EVALUATION SUMMARY

Fampridine

for symptomatic improvement of walking ability in adult patients with Multiple Sclerosis

South Australian Medicines Evaluation Panel

Government of South Australia
SA Health

Summary of SAMEP review

Receipt of High Cost Medicine (HCM) formulary application:	22th March 2012
Date of SAMEP meeting:	9th May 2012

Name of medicine	**Fampridine (Tradename: Fampyra®)**
Dosage form	Modified release tablets
Requested Statewide HCM Formulary Listing	Symptomatic improvement of walking ability in adult patients with multiple sclerosis (MS), able to complete two trials of the timed 25 foot walk (T25FW)[1]
Cost	The cost of the usual dose (10mg twice daily) per patient per year for this indication is $7008. (Refer to appendix 1 for the predicted usage in the state).

SAMEP recommendations

Following the review of the current available evidence (appendix 2) and consideration of formal feedback from neurology department heads / neurologists with an interest in this area, SAMEP recommend rejecting the application to list fampridine on the Statewide High Cost Medicines formulary for the following reasons:

- From the two published phase III randomised controlled trials, there is no overall benefit by intention to treat in total trial population. Of the approximate one-third of trial participants who were labelled “responders”, the mean benefit was a 25% increase in walking speed which correlated to an approximate gain of 2 seconds over the 25 feet distance. The clinical relevance of this is unclear. (A “responder” was defined as a patient who had a higher speed in 3 out of 4 tests on the intervention compared to maximum speed pre-intervention).
- The long-term safety of treatment with fampridine is unknown. SAMEP noted that fampridine, also known as 4-aminopyridine, is a potential carcinogen in animals. Members also noted that it is marketed elsewhere as a pesticide for birds. As there is no long-term safety data for the use of fampridine in humans, and the proposed clinical pathway (appendix 3) had no proposed end timeframe for “responders”, SAMEP felt the safety of long term treatment was questionable.

[1] T25FW is Timed 25 Foot Walk Test, the novel endpoint used in two RCTs, and is a quantitative measure of leg function whereby the patient is instructed to walk 25 feet as quickly as possible whilst remaining safe. (25 feet = 7.6 metres).

- While SAMEP agree that both the phase III trials are robust and well-designed, it remains unclear whether the effect and the outcome measure, although statistically significant, is clinically relevant. The trials were performed predominantly in patients with mild disability. Members noted that no Quality of Life measurements were linked to the two phase III trials, which was considered unusual for a treatment for MS. Other reasons for walking impediments were not documented or addressed in the trials, such as spasticity, balance or sight. It was also noted that the trials excluded patients who had experienced a relapse of their MS in the prior 60 days.
- The duration of benefit in "responders" is not known because of the short duration of the phase III trials (9 and 14 weeks). The proposed clinical pathway has no schedule to test on going efficacy by interrupting therapy periodically.
- The walk test used in the trials, although an objective measurement, may be subject to performance bias and training effects. As it is not measured in routine care of MS in SA, both the initial and subsequent walk tests may be influenced by the patient and clinician's expectations.
- Monitoring of renal impairment would be required, as fampridine is contraindicated in mild, moderate and severe renal impairment (Creatinine clearance < 80mL/min). In addition, members noted that in one of the phase III clinical trials, there was a significantly higher incidence of urinary tract infections in patients on fampridine compared to placebo (17.5% vs 8.4%), which would have significant implications in MS.
- From the consumer perspective, while SAMEP are mindful of the plight of MS sufferers, there was concern that fampridine may give patients false hope of effective treatment.
- Cost-effectiveness: The drug (fampridine) is not cost-effective for the proposed use, even with very generous assumptions about the effect size and the value of this effect (cost per QALY>$100,000). The panel felt that there may be more cost-effective ways to improve health and wellbeing of these patients. In summary, the effect size is small, and not immediately clinically relevant, therefore cost-effectiveness is likely to be unfavourable.

Appendix 1 Current usage and cost to the State

To date, fampridine has not been dispensed in any South Australian public hospital.

Cost of medicine per treatment course

$9.60 per 10mg tablet. At recommended dose of 10mg twice daily, annual cost per patient would be $7,008.00.

Projected cost per year to SA Health for proposed indication

Costs to the SA Government include the cost of inpatient treatment and the cost of out-patient treatment not covered by the Pharmaceutical Benefits Schedule (PBS). Although the intended population is likely to predominantly outpatients, because fampridine is currently not listed on the PBS, any use of the medicine in public hospitals is a potential cost to SA Health.

