CNS Neuroscience & Therapeutics

CLINICAL GUIDELINES

CNS Neuroscience & Therapeutics

Recommendations for the Use of Prolonged-Release Fampridine in Patients with Multiple Sclerosis (MS)

Jana Lizrova Preiningerova,[1] Ulf Baumhackl,[2] Tunde Csepany,[3] Adam Czaplinski,[4] Florian Deisenhammer,[5] Tobias Derfuss,[6] Tanja H. Fabjan,[7] Franz Fazekas,[8] Siegrid Fuchs,[8] Eva Havrdova,[1] Alenka Horvath Ledinek,[9] Zsolt Illes,[10] Sasa Sega Jazbec,[9] Eleonora Klimova,[11] Samuel Komoly,[10] Egon Kurca,[12] Michael Linnebank,[13] Lubomir Lisy,[14] Jan Mares,[15] Lubica Prochazkova,[16] Rozsa Csilla,[17] Jarmila Szilasiova,[11] Pavel Stourac,[18] Radomir Talab,[19] Peter Turcani,[20] Marta Vachova,[21] Laszlo Vecsei,[22] David Vodusek,[23] Olga Zapletalova[24] & Thomas Berger[5]

1 Department of Neurology and Center for Clinical Neuroscience, Charles University, General Hospital, Prague, Czech Republic
2 Neurological Practice, Vienna, Austria
3 Department of Neurology, University of Debrecen, Medical and Health Science Center, Debrecen, Hungary
4 Department of Neurology, University of Basel, Basel, Switzerland
5 Department of Neurology, Innsbruck Medical University, Innsbruck, Austria
6 Department of Neurology, University Hospital Basel, Basel, Switzerland
7 Department of Neurology, School of Medicine, Maribor, Slovenia
8 Department of Neurology, Medical University of Graz, Graz, Austria
9 Department of Neurology, University of Ljubljana, Ljubljana, Slovenia
10 Department of Neurology, University of Pécs, Pécs, Hungary
11 Department of Neurology, School of Medicine, Kosice, Slovak Republic
12 Department of Neurology, School of Medicine, Martin, Slovak Republic
13 Department of Neurology, University Hospital Zurich, Zurich, Switzerland
14 Department of Neurology, School of Medicine, Bratislava, Slovak Republic
15 Department of Neurology, University of Palacky, Olomouc, Czech Republic
16 Department of Neurology, University Hospital, Bratislava, Slovak Republic
17 Department of Neurology, Jahn Ferenc Hospital, Budapest, Hungary
18 Department of Neurology, University Hospital, Brno, Czech Republic
19 Department of Neurology, University Hospital, Hradec Kralove, Czech Republic
20 Department of Neurology, Comenius University, Bratislava, Slovak Republic
21 Department of Neurology, Hospital of Teplice, Teplice, Czech Republic
22 Department of Neurology, University of Szeged, Szeged, Hungary
23 Division of Neurology, University of Ljubljana, Ljubljana, Slovenia
24 Department of Neurology, University Hospital Ostrava, Ostrava, Czech Republic

Keywords
Aminopyridines; Fampridine; Multiple sclerosis; Walking.

Correspondence
J. Lízrová Preiningerová, Department of Neurology and Center for Clinical Neuroscience, Charles University, General Hospital, Katerinska 30, Prague 2, 120 00, Czech Republic.
Tel.: +420-224966515;
Fax: +420-224917909;
E-mail: janaprei.lizr@gmail.com
Received 15 January 2013; revision 18 February 2013; accepted 18 February 2013.

SUMMARY

Prolonged-release fampridine (fampridine PR) is a potassium channel blocker that improves conductivity of signal on demyelinated axons in central nervous system. Fampridine PR has been approved to improve speed of walking in patients with multiple sclerosis. This statement provides a brief summary of data on fampridine PR and recommendations on practical use of the medication in clinical practice, prediction, and evaluation of response to treatment and patient management.

doi: 10.1111/cns.12101

Objectives of This Expert Statement

A panel of experts representing 27 centers for treatment of multiple sclerosis from six European countries convened in 2012 to formulate the recommendations for use of prolonged-release (PR) fampridine (Fampyra®) in patients with impairment of walking due to multiple sclerosis.

This statement provides a brief summary of data on fampridine PR and recommendations on practical use of the medication, prediction of response to treatment, and patient management.

