PUBLIC SUMMARY DOCUMENT

Product: FAMPRIDINE, tablet (modified release), 10 mg, Fampyra®
Sponsor: Biogen Idec Australia Pty Ltd
Date of PBAC Consideration: March 2014

1. Purpose of Application

The major resubmission sought an Authority Required listing for the treatment for the symptomatic improvement of walking ability of an ambulatory patient with clinically definite multiple sclerosis (MS) who meets certain criteria.

2. Background

This was the second submission for fampridine considered by the PBAC.

In November 2012, the PBAC rejected a major submission seeking an Authority Required listing for the symptomatic improvement of walking ability in adult patients with multiple sclerosis meeting certain criteria, on the basis of unclear evidence of clinical benefit and that the economic evaluation did not provide a 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 who truly respond to treatment.

3. Registration Status

Fampridine was TGA registered on 24 May 2011 and is indicated for the symptomatic improvement of walking ability in adult patients with multiple sclerosis (MS).

4. Listing Requested and PBAC's View

The submission sought the following listing:

Authority required
Initial treatment
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 have impaired walking ability as demonstrated by an EDSS score of 4 or more, but less than 7

AND

(c) The patient's MSWS-12 is recorded for baseline measurement

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

Authority required
Continued treatment
Continuing PBS subsidised treatment of a patient who has demonstrated improvement in their MSWS-12 score. An adequate response is defined as at least a 6 point improvement in the MSWS-12 during the 8 week initiation trial.

Authority required
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, who are no longer responding to fampridine, or who experience intolerable adverse events are no longer eligible for continued treatment.

Maximum Quantity: 56 tablets
Number of Repeats: 5

Listing was sought on a cost-utility basis with fampridine compared to placebo. Utility was measured in quality adjusted life years (QALYs) gained.

The PBAC noted that the proposed restriction had changed from the November 2012 submission. The requirement that the patient complete a timed 25-foot walk test (T25FW) had been replaced by use of the Expanded Disability Status Scale (EDSS) to demonstrate walking impairment as the requirement to qualify for trialling fampridine, as well as measurement using the 12-point Multiple Sclerosis Walking Scale (MSWS-12) to identify responders for continued treatment. The PBAC recalled that it considered that the T25FW would be extremely difficult to rely on for differentiating responders and non-responders and that the T25FW is not routinely used in clinical practice. The PBAC was not convinced that the use of these 2 new scales would significantly improve the reliability of the identification of responders and non-responders. The PBAC therefore considered that the restriction would not effectively confine access to treatment to a patient population in whom cost-effectiveness has been demonstrated. In one of the supporting trials using the MSWS-12, the PBAC noted that 50.8% of participants in the placebo group satisfied the 6-point improvement criteria, compared to 55.4-57.0% in the fampridine 5 mg and 10 mg groups respectively.

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 for symptomatic improvement of walking ability, in addition to current management of MS patients.

6. Comparator

The re-submission nominated placebo, as a proxy for best supportive care.

The PBAC recalled that it had previously accepted placebo as an appropriate comparator, but considered that a comparison with physiotherapy may be appropriate.

The re-submission claimed that fampridine is not expected to replace physiotherapy, thus placebo should remain the comparator.

The PBAC noted that the ESC agreed that placebo, as a proxy for best supportive care, was an appropriate comparator and that the ESC considered that fampridine would not replace physiotherapy.

7. Clinical Trials

The November 2012 submission presented three randomised trials comparing fampridine 10 mg twice daily with placebo in 638 patients: Trials MS-F202 (supportive dose-finding study); MS-F203 and MS-F204 (pivotal trials). The re-submission stated that the pivotal trials presented in the November 2012 submission still form the key evidence to demonstrate the benefit of fampridine in improving walking ability. Details of these trials have been previously reported in the November 2012 Public Summary Document.

Trial DER-401 was new to the re-submission and was described as a supportive trial. 'Top-line' (i.e. preliminary) results were available during the November 2012 PBAC meeting.

Trial DER-401 is a US multi-centre, placebo-controlled, parallel-group trial with a 4-week double-blind period to investigate the safety and efficacy of a lower fampridine dose. A total of 430 patients were randomised to receive placebo, fampridine 5 mg twice daily or fampridine 10 mg twice daily.