35-40% of MS patients with a T25FW of 8-45 seconds at baseline, are likely to “respond” to treatment with fampridine. The exact number of MS patients in South Australia is unknown. The Multiple Sclerosis Society of South Australia and the Northern Territory has approximately 2000 South Australian MS patients registered with them but they estimate 1-2% of patients do not register with them.

The applicant has not provided an estimate of the proportion of MS patients who would have an ambulatory deficit sufficient to meet the criteria for treatment with fampridine, although the applicant expected that at Flinders Medical Centre (FMC) there would be approximately 10 patients per year who would qualify for treatment.

Cost-effectiveness

SAMEP considered that fampridine is not cost-effective for the proposed use, even with very generous assumptions about the effect size and the value of this effect.

If the effect is estimated at 2-6 seconds (that is, it takes 2-6 seconds less to walk 25 feet when on the medication as opposed to no treatment) and a patient walks the 25 foot distance 100 times in a day, this equates to a time saving of between 3.3 – 10 minutes. The additional time saved is quite small even with generous assumptions of effect. If a generous estimation of QALY (Quality-adjusted life year) gained is assumed to be between 0.05-0.07 (which does not take into account the increased risk of adverse events), the incremental cost-effectiveness ratio (ICER) is estimated to be between $100,000 and $140,000.

Appendix 2 Review of the evidence

Comparator: No treatment

Evaluation by other jurisdictions:

Pharmaceutical Benefits Advisory Committee (PBAC)	Fampridine has not been evaluated by PBAC
Canadian Agency for Drugs and Technologies in Health (CADTH)	Fampridine has not been evaluated by CADTH
Scottish Medicines Consortium (SMC)	Fampridine has not been evaluated by SMC
National Institute for Health and Clinical Excellence (NICE)	Fampridine has not been evaluated by NICE
NHS - Regional Drug and Therapeutics Centre (Newcastle, UK)	'The use of fampridine for the improvement of walking ability in multiple sclerosis' (Sept 2011)

Summary of efficacy data

Evidence base: A (NHMRC rating guide – see under references)
Consistency: A
Clinical impact: D
Generalisability: B-C
Applicability: B

Randomised controlled trials

Two phase III randomised controlled trials (RCTs) with fampridine for this indication have been published: one was 9 weeks duration (Goodman, Brown et al. 2010) and one was 14 weeks in duration (Goodman, Brown et al. 2009). Both of these trials were randomised, double-blind, placebo-controlled trials investigating the efficacy and safety of fampridine 10mg twice daily (12-hourly) in adult patients with Multiple Sclerosis with walking impairment.

Both the above trials were industry-sponsored and were identical in design except for the duration of follow-up.

	(Goodman, Brown et al. 2010)	(Goodman, Brown et al. 2009)
Funding of study	Acorda Therapeutics Inc	Acorda Therapeutics Inc
Design	Double-blind placebo-controlled RCT	Double-blind placebo-controlled RCT
Duration of treatment	9 weeks	14 weeks
Patient population	Adults (18-70yrs) Clinically defined MS T25FW (average of 2) = 8-45 seconds Exclusions: Prior treatment with fampridine MS exacerbation within 60 days History of seizures Epileptiform activity on EEG	Adults (18-70yrs) Clinically defined MS T25FW (average of 2) = 8-45 seconds Exclusions: Prior treatment with fampridine MS exacerbation within 60 days History of seizures Epileptiform activity on EEG
Intervention	Fampridine 10mg orally twice daily	Fampridine 10mg orally twice daily
No. of patients on intervention	120	229