Introduction

The goal of symptomatic treatment in general is to minimize the impact of the disease on bodily functions, allowing patients to function longer in their established roles and improving patient's quality of life. Sixty-four to eighty-five percentage of all patients with MS experience difficulty in walking [1]. Impairment of walking can occur in all stages of MS and represents the most disabling symptom in progressive MS. Patients perceive limited walking speed as an increase in disability [2,3]. Correlation between walking speed and maximum distance walked is evident across the full range of walking disability in MS [4]. Until recently, there had been no specific medical treatment approved for improving speed of walking in patients with multiple sclerosis. Research of biological properties of 4-aminopyridine as a potassium channel blocker in 1980s led to a discovery that 4-aminopyridine improves nerve conduction in demyelinated fibers in multiple sclerosis [5,6]. Preparation of 4-aminopyridine into oral compound with time release technology resulted in development of prolonged-release fampridine (fampridine PR). Fampridine PR has received approval from several regulatory agencies, including the FDA in the USA, where it is known as dalfampridine extended release tablets (Ampyra®, Acorda Therapeutics), in July 2011 from the European Medical Agency with the generic name prolonged-release fampridine (Fampyra®, Biogen Idec) and in November 2012 from the Australian Therapeutic Goods Administration as fampridine modified release tablet (Fampyra®) [7–9]. It is the first medication with an indication for the improvement in walking in adult patients with MS and represents a novel treatment option for patients with MS.

Mode of Action and Drug Formulation

4-aminopyridine (the chemical name for fampridine) is an organic lipid-soluble molecule that readily crosses the blood–brain barrier. Demyelination in the central nervous system exposes internodal potassium channels, which leads to abnormal leakage of potassium ions through the axonal membrane and decrease in action potential. The presumed mechanism of action of 4 aminopyridine involves correction of the leakage of potassium ions by blocking the exposed potassium channels and thus increasing the duration of the presynaptic action potential and improving conductivity. The results of *in vitro* studies suggested that the potassium channel subtypes Kv1.1, Kv1.2, and Kv1.4 might mediate the pharmacodynamic effects of fampridine, because their distribution coincides with changes in fampridine sensitivity of demyelinated fibers.

The compounded immediate release formulation of 4 aminopyridine (IR-4AP) has been available for clinical use in some countries for several decades despite lack of registration. A major disadvantage of the IR-4AP is its rapid absorption and elimination. Administration of IR-4AP leads to high peak plasma levels that are associated with epileptic seizures and has a short half-life, which limits its efficacy and tolerability [10,11]. These safety issues and the lack of regulatory approval prevented a broad-scale use of IR-4AP in clinical practice.

A prolonged-release fampridine has been developed to improve the pharmacokinetics and to reduce the side effects associated with IR-4AP. Fampridine PR has a reduced peak plasma levels and a prolonged half-life that allows administration every 12 h.

Efficacy Data

Dose–Response Study

Safety, tolerability, and efficacy of fampridine PR at a dose of 10 mg, 15 mg, or 20 mg given twice a day was tested in a phase II, double-blind, placebo-controlled, dose escalation study (MS-F202) [12]. The primary outcome of the study defined as an increase in walking speed by at least 20% was not reached in any of the groups studied. However, post hoc analysis of the study revealed that about 30% of patients responded to fampridine PR treatment, demonstrating consistent improvement in walking speed, while others had no improvement. This fact influenced the design of phase III studies that used the definition of a responder to the treatment in outcome measures. Note that this phase II study revealed little difference in efficacy among the three doses examined but a favorable safety profile of the 10-mg dose. Therefore, only the 10-mg dose of fampridine PR was selected for further studies.

Clinical Phase III Studies with Fampyra®

Two randomized, multicenter, placebo-controlled, phase III clinical trials have been conducted to test whether fampridine PR is effective in improving walking speed in patients with multiple sclerosis. Responders were prospectively defined in both studies as subjects, who experienced increased speed of walking in at least three of four on-treatment visits versus five off-treatment visits, as measured by the Timed 25 Foot Walk (T25FW) test. Both studies enrolled patients with MS (relapsing, secondary progressive, or primary progressive MS) with walking speed between 8 and 45 seconds on the T25FW test.

In the first study (MS-F203) [13], 301 patients with MS (aged 18–70 years) were randomized at a ratio of 3:1 to receive either fampridine 10 mg twice daily or placebo. The study was comprised of a single-blind 2-week placebo run-in phase, 14 weeks of double-blind, randomized treatment, and a 4-week period of no treatment for follow-up.

In the second study (MS-F204) [14], 239 patients with MS were randomized at a ratio of 1:1 for either fampridine 10 mg twice daily or placebo. The study was comprised of a single-blind 2-week placebo run-in phase, followed by 9 weeks of double-blind randomized treatment and a 2-week period of no treatment for follow-up.