The economic evaluation in the re-submission did not rely on the included trials – instead, an open-label observational study (ENABLE) was relied upon to inform the economic comparison. The ENABLE study was new to this re-submission. Data from this study and other sources were used in the pre-modelling studies to address issues of applicability (applicability of the patient population and the likely extent of continuation in clinical practice), transformation (utility values and health care costs for responders and non-responders) and extrapolation (48 weeks of follow-up).

The ENABLE study is an international (Europe and Australia), multi-centre, open-label study to evaluate the impact of long-term fampridine treatment on quality of life. The study had a four week run-in period to identify responders, and an observational period between 44 and 46 weeks. Response was defined as any improvement from baseline in timed 25-foot walk test (T25FW) at Week 2 and Week 4, and, improvement in the 12-point multiple sclerosis walking scale (MSWS-12) score at Week 4 - this was different to the proposed PBS-restriction, which now omitted the use of a T25FW. Responders continued therapy, whereas non-responders were given the option to continue completing quarterly measurements (control arm). A total of 901 subjects enrolled in the study.

The PBAC noted that a limited evaluation of the clinical study report from the ENABLE trial (made available with the Pre-Sub-Committee Response, p.2) was carried out and presented in the Pharmaceutical Evaluation Section Addendum to this item. The PBAC noted that analyses presented in the submission were consistent with the clinical study report.

A table summarising the published trials new to the re-submission is shown below.

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Supportive trial		
DER-401 Thrower	Safety and Efficacy of 5 mg and 10 mg Dalfampridine Extended Release Tablets in Patients with Multiple Sclerosis: First Results from a Double-Blind, Placebo-Controlled Trial.	*Neurology* 2013; 80(Meeting abstracts 1): P04.096.
Open-label observational study		
ENABLE Pozzilli	Health-Related Quality of Life Outcomes Following Long-Term Treatment With Prolonged-Release Fampridine: Impact on Psychological Outcomes in the ENABLE Study.	October 2013. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis [various posters].
Sorensen	Changes in Physical Functioning and Activity Following Long-Term Treatment With Prolonged-Release Fampridine in the ENABLE Study.	
Macdonell	Long-Term Prolonged-Release Fampridine Treatment and Health-Related Quality of Life Outcomes: 12-Month Analysis of the ENABLE Study.	

The PBAC noted and welcomed the input from individuals (115), health care professionals (6) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with fampridine including:

- Quality of life benefits;
- Improvement in function through increased mobility, balance, improved gait and strength, increased walking speed;
- Reduced need for external support;
- Improved equity in access;
- Improved cognitive and visual performance; and
- Reduction in fatigue and risk of falls.

The PBAC noted the support for listing from MS Australia, MS Australia (ACT/NSW/VIC branch), the Australian and New Zealand Association of Neurologists, and, Multiple Sclerosis Research Australia.

The sponsor requested a hearing for this item. The clinician presented clinical case studies including a video of a patient undertaking a walking speed test, discussed the natural history of MS related disability progression, how the benefits of the drug would translate into real improvements in quality of life, the percentage of patients likely to respond to treatment, the other benefits of treatment including an increase in leg strength and possible improvements in cognitive function, fatigue symptoms and vision. When asked about the durability of a response to fampridine, his opinion was that the drug will not stop progression and that the benefits will eventually wear-off after approximately 5 years.

The PBAC considered that the information presented at the hearing did not substantially influence the conclusions that could be drawn from the information already presented in the submission and evaluation.

8. Results of Trials

Results of MS-F202, MS-F203 and MS-F204 have been previously reported in the November 2012 Public Summary Document.

The primary outcome of the new supportive trial, DER-401, was the change from baseline in walking speed (T25FW) at the end of the 4 week double-blind trial. There were no statistically significant differences between the fampridine 10 mg twice daily and placebo groups. Trial DER-401 included a modified six-minute walk test (6MWT) in a subset of patients from selected centres. The change from baseline in the 6MWT distance was statistically significantly greater for the fampridine 10 mg twice daily arm compared to the placebo arm (difference 87.1 feet; 95% CI 18.2, 156.1).

Placebo-treated patients in Trial DER-401 on average had improvements in MSWS-12 exceeding the nominated threshold of 6-points to qualify for continuing PBS fampridine (i.e. mean improvement (reduction) of 9.48 at Visit 2 and 8.35 at Visit 3). The PBAC noted that 50.8% of participants in the placebo group satisfied the 6-point improvement criteria, compared to 55.4-57.0% in the fampridine groups. This raised concerns about whether the proposed PBS continuation criterion would identify genuine responders. The PBAC considered that it would have been helpful to examine the proportion of participants with 6-point MSWS-12 improvement in various treatment groups, from the other three trials.