Comparator	Placebo		Placebo	
No. of patients on comparator	119		72	
Primary efficacy outcome(s)	Timed 25 Foot Walk Test (T25FW) 12-Item MS Walking Scale (MSWS-12)		T25FW MSWS-12	
Primary efficacy variable(s)	Responder Status[2]		Responder Status	
Secondary outcome(s)	Lower Extremity Manual Muscle Test (LEMMT)		LEMMT Ashworth Spasticity Score[3]	
Blinding of patients	Yes		Yes	
Blinding of outcome assessors	Yes		Yes	
Allocation concealment	Yes		Yes	
Withdrawals from intervention arm of study	1 (not induced efficacy outcomes). All patients included in safety outcomes		5	
Withdrawals from placebo arm of study	1 (not induced efficacy outcomes). All patients included in safety outcomes		0	
Efficacy Variable Outcomes	Responders(R):Non-Responders(NR) Fampridine = 51:68 (42.9%), Placebo = 11:107 (9.3%)		Responders(R):Non-Responders(NR) Fampridine = 78:146 (35%), Placebo = 6:66 (8%)	
Outcomes	Δ T25FW (post-treat): Placebo = 0.11 ft/sec Fampridine = 0.22 ft/sec P = 0.04		Δ T25FW (post-treat): Placebo = 0.05 ft/sec Fampridine = 0.21 ft/sec P = 0.03	
	% change T25FW (ft/sec) post-treat: Placebo = 7.7 (95%CI = 4.4-11.0) Fampridine R = 24.7 (95%CI = 21.0-28.4) Fampridine NR = 6.0 (95%CI = 2.2-9.7)		% change T25FW (ft/sec) post-treat: Placebo = 4.7 (95%CI = 1.0-8.4) Fampridine R = 25.2 (95%CI =24.5-28.8) Fampridine NR = 7.5 (95%CI = 5.0-10.0)	
	Δ MSWS-12(post-treat): Placebo: 0.83 Fampridine: -2.59 P value = 0.036		Δ MSWS-12(post-treat): Placebo: 5.05 Fampridine: -0.04 P value = 0.060	
Adverse Events	**Placebo n=119**	**Fampridine n=120**	**Placebo n=72**	**Fampridine n=228**
Fall	20 (16.8%)	14 (11.7%)	11(15%)	36 (16%)
UTI	10 (8.4%)	21 (17.5%)	10 (14%)	31 (14%)
Dizziness	1 (0.8%)	10 (8.3%)	4 (6%)	19 (8%)
Insomnia	2 (1.7%)	12 (10.0%)	3 (4%)	14 (6%)
Fatigue	2 (3%)	14 (6%)	-	-
Nausea	1 (0.8%)	10 (8.3%)	3 (4%)	14 (6%)
Asthenia	5 (4.2%)	10 (8.3%)	4 (6%)	13 (6%)
Back pain	3 (2.5%)	7 (5.8%)	0	13 (6%)
Balance Disorder	2 (1.7%)	7 (5.8%)	2(3%)	13 (6%)
Headache	1 (0.8%)	11 (9.2%)	4 (6%)	13 (6%)

2 Responder = patient with faster T25FW for ≥3/4 visits whilst on treatment, compared to the max T25FW for any off drug visits (including screening & follow-up).

[3] Ashworth Spasticity Score is a qualitative score for measurement of spasticity, measured on a scale of 0-4, where 0= No increase in muscle tone and 4 = Limb rigid in flexion and extension.

Clinical Trials in progress

The following trials are currently in progress:

- An Open-Label, Multicenter, Multinational Study to Assess the Effect of Long-Term Prolonged-Release Fampridine (BIIB041) 10 mg Twice Daily on Quality of Life as Reported by Subjects With Multiple Sclerosis
    a. Phase IV study
    b. Primary outcome measure: Physical component scale of the SF36 health questionnaire in treatment responders [Time Frame: Change is measured over months 3,6,9 and 12]
    c. Estimated Primary Completion Date: September 2013
- Open-Label Extension Study to Evaluate the Safety and Tolerability of Oral Fampridine SR in Canadian Subjects With Multiple Sclerosis Who Participated in Acorda Extension Trials
    a. Phase III study
    b. Primary outcome measures: Adverse events (AEs) and serious adverse events (SAEs) as well as changes in vital signs and clinical laboratory assessments
    c. Estimated Primary Completion Date: March 2013 (Final data collection date for primary outcome measure)
- Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of Two Doses of Oral Dalfampridine Extended Release Tablets (5 mg and 10 mg Twice Daily) in Patients With Multiple Sclerosis
    a. Phase III study
    b. Primary outcome measure: To evaluate the efficacy of two doses of Dalfampridine-ER (5 and 10 mg) twice daily, using the Timed 25 Foot Walk (T25FW). [Time Frame: 18 months]
    c. Estimated Primary Completion Date: October 2012 (Final data collection date for primary outcome measure)

Summary of Efficacy Data

Two phase III randomised clinical trials (RCTs) have been published (Goodman *et al* 2009 and Goodman *et al* 2010).

The primary outcome measure was the Timed 25 Foot Walk Test (T25FW). Although patients who were classified as "*Responders*" showed an approximate increase of walking speed of 25%, this was an absolute increase of 2.3 seconds. That is, patients took on average 9.6 seconds to walk 7.6 metres compared to 11.9 seconds at baseline. The clinical relevance of this improvement in walking speed is unclear, as an increase in speed does not necessarily correlate to an improvement in walking ability or endurance, which is considered to be of greater importance to MS patients.

