claim with regard to relative safety is reasonable but that the claim with regard to comparative efficacy was not reasonable. The PBAC noted also that the absolute treatment effect of fampridine was of uncertain clinical relevance.

The submission presented a stepped economic evaluation, which included a cost utility analysis with an economic model based on the superiority claim over placebo for comparative benefit. The time horizon of the model was 5 years, with one month cycles with walking speed as the only baseline characteristic, extrapolated over time for all patients (responders, non-responders and placebo). Patients on treatment were assumed to receive eight weeks of treatment, with responding patients discontinuing with no retrial. Responding patients were assumed to have the same probability of discontinuing in each cycle. For responding patients the incremental benefit was assumed to be maintained over placebo but walking speed for all patients was assumed to decline over the course of the model.

The PBAC considered that there were numerous problems with the economic model:

- Quality of life (QoL) data were not directly measured in the pivotal trials; therefore utilities were calculated by mapping walking speed to Expanded Disability Status Scale (EDSS) scores as a linear function. An approach similar to that used by Cohen (2010) is used to map T25FW to EDSS and EDSS to utilities but using different data sources (fampridine trial data and Australian observational data). Baseline fampridine trial data are used to map T25FW to EDSS. Data from the Australian MS Longitudinal Study (AMSLS) are used to map the self-reported Disease Steps scale to approximate equivalence with EDSS; EDSS to WHOQoL-100; and WHOQoL-100 to EQ-5D utilities. Based on this series of mapping calculations an increase in walking speed of 1 foot per second results in an improvement in utility of 0.18. The PBAC noted that EDSS is a categorical, not a linear, scale and that a patient may progress slowly through earlier EDSS categories and more quickly through higher levels of disability and therefore that that this type of mapping between the categorical ordinal EDSS score and continuous utility did not have a valid basis. The PBAC therefore considered it inappropriate to conclude that a patient's quality of life or EDSS category would change in direct proportion to change in walking speed.
- AMSLS results for WHOQoL-100 (which was mapped to EQ-5D) and self-report disease stage were not necessarily collected contemporaneously with one another.
- These results were used to generate three data points for EDSS1, EDSS4-6.5 and EDSS7-9, which were then used to estimate a linear relationship between EDSS score and utility, ultimately giving a linear relationship between walking speed and utility. The PBAC considered that the derivation of a linear relationship based on only three data points was inappropriate and could not be relied upon. Further, the resulting utility equations included values that were greater than 1 which is not valid for a utility weight. At each cycle of the model, economic costs were modelled to walking speed via EDSS based on data from the AMSLS. The approach is subject to the same flaws as for the mapping between walking speed and utility. In addition, the PBAC noted that the resource use items that were included in the mapping were inadequately justified, appeared to be ad hoc and that this approach missed important aspects of resource use relevant for fampridine including baseline assessments, response assessments and management of AEs (e.g. ECG, EEG, creatinine, etc).
- Rebates were included in the model for non-responding patients; however, given the difficulty in reliably identifying non-responding patients the PBAC did not consider that this cost offset was likely to be observed in practice.
- The model assumed that patients discontinue treatment upon reaching EDSS 7, however the PBAC noted that the modelling approach appeared to apply utility gains from improvement in walking speed to patients with an EDSS category that would mean they were unable to walk and require a wheelchair. The PBAC considered this inappropriate.
- The PBAC noted that despite the assumption of a linear relationship between walking speed and EDSS, and therefore between EDSS and healthcare costs, a patient with EDSS score 4 to 5 (able to walk 200-500m without aid or rest) attracted an annual resource cost of $2,791 while a patient with EDSS score 6 (requires a walking aid such as a cane or crutch to walk 100m, with or without resting) attracted an annual cost of $1,902. The calculation of a higher resource cost for a lower level of disability was considered contradictory to the fundamental assumptions of the model.
- The extension study results assumed that treatment benefits are maintained over the life of the model, with treated patients returning to baseline at 2 years and patients on placebo declining at the same rate.

- The median treatment duration was assumed to be 250 weeks and a constant probability was applied for discontinuation at each cycle.
- 100% of responding patients were assumed to persist with treatment, an assumption the PBAC considered unrealistic.
- The PBAC considered that the extrapolation of trial results of 9 and 14 weeks' duration out to the 5 year time horizon of the model was highly uncertain and potentially overestimated treatment benefits.

Overall, the PBAC considered that although walking speed is related to quality of life it does not serve as a proxy measure of quality of life, nor is there a linear relationship between the two factors. This contributed to difficulty in establishing a robust measurement of value for money in treatment with fampridine. The multiple steps in mapping walking speed to utilities, each step with its own inherent assumptions and uncertainty, significantly affected the reliability of the utility values. The PBAC noted that the base case ICER in the range of $15,000 - $45,000 was most sensitive to the choice of utilities and that the application of an alternative relationship between walking speed and utility, using Cohen (2010) and AMSLS resulted in an ICER greater than $200,000.

The estimated total net cost to the PBS was less than $10 million in Year 5, with a cumulative total in the range of $30 - $60 million over the first 5 years. When the proposed non-responder rebate is included, the estimated total net cost to the PBS was still less than $10 million in Year 4, with a cumulative total still in the range of $30 - $60 million over the first 5 years. The PBAC considered the true number of patients and costs to be highly uncertain.

Additionally a rebate was offered to cover the cost of treatment in patients who do not respond to fampridine. The sponsor suggested defining all initiating patients with less than two packs to be non-responders with the costs associated with these scripts to be refunded to the Commonwealth. The PBAC considered that, given the issues with reliably identifying non-responders via the proposed PBS restriction and the high rate of placebo response in the trial, it was highly likely that non-responding patients would remain on treatment. The PBAC therefore did not consider this proposal to be a viable means of limiting financial risk to the Commonwealth.

The PBAC therefore rejected the submission on the basis of unclear evidence of clinical benefit and that the economic analysis did not provide sufficient basis to conclude that treatment with fampridine is cost-effective. The PBAC considered that the proposed restriction would not adequately limit access to patients with a genuine response to treatment.

The PBAC acknowledged and noted the consumer comments on this item.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the

medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Biogen Idec believes improvements in mobility represent an important outcome for individuals with multiple sclerosis. Although disappointed with the PBAC's decision, Biogen Idec is committed to finding a path forward for the listing of fampridine on the Pharmaceutical Benefits Scheme for the improvement of walking ability in Australians with multiple sclerosis.