In the ENABLE study, there were statistically significant improvements in the SF-36 physical component scale scores from baseline at Weeks 12, 24, 36 and 48 (shown in the table below) among responders receiving fampridine. However, the final analysis of the primary outcome did not appear to be presented in the available poster presentations.

Change from baseline in the physical component scale of the SF-36

	SF-36 physical component scale summary scores				
	Treated fampridine responders (N=704)		Not treated non-responders (N=129)		p-value
	N		n		
Mean baseline (SD)	700	36.0 (7.6)	127	36.5 (6.9)	
Mean change (95% CI)					
Week 12	664	4.32 (3.84, 4.79)	82	-0.72 (-2.21, 0.77)	<0.0001
Week 24	629	3.76 (3.24, 4.28)	70	-0.43 (-1.79, 0.93)	<0.0001
Week 36	608	3.49 (2.98, 4.00)	60	-1.81 (-3.34, -0.29)	<0.0001
Week 48	575	3.29 (2.77, 3.82)	49	-1.14 (-2.81, 0.54)	<0.0001

The EQ-5D-3L index scores from the ENABLE study informed the economic model and are shown in the table below.

Change from baseline in EQ-5D-3L index scores (ENABLE study)

	EQ-5D-3L index scores				
	Treated fampridine responders (N=704)		Not treated non-responders (N=129)		p-value
	N		n		
Mean baseline (SD)	693	0.6 (0.22)	127	0.6 (0.24)	
Mean change (95% CI)					
Week 12	652	0.06 (0.05, 0.08)	78	0.02 (-0.04, 0.07)	0.002
Week 24	624	0.05 (0.03, 0.07)	69	0.01 (-0.05, 0.08)	0.063
Week 36	598	0.03 (0.02, 0.05)	58	0.01 (-0.06, 0.07)	0.1004
Week 48	568	0.04 (0.02, 0.06)	47	0.00 (-0.08, 0.08)	0.1448

The PBAC recalled that in the November 2012 submission, the PBAC considered that the absolute treatment effect with fampridine was modest and there was considerable doubt about whether it could be reliably replicated in practice. In addition the clinical relevance of the treatment response was considered questionable. Considering the clinical evidence presented in the current re-submission, the PBAC still considered that there is insufficient evidence of a clinically relevant absolute treatment effect with fampridine, noting that patient relevant outcomes, such as the effect on fatigue and cognitive function were not assessed directly in any of the studies. The PBAC noted that none of the responder analyses presented in the re-submission were consistent with the requested PBS continuation criterion.

In Trial DER-401, 50.8% of participants in the placebo group satisfied the 6-point improvement criteria of the MSWS-12, compared to approximately 57.0% in the fampridine groups. The PBAC considered that the high response rate in the placebo group made it difficult to determine the true benefit of fampridine over placebo.

The PBAC agreed with the ESC advice that comparisons in the ENABLE study are likely to be biased in favour of fampridine as treatment arms were selected based on response to therapy. The PBAC considered that a comparison based on a single arm open label observational study was inadequate for decision making. The PBAC noted that Pre-Sub-Committee Response justified the use of the ENABLE comparison as "real world". The PBAC noted that the results for the ENABLE study were based on preliminary data from posters, with insufficient information provided to fully evaluate the study.

The PBAC noted that fampridine's marketing approval in Europe was conditional upon the sponsor undertaking to perform an ongoing study of the benefits of fampridine apart from walking speed. It was the PBAC's understanding that the sponsor is to provide to the European Medicines Agency by the 30 June 2016, the results of a double-blinded, placebo controlled, long-term efficacy and safety study to investigate a broader primary endpoint that is clinically meaningful in terms of walking ability and to further evaluate the identification of responders in order to guide further treatment based on a CHMP (Committee for Medicinal Products for Human use) agreed protocol. An update of the progress in completing the obligation should be provided every 6 months.

The PBAC considered that such a directive was consistent with its view that the current trial evidence lacks clinically meaningful outcome measures. Such a study is likely to be highly informative in any assessment of cost-effectiveness.

No new safety signals were identified in Trial DER-401 and the interim analysis of the ENABLE study. Newly identified signals in the Periodic Safety Update Report were trigeminal neuralgia (ongoing) and hepatitis acute (follow-up on case report). There were no reports of seizures with fampridine 10 mg twice daily in the randomised trials, but there were reports of seizures in the ENABLE study (0.8% discontinued due to seizures, analysis dated 19 September 2013).