An outcome measure used in both RCTs to validate the clinical significance of the T25FW was the 12-tiem MS walking scale (MSWS-12), a rating scale that captures patients' perceptions on the effect that their walking problems are having on their daily lives. There was a significant improvement in the MSWS-12 in fampridine "*Responders*" compared to placebo in the Goodman *et al* 2010 study, and a non-statistically significant trend in favour of fampridine in the Goodman *et al* 2009 study. In both studies there were significant MSWS-12 changes from baseline in fampridine "*Responders*" compared to "*Non-Responders*", which serves to validate the clinical meaningfulness of the 25% change in the T25FW. It must, however be noted that the MSWS-12 is a subjective measure and so the reliability cannot be entirely certain. In addition, both the T25FW and MSWS-12 measure walking ability and do not provide an indication of the overall clinical benefits.

Although secondary outcome measures in both RCTs (LEMMT and Ashworth Score for Spasticity), were found to be in favour of fampridine, these improvements were not significant.

Summary of Safety Data

Immediate release preparations of fampridine have been associated with an increased risk of seizure. Fampridine was generally well tolerated in the phase III clinical trials but with significantly higher rate of some adverse effects in the treatment group, including balance disorders and dizziness. It is difficult to assess potential harm with regard to seizures as the necessity for screening with EEG has not been proposed in the clinical pathway.

Fampridine is contraindicated in moderate to severe renal impairment (creatinine clearance <50 ml/min) and was an exclusion criterion in both RCTs. SAMEP were unclear why the FDA and the TGA both recommend 50ml/min as the minimum renal function required for therapy with fampridine, whereas Health Canada specify 80ml/min as the minimum renal function required. This was not clarified by the applicant.

The long-term safety of treatment with fampridine is unknown. SAMEP noted that fampridine, also known as 4-aminopyridine, is a potential carcinogen in animals. Members also noted that it is marketed elsewhere as a pesticide for birds (United States Environmental Protection Agency, 2006). As there is no long-term safety data for the use of fampridine in humans, and the proposed clinical pathway had no proposed end timeframe for “responders”, SAMEP felt the safety of long term treatment was questionable.

Cost-effectiveness

From clinical trial data, the effect size of fampridine is small, and not immediately clinically relevant, therefore the cost-effectiveness is likely to be unfavourable. Even with very generous assumptions about the effect size and the value of this effect, the cost per QALY is likely to exceed $100,000. The panel felt that there may be more cost-effective ways to improve health and wellbeing of these patients.

References

Goodman, A. D., T. R. Brown, et al. (2010). "A phase 3 trial of extended release oral dalfampridine in multiple sclerosis." Annals of neurology **68**(4): 494-502.

Goodman, A. D., T. R. Brown, et al. (2009). "Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial." The Lancet **373**(9665): 732-738.

Hobart, J. C., A. Riazi, et al. (2003). "Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12)." Neurology **60**(1): 31-36.

United States Environmental Protection Agency. (2006). “4-aminopyridine”. Office of Prevention, Pesticides and Toxic Substances. Washington DC. Cited 2012, May 2. Available from: https://docs.google.com/viewer?a=v&q=cache:ueFU3_dS3RwJ:www.epa.gov/hsrb/files/meeting-materials/jun-27-29-2007-public-meeting/epa-woe-document-4-Aminopyridine.pdf+NCI+4-aminopyridine&hl=en&gl=au&pid=bl&srcid=ADGEESilGRFUqe4ktjFjWNKFssJeWudZks3jjpIiemUHji4XUs0b-O6D-ZCfPtgTd8FVYc5Yo6W1BY3J6hFnjp71bINn1FY53fcQYAEBbxHXsKnByGYyFC0Q4m_c68PUp4JGgwPFjHVd&sig=AHIEtbS_ELXxOiKydIWdMmHqGp9-5BVhbg

Rating guide – adapted from NHMRC 2009

1. Evidence base (number of studies, level of evidence and risk of bias in the included studies)		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency (if only one study was available, rank this component as 'not applicable')		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)		
	A	Very large
	B	Moderate
	C	Slight
	D	Restricted
4. Generalisability (How well does the body of evidence match the population and clinical settings being targeted by the Formulary Submission?)		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability (Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)		
	A	Evidence directly applicable to *South Australian public hospital* context
	B	Evidence applicable to *South Australian public hospital* context with few caveats
	C	Evidence probably applicable to *South Australian public hospital* context with some caveats
	D	Evidence not applicable to *South Australian public hospital* context

Appendix 3 Clinical pathway / Proposed place in therapy

Pathway recommended by the applicant: