Prolonged-release fampridine (Fampyra®) for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7)

August 2012

Summary

1. Fampridine (Fampyra®) is indicated for the improvement of walking in adult patients with multiple sclerosis (MS) with walking disability (EDSS 4-7). Conditional authorisation from the European Commission was granted on 23rd June 2011 on condition that a further study is conducted to investigate long term efficacy and safety, utilising a broader, clinically meaningful primary endpoint.

   Walking impairment is a principal clinical hallmark of MS and has a substantial impact on activities of daily living. Fampridine is the only drug approved for the symptomatic treatment of walking disability in patients with MS and as such is considered to address an unmet need.

2. Biogen Idec has not submitted a full pharmacoeconomic assessment to the National Centre for Pharmacoeconomics (NCPE) as they cannot currently accurately estimate the cost-effectiveness of fampridine. Future work to determine the cost-effectiveness of fampridine is planned by the company. On May 23rd 2012, a dossier incorporating a review of clinical evidence and a budget impact analysis (BIA) was submitted to the NCPE.

3. The primary efficacy endpoint in fampridine randomised controlled trials was based on changes in walking speed over the study period as measured by the timed 25 feet walk (T25FW). A responder was defined as a patient with higher walking speed for at least three out of four visits during the double-blind period as compared to the maximum value among the non-treatment visits. The proportion of responders was significantly higher in the fampridine group than in the placebo group in both studies, 34.8% vs 8.3% in study MS-F203 and 42.9% vs 9.3% in study MS-F204 ($p<0.0001$). The change in walking speed was approximately 14% (or 0.3ft/sec) for fampridine versus 5.2%-7.7% (0.1-0.2 ft/sec) for placebo. A 20% improvement in walking speed has been suggested by some investigators to represent a clinically meaningful change. In a pooled analysis of phase II and III fampridine trials, the proportion of responders with >20% improvement in walking speed was 13% versus 31% for placebo and fampridine, respectively. The statistically significant but small improvements in walking speed were not

reflected in secondary endpoints including Ashworth assessment of spasticity, Lower extremity Manual Muscle Testing, Subject Global Impression and Clinician Global Impression. The majority of subjects in phase III trials perceived no improvement.

4. Within the subgroup of fampridine-responders, the mean change from baseline in walking speed was approximately 25% (0.51 ft/sec). Timed-walk responders also showed an improvement from baseline in MSWS-12 score (subjective perceptions of change) which correlated with improvement in walking speed. Among responders, the increase in walking speed was maintained over the study period and lost after cessation of treatment. In open-label extension studies, walking speed while on treatment decreased gradually over two years.

5. The Committee for Medicinal Products for Human Use (CHMP) initially rejected marketing authorisation for fampridine due to uncertainties concerning the clinical meaningfulness of observed differences between fampridine-treated and placebo-treated groups in the pivotal randomised controlled trials, and the absence of any outcomes addressing the broader aspects of walking that can be affected by MS, including coordination, balance and stamina. Following initial rejection, a re-submission was made to the CHMP who concluded a favourable risk/benefit balance, acknowledging the potential relevance of the 20% improvement in walking speed when correlated to MSWS-12, a patient-reported outcome. Approximately one third of patients may be anticipated to benefit from the treatment. A modified indication was accepted, restricting use to patients with MS and walking disability (EDSS 4-7). Initial prescription should be limited to two weeks of therapy as clinical benefits should generally be identified within two weeks after starting fampridine. If no improvement in a timed walking test is observed after two weeks, fampridine should be discontinued. The CHMP requested