CDEC FINAL RECOMMENDATION

FAMPRIDINE
(Fampyra – Biogen Idec Canada Inc.)
Indication: Multiple Sclerosis – Improve Walking Disability

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that fampridine not be listed.

Reasons for the Recommendation:

1. In two double-blind randomized controlled trials (RCTs) in patients with multiple sclerosis (MS) and walking disability, compared with placebo groups, fampridine groups reported statistically significant improvements in walking speed; however, no between-treatment differences in quality of life were reported.
2. The manufacturer's cost-utility analysis was based on an assumed relationship between improvements in walking speed and utility gains that was likely overestimated. When accounting for limitations in the manufacturer's cost-utility analysis, CDR estimated that compared with supportive care the incremental cost per QALY for fampridine ranges from $54,000 to $500,000; however, CDEC noted that the most likely estimate is closer to $500,000 per QALY.

Background:
Fampridine has a Health Canada indication for the symptomatic improvement of walking in adult patients with MS who have walking disability (Expanded Disability Status Scale [EDSS] 3.5 to 7). Fampridine is a potassium channel blocker. It is available as 10 mg sustained-release tablets, and the Health Canada-approved dose is 10 mg twice daily. The product monograph states that the initial prescription should be for no more than four weeks, and assessment for improvement in walking should be carried out within that time frame.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of fampridine, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients with MS. The manufacturer submitted a confidential price for fampridine.

Clinical Trials

The systematic review included three double-blind RCTs of patients with MS and walking disability. MS-F202 (N = 206) was a 15-week phase 2 dose-ranging trial that randomized patients to fampridine (10 mg, 15 mg, or 20 mg) or placebo, all twice daily. MS-F203 (N = 301) and MS-F204 (N = 239) were similarly designed phase 3 trials that randomized patients to fampridine 10 mg or placebo twice daily; trial durations were 14 and nine weeks respectively.

At screening, patients were able to complete the timed 25-foot walk (T25FW) test within eight to 60 seconds in MS-F202 and within eight to 45 seconds in studies MS-F203 and MS-F204. Patients with longer walk times were excluded; thus, limiting generalizability to such patients.

The frequency of premature study discontinuation was similar in the fampridine and placebo groups in studies MS-F202 and MS-F204 (range 3.8% to 5.8%). In MS-F203 the percentage of patients discontinuing was higher in the fampridine group compared with placebo (6.6% versus 1.4%).

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: walking speed, measured using the T25FW; patient-reported impact of MS on ability to walk; muscle strength and spasticity; serious adverse events; adverse events; and withdrawal due to adverse events. The primary efficacy outcome in MS-F203 and MS-F204 was the T25FW responder rate. The primary outcome of MS-F202 was the change in walking speed measured using the T25FW.

The T25FW assessment requires a patient to walk a clearly marked 25-foot course as quickly as possible; assistive devices (e.g., canes, crutches, or walkers) may be used. In MS-F203 and MS-F204, a responder was defined as a patient with a faster walking speed for at least three visits during the double-blind treatment period as compared with the maximum speed for any of the pre-treatment visits or post-treatment visits. A change of at least 20% in the T25FW is commonly cited as the minimal clinically important difference for patients with MS.

The 12-item Multiple Sclerosis Walking Scale (MSWS-12) is a patient-reported questionnaire. Total scores range from 0 to 100, and larger scores indicate greater impact of MS on a patient's ability to walk. A manufacturer-sponsored study has suggested the minimal clinically important difference on the MSWS-12 to be 6.2 points. In addition, patients' assessment of the treatment effects on their physical well-being was assessed using the Subject Global Impression (SGI) scale.

Muscle strength was measured using the Lower Extremity Manual Muscle Test (LEMMT), and spasticity was assessed using the Ashworth Scale score; the minimal clinically important difference for these scales has not been established for patients with MS.

Results

Efficacy or Effectiveness

- Both MS-F203 and MS-F204 reported statistically significantly greater change in walking speed, favouring fampridine compared with placebo; mean difference (MD), 0.19 feet per second and 0.12 feet per second respectively. In MS-F202, change in walking speed was not statistically significantly different between treatment groups.
- The percentage of patients achieving at least a 20% improvement in walking speed was statistically significantly greater for fampridine compared with placebo in both MS-F203 and MS-F204: 31.7% versus 11.1% and 34.5% versus 15.3% respectively. No statistically significant between-treatment differences were reported in MS-F202.
- Compared with placebo groups, improvement in the MSWS-12 score was statistically significantly greater for fampridine in study MS-F204, but not in MS-F203; average improvement in the MSWS-12 did not exceed the minimal clinically important difference in any treatment group. No statistically significant between-treatment differences were reported in MS-F202.
- There were no statistically significant between-treatment differences in SGI score changes in any of the trials.
- Compared with placebo, fampridine-treated patients demonstrated statistically significant improvements in Ashworth spasticity scores in MS-F203 and MS-F204, but not in MS-F202. In addition, fampridine-treated patients demonstrated statistically significant improvement in the LEMMT in MS-F203 and MS-F202, but not in MS-F204. The clinical importance of the observed between-treatment differences in the Ashworth spasticity scores and the LEMMT is uncertain.