More than one-third of the patients treated with fampridine PR experienced consistent improvement in walking speed as per predefined responder definition (MS-F203: 34.8% with fampridine PR versus 8.3% with placebo; MS-F204: 42.9% with fampridine PR versus 9.3% with placebo; $P < 0.0001$). The responder group (i.e., patients, who had improvement in walking speed on at least three of four on-treatment visits) showed average improvements in walking speed above 20%, which had been characterized as a clinically relevant change in walking speed previously [15,16]. The results of patient self-reported measure of walking ability, the MS Walking Scale-12 (MSWS-12) [17], showed a correlation with the fampridine PR responder status in both studies. Fampridine PR responders showed 7.2 point improvement in the MSWS-12 questionnaire, which exceeds the 4–6 point threshold of change that represents a clinically significant subjective improvement [18,19].

Safety and Contraindications

The clinical efficacy of 4-AP formulations is directly related to the total serum concentration, while toxicity and adverse side effects are directly related to the peak serum dose [20]. Although the prolonged-release formulation of fampridine has a lower risk of seizures than immediate release 4-AP, patients treated with fampridine PR have increased seizure risk. Fampridine PR is contraindicated in patients with a history of seizures. Incidence of seizures in clinical trials was not substantially different from incidence of seizures in MS population, which was estimated in Swedish population to be about 0.35 of 100 patient-years [21]. Postmarketing experience has revealed importance of performing detailed medical history and review of concomitant medications prior to starting treatment with fampridine PR, as there have been reported epileptic seizures in patients using concomitant medication lowering seizure threshold, such as psychostimulants, recreational drugs [22], or bupropion [23]. Animal experimental studies with 4-AP showed epileptic seizures induced by the stimulation of glutamate release. The daily dose of 10 mg given every 12 h should not be exceeded, and any unintentional overdose must be avoided. Safety data on long-term experience with fampridine PR in MS population exceeding a period of 2 years are currently not available [24].

Elimination of fampridine PR is by renal route. No evidence of clinically significant accumulation of fampridine PR has been identified in patients with normal renal function. Renal function should be known before initiation of therapy as even mild renal insufficiency (creatinine clearance < 80 mL/min) represents a contraindication for use. Caution is indicated with the concomitant use of medications that are substrates of the organic cation transporter (OCT2 transporter) such as carvedilol, propranolol, and metformin as they may affect renal elimination; use of OCT2 inhibitors, such as cimetidine, is contraindicated.

During the first weeks of treatment, increased occurrence of dizziness, nausea, and balance disorder was observed. This should be considered with respect to the ability to drive vehicles. Urinary tract infections were seen in about 12% of patients in the clinical studies with fampridine PR.

In animal experiments, reproductive toxicity has been observed, but data on the use in pregnant women are lacking. Therefore, the use of fampridine PR during pregnancy is contraindicated.

Drug interaction studies were performed with baclofen and interferon beta, which showed no effect of these common concomitant drugs on PK of fampridine PR. Most of the patients evaluated in the phase III studies had been treated with a disease-modifying drugs throughout the studies. Concomitant disease-modifying drugs seem to have no interactions with fampridine.

Recommendations

Indication for Treatment with Fampridine PR

European Medical Agency approved the drug with the following indication: Fampyra® is indicated for the improvement in walking in adult patients with multiple sclerosis with walking disability (EDSS 4.0–7.0). As such, it can be used in patients with all types of MS (relapsing, secondary progressive, or primary progressive MS). The approval of Fampyra® by the Canadian agency specifies the range of EDSS 3.5-7.0; approval of Fampyra® by the Australian agency does not specify a limitation by EDSS score. The identical medication has been approved by Food and Drug administration in United States under the name Ampyra® with limitation to ambulatory patients (EDSS < 8.0). The differences in indication by level of disability are not driven by safety concerns, but pharmacoeconomic factors. Prescribing physicians need to consider labeling and indication according to their geographical area.

Dosing

The recommended dose is one 10-mg tablet of fampridine PR administered every 12 h. The tablets should not be crushed, chewed, or dissolved as it would destabilize the prolonged-release formulation and could increase a risk of seizures. Fampridine PR should be taken without food for optimal pharmacokinetic profile; however, ingestion of fampridine PR with food does not put patients at risk of seizures.