A summary of the comparative benefits and harms for fampridine versus placebo is presented in the table below.

Benefit/harm summary

Outcome	№ studies (№ pts)	RR (95%CI)	Event/100 patients		Increment
			Fampridine	Placebo	
Benefits					
Post-hoc proportion of responders (≥ 20% improvement in average walking speed; T25FW)					
Meta-analysis (Nov 12) 9-14 weeks	3 (631 pts)	2.41 (1.67, 3.49)	31.5	13.1	18.4
DER-401 (new) 4 weeks	1 (272 pts)	1.62 (1.16, 2.26)	44.1	27.2	16.9
Proportion of ENABLE responders (any improvement in T25FW at Week 2 and 4; AND any improvement in MSWS-12 at Week 4)					
ENABLE (new) Assessed at weeks 2 & 4	1 (833 pts)	NA	84.5	0 (Assumption)	NA
Proportion of responders (≥ 6 points improvement in MSWS-12) – unclear if pre-specified					
DER-401 (new) At week 4	1 (260 pts)	NE	57.0	50.8	-
Harms[a]					
Urinary tract infections					
Pooled Nov 2012	3 (638 pts)	NE	14.5	9.2	NE
DER-401 (new)	1 (285 pts)	NE	9.9	5.6	NE
Insomnia					
Pooled Nov 2012	3 (638 pts)	NE	9.3	3.8	NE
DER-401 (new)	1 (285 pts)	NE	7.7	4.2	NE
Asthenia					
Pooled Nov 2012	3 (638 pts)	NE	8.3	4.2	NE
DER-401 (new)	1 (285 pts)	NE	0.7	1.4	NE

Source: Compiled during the evaluation
Abbreviations: BD, twice daily; MSWS-12, 12-point multiple sclerosis walking scale; NA, not applicable; NE, not estimated; RR, relative risk; T25FW, timed 25-foot walk test
[a] 3 most frequent treatment-emergent AEs from pooled fampridine 10 mg BD data (≥ 1% difference vs. placebo; MS-F202, MS-F203 & MS-F204). Only fampridine 10 mg BD included.

The PBAC noted that based on these trials, for every 100 patients treated with fampridine compared to placebo:

- Approximately 18 more patients would achieve a 20% improvement in average walking speed as measured by the T25FW test;
- Approximately 5 more patients would suffer from a urinary tract infection;
- Approximately 6 more patients would suffer from insomnia; and
- Approximately 4 more patients would suffer from asthenia (lack of strength/feeling of muscle weakness).

9. Clinical Claim

The re-submission described fampridine as superior in terms of comparative effectiveness and inferior in terms of comparative safety compared to placebo.

The PBAC considered that the claim of inferior comparative safety was reasonable. With respect to comparative effectiveness, the PBAC considered the absolute treatment effect with fampridine is modest, and there is considerable doubt over whether it will be seen in practice.

10. Economic Analysis

Compared to the November 2012 submission, the key change in the current model was the use of the ENABLE study to inform inputs. The model no longer transformed walking speed to utilities via multiple steps, but maintained the transformation of walking speed to generate cost-offsets.

With respect to the submission's approach to calculating healthcare cost-offsets, the same approach as November 2012 was undertaken with indirect mapping of walking speed to healthcare costs, using EDSS as a "bridge". The re-submission did not adequately address the PBAC's concerns about this approach. The PBAC agreed with the ESC that the mapping approach to estimate of cost-offsets was not appropriate. The PBAC further noted that the pre-sub-committee response agreed that *'the methodology of bridging resource utilisation and costs via EDSS is not perfect. However, it is an approach based on a reasonable, evidence-based premise'*.

The PBAC noted that the model relied on a comparison of treated responders with untreated non-responders from the ENABLE study as a proxy for placebo. The ESC advised that this would likely have favoured fampridine and that the relevant comparison would be between a fampridine-treated population (responders and discontinuers/non-responders) and the same population without fampridine. The approach in the model assumed all differences between responders and non-responders were due to fampridine. Given the significant placebo-effect noted in the DER-401 trial, the PBAC did not consider this to be reasonable (i.e. a 0% placebo response rate versus 84% response rate with fampridine).