Harms (Safety and Tolerability)

- Compared with placebo, the percentage of patients experiencing a serious adverse event was numerically higher in the fampridine groups in both MS-F203 and MS-F204: 7.0% versus 0% and 4.2% versus 2.5% respectively. In MS-F202, the percentage of patients with a serious adverse event was 4.3% and 0% in the placebo and fampridine groups respectively.
- Adverse events that were more commonly reported in fampridine groups compared with placebo, in studies MS-F203 and MS-F204, included urinary tract infection, insomnia, dizziness, nausea, back pain, and balance disorder.
- In MS-F203, withdrawals due to adverse events occurred for eight fampridine-treated patients (3.5%) compared with no placebo-treated patients. In MS-F204, withdrawal due to adverse events was reported for three patients (2.5%) in the fampridine group and four patients (3.4%) in the placebo group. In MS-F202, there was one withdrawal due to an adverse event in the placebo group and none in the fampridine 10 mg group.

Cost and Cost-Effectiveness

The manufacturer submitted a cost utility analysis comparing fampridine with supportive care (physiotherapy and exercise programs) for the symptomatic treatment of walking in adults with MS at a walking disability level of EDSS 3.5 to 7, over a 4-year time horizon. The analysis was based on a Markov model where patients transitioned between 15 states defined by EDSS level, and death as a final state. Transition probabilities were obtained from the literature and mortality rates from Statistics Canada life tables. The health-related utility associated with each

state was derived from a series of linear regressions based on an indirect approach quantifying the association between walking speed and utility, walking speed derived from fampridine trials, and utility values obtained from a Canadian study. The manufacturer assumed that health care resource use was affected by walking speed. The manufacturer reported that the incremental cost per QALY of fampridine compared with supportive care was $30,000.

CDR noted a number of limitations with the manufacturer's analysis. The manufacturer established an association between walking speed and utility values through methods which likely overestimated the size of the association, using a simple regression to establish the relationship between walking speed and utility value. CDR compared the improvement in QALYs reported by the manufacturer for fampridine with the benefits reported in published economic evaluations in MS for disease modifying drugs that potentially slow the progression of disease, thereby, affecting a number of symptoms beyond walking speed. CDR noted that, when considering the same analysis time horizon, the improvement in QALYs for fampridine would exceed those reported for disease modifying drugs; a finding which raises questions regarding the validity of the gain in QALYs, focussed on walking speed, for fampridine. Furthermore, the manufacturer assigned the percentage improvement in walking speed for the comparator to be 0%, which does not reflect the clinical data from the reviewed trials. When adjusting for the above limitations (considering a multiple regression to account for EDSS class as an independent variable, including utility gains for patients who improve on supportive care), the incremental cost per QALY increased to ~$500,000 per QALY.

At the recommended dose (10 mg twice daily), the daily cost of fampridine is ***[****confidential price removed at manufacturer's request****]***. The confidential price was used by the Committee in making the listing recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Patient Input Information:
The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input:

- Patients indicated that MS has a major impact on their ability to work and that mobility problems contribute significantly to their decisions about whether or not to continue working.
- Patients expressed a desire for treatments that would improve their ability to walk, to accomplish daily tasks, and perform routine activities; thus, improving quality of life and potentially allowing them to re-enter the work force.
- The majority of patients noted that they are willing to balance perceived benefits (improved walking) with manageable side effects.

Other Discussion Points:

- The Committee noted that the T25FW test is not routinely conducted in clinical practice and that, based on patient group input, walking speed is not directly linked to patients' desire for improved ability to walk to accomplish daily tasks and perform routine activities.
- The Committee considered that of the outcomes reported from the reviewed trials the MSWS-12 and the SGI may be the most relevant for patients. The Committee noted that there were few statistically significant or clinically important between-treatment differences for these outcomes, but recognized that the reviewed trials were not specifically designed to detect important between-treatment differences in these outcomes.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets:
September 19, 2012
Two CDEC members did not attend.

November 21, 2012
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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