Predictive Factors of Response

Due to the fact that only a portion of patients responds to treatment with fampridine PR, a great deal of attention in post hoc analysis of phase III studies was given to characteristics of responders. Subgroup analysis revealed that gender, age, type of MS, disease duration, concomitant treatment with immunomodulatory drugs, EDSS score, or severity of walking impairment as measured by walking speed or MSWS12 score had no influence on response to treatment [11]. Also, the response was not different in patients with various degrees of heat sensitivity or cerebellar symptoms.

Evaluation of Treatment Response

Because it cannot be predicted which patients with MS will benefit from fampridine PR, clinicians need to carefully evaluate treatment response in each individual patient at the clinical setting. The initial prescription should be for the smaller pack size of 28 tablets that allows patients to experience the effects of the treatment for 2 weeks. The treatment response should be evaluated at the follow-up visit by the prescribing physician and is primarily

based on the patient report. It is recommended to document a walking test such as the T25FW test prior to initiating and during the treatment with fampridine PR to quantify the response. Attention needs to be paid to the methodology of measuring the speed of walking at the clinic setting, as the measurement can be influenced by choice of support, shoes, surface, overheating of the patient, fatigue, and other factors. Optionally, the MSWS-12 may be used as a patient self-reporting outcome assessment of difficulty in walking.

The speed of walking is a practical and objective composite measure that reflects status of functional systems that contribute to walking, such as spasticity, muscle strength, sensation, and balance. The effect of the medication does not apply selectively to long motor pathways, and patients may report other effects than improvement in speed of walking.

The treatment with fampridine PR should be discontinued in patients, who do not experience improvement after the 2-week trial. It is important to educate patients that not all patients will experience improvement in walking speed and that there is no benefit in taking the medication without a clear clinical effect.

Fampridine PR is a symptomatic medication with no demonstrated effect on disease progression, so it is expected that patients with progressive MS will continue to decline. This may raise a question whether the medication continues to be effective.

Patient and the physician can reassess the benefits of treatment by a treatment interruption (i.e., stopping and starting treatment). Discontinuation of treatment with fampridine is not associated with withdrawal symptoms or other adverse events.

Patient Management Issues

It is very important to educate patients on a potential role of fampridine PR in their treatment of walking symptoms associated with multiple sclerosis. It is a symptomatic medication that does not influence natural course of the disease. Many patients eligible for treatment with fampridine PR have secondary progressive MS and are no longer treated with disease-modifying drugs. It should be emphasized that this medication does not have any preventive effects on disease worsening, and although this medication can symptomatically improve the speed of walking, it does not stop a progression of the disease.

Patients should be strongly discouraged to try doses beyond the recommended dose of 10 mg every 12 h as the risk of seizures increases with serum level. Moreover, phase II study had shown that there was no difference in percentage of responders in treatment groups using 10, 15 and 20 mg BID [11]. Treatment with fampridine PR should be restricted to supervision by physicians experienced in treatment of multiple sclerosis.

Acknowledgments

Dr. Jana Lizrova Preiningerova has been supported by funds from MSM 0021620849 and PRVOUK-P26/LF1/4.

Disclosure

All authors have received consulting fees for advisory board meetings from Biogen Idec (distributor of Fampyra) and other pharmaceutical companies. Dr. Jana Lizrova Preiningerova has received grant support from Biogen Idec, Novartis and Ministry of Health for MS research.

Conflict of Interest

The authors declare no Conflict of interest.

Box 1 Summary of recommendations

- Fampridine PR is indicated for the improvement in walking in adult patients with multiple sclerosis with walking disability.
- Fampridine PR at the dose of 10 mg orally every 12 h can be used in patients with all types of MS (relapsing, secondary progressive, or primary progressive MS) and regardless of the disease duration, patient's age, gender, body mass index, or use of disease-modifying drugs.
- Patients should be specifically advised not to chew, crush, or divide the tablets, not to catch up on missed doses or increase the dose.
- Fampridine PR is contraindicated in patients with a history of seizure disorder, and treatment must be discontinued in patients who experience a seizure.
- Fampridine PR is contraindicated in patients with mild, moderate, or severe renal dysfunction and in patients who use OCT2 inhibitors such as cimetidine, due to a risk of increase in serum levels of the medication.
- The treatment with fampridine PR should be started and continued by a neurologist, who is regularly following the patient and is able to evaluate the treatment effects.
- The efficacy of the drug should be evaluated after about 2 weeks of regular dosing at the office visit primarily using information provided by the patient regarding the perceived effects of the drug.
- Patients should be initially prescribed a pack of 28 tablets of fampridine PR to evaluate the response to drug.
- Improvement in the speed of walking can be quantified by one of the objective measures, such as timed T25FW or MSWS12 scale.
- Prescription of fampridine PR should be discontinued in patients who report no improvement in function.