The submission claimed that the proposed PBS restriction is more restrictive than ENABLE trial criteria and therefore the trial overestimated responders and under-estimated treatment effect. The ESC advised that there were no data to support this claim. It was noted that the responder rate applied from ENABLE was much higher than in the previous submission (84.5% versus 33%). The re-submission claimed that the high responder rate from the ENABLE study was "supported" by the results of Trial DER-401. The PBAC considered that such a claim is largely inconsistent with the results of Trial DER-401, given that the proportion of patients with at least a 20% improvement in average walking speed was 44.1% for fampridine 10 mg twice daily versus 27.2% for placebo. The PBAC agreed with the ESC advice that the key issue was the variability in the evidence in terms of defining 'responders', which made it difficult to quantify the benefit and estimate the number of patients who would benefit from treatment.

The submission calculated an incremental cost per QALY gained in the range of $15,000 - $45,000.

The inclusion of non-drug cost offsets increased the cost of the fampridine arm and in the placebo arm. Without including the non-drug cost offsets, the ICER was in the range of $45,000 - $75,000/QALY. The PBAC considered that the model was most sensitive to the estimate of utility gains, the durability of treatment effect, and the price of fampridine. Overall, for the reasons outlined above, the PBAC did not consider the submission's estimate of the incremental cost per QALY gained to be reliable and that at the price proposed, the ICER is likely to be unacceptably high.

11. Estimated PBS Usage and Financial Implications

This re-submission was not considered by DUSC.

The likely number of patients per year was estimated in the submission to be less than 5,000 in Year 5, at an estimated net cost per year to the Government of between $10 million and $20 million in Year 5.

The PBAC considered the submission's estimates may not be realised in practice for the following reasons:

- The assumed proportion of responders (84.5% versus 33% in the November 2012 submission) was derived from the ENABLE study data. The PBAC noted that there were differences in the definition of a responder between the current and November 2012 submissions, in addition to differences in the data source for the proportions as well as differences in the definition of an ENABLE responder and a PBS responder.
- Persistence rates with fampridine treatment is variable depending on the data source used to estimate such rates. Data from open-label extensions of the MS-F202, MS-F203 and MS-F204 trials were used in the re-submission. A different approach compared to that taken in November 2012 was undertaken to apply the data from the extension studies, resulting in different persistence rates between submissions. The approach also differed from the economic evaluation, where a probability of discontinuation was calculated from ENABLE study data.
- The number of fampridine packs dispensed per year for a responder was determined from the ENABLE study. The duration of treatment exposure over 48 weeks was 308.1 days (equivalent to 11 packs). Given that the duration of the study was 48 weeks and not 52 weeks, the direct use of the data was considered inappropriate.

The PBAC noted the sponsor's request for a special pricing arrangement to apply and indication that it was also willing to consider an appropriate risk sharing arrangement. No details of such an arrangement were proposed or provided.

12. PBAC Outcome

The PBAC rejected the submission on the basis of inadequate evidence of comparative effectiveness based on clinically meaningful outcome measures. Therefore the cost-effectiveness of fampridine compared to placebo had not been established.

The PBAC considered that there is insufficient evidence of a clinically relevant absolute treatment effect with fampridine, noting that patient relevant outcomes, such as the effect on fatigue and cognitive function are not assessed directly in any of the studies.

The PBAC noted the substantial number of consumer comments expressing the quality of life benefits of fampridine for MS patients. The PBAC acknowledged the views of consumers on the perceived benefits of fampridine, but agreed that these benefits were not evident in the data presented in the submission. The PBAC noted from the consumer input that patients were reporting what they considered to be a significant response to treatment (including improved mobility and functioning, less fatigue, greater endurance). However the PBAC considered that it was difficult to use this as a basis for defining a patient responder population for the purposes of the PBS restriction.

The PBAC considered that the claim of inferior comparative safety was reasonable and noted the increase in potential adverse effects from fampridine compared to placebo.

The PBAC did not consider the submission's estimate of the incremental cost per QALY gained to be reliable and that at the price proposed, the true ICER is likely to be unacceptably high.

The PBAC noted that the submission meets the criteria for an independent review.

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 is disappointed with the rejection made by the PBAC, and is concerned that people living with multiple sclerosis who experience mobility dysfunction will not be able to receive FAMPYRA under the Pharmaceutical Benefits Scheme (PBS). We believe we made a strong case for FAMPYRA to be listed on the PBS including a price that would make FAMPYRA cost effective for the Government. We incorporated the feedback from the PBAC from our prior submission, and we utilised all the clinical data available to us to make our submission. We are currently evaluating options for FAMPYRA given the feedback we have received from the PBAC.