References

1. Julian LJ, Vella L, Vollmer T, Hadjimichael O, Mohr DC. Employment in multiple sclerosis. Exiting and re-entering the work force. *J Neurol* 2008;**255**:1354–1360.
2. Heesen C, Böhm J, Reich C, Kasper J, Goebel M, Gold SM. Patient perception of bodily function in multiple sclerosis: Gait and visual function are the most valuable. *Mult Scler* 2008;**14**:988–991.
3. Hemmett L, Holmes J, Barnes M, Russel N. What drives quality of life in multiple sclerosis? *QJM* 2004;**10**:671–676.
4. Creange A, Serre I, Levasseur M, et al. Walking capacities in multiple sclerosis measured by global positioning system odometer. *Mult Scler* 2007;**13**:220–223.
5. Stefoski D, Davis FA, Fault M, Schauf CL. 4 Aminopyridine improves clinical signs in multiple sclerosis. *Ann Neurol* 1987;**21**:71–77.
6. Jones RE, Heron JR, Foster DH, Snelgar RS, Mason RJ. Effects of 4-aminopyridine in patients with multiple sclerosis. *Neurol Sci* 1983;**60**:353–362.
7. *FDA Approves Ampyra to Improve Walking in Adults with Multiple Sclerosis*. FDA press release Jan 22, 2010. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm198463.html
8. European medicines agency, Public assessment report, June 23, 2011, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002097/WC500109957.pdf
9. Australian Public assessment report, June 2011 http://www.tga.gov.au/pdf/auspar/auspar-fampyra.pdf
10. Hayes K. The use of 4-aminopyridine (fampridine) in demyelinating disorders. *CNS Drug Rev* 2004;**10**:295–316.
11. Bever CT Jr, Young D, Anderson PA, et al. The effects of 4-aminopyridine in multiple sclerosis patients: Results of a randomized, placebo-controlled, double-blind, concentration-controlled, crossover trial. *Neurology* 1994;**44**:1054–1059.
12. Goodman AD, Brown TR, Cohen JA, et al. Fampridine MS-F202 Study Group. Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology* 2008;**71**:1134–1141.
13. Goodman AD, Brown TR, Krupp LB, et al. Fampridine MS-F203 Investigators. Sustained-release oral fampridine in multiple sclerosis: A randomized, double-blind, controlled trial. *Lancet* 2009;**373**:732–738.
14. Goodman AD, Brown TR, Edwards KR, et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol* 2010;**68**:494–502.
15. Van Winsen LM, Kragt JJ, Hoogervorst EL, Polman CH, Uitdehaag BM. Outcome measurement in multiple sclerosis: Detection of clinically relevant improvement. *Mult Scler* 2010;**16**:604–610.
16. Hoogervorst EL, Zwemmer JN, Jelles B, Polman CH, Uitdehaag BM. Multiple Sclerosis Impact Scale (MSIS-29): Relation to established measures of impairment and disability. *Mult Scler* 2004;**10**:569–574.
17. Schwid SR, Goodman AD, McDermott MP, Bever CF, Cook SD. Quantitative functional measures in MS: What is a reliable change? *Neurology* 2002;**58**:1294–1296.
18. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: The 12-Item MS Walking Scale (MSWS-12). *Neurology* 2003;**60**:31–36.
19. Coleman CI, Sobieraj DM, Marinucci LN. Minimally important clinical difference of the Timed 25-Foot Walk Test: Results from a randomized controlled trial in patients with multiple sclerosis. *Curr Med Res Opin* 2012;**28**:49–56.
20. Hersh C, Rae-Grant A. Extended-release dalfampridine in the management of multiple-sclerosis-related walking impairment. *Ther Adv Neurol Disord* 2012;**5**:199–204.
21. Eriksson M, Ben-Menachem E, Andersen O. Epileptic Seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis. *Mult Scler* 2002;**8**:495–499.
22. De Gusmao CM, Ortega MR, Wallace DM. Status epilepticus associated with dalfampridine in a patient with multiple sclerosis. *J Neuropsychiatry Clin Neurosci* 2012;**24**:E47–E48.
23. Rissmiller DJ, Campo T. Extended-release bupropion induces grand mal seizures. *J Am Osteopath Assoc* 2007;**107**:441–442.
24. Jara M, Henney HR, Wessel T, et al. Dalfampridine extended release tablets: One year of post marketing safety experience in the United States. *Mult Scler* 2011;**17**:S216–S217 (P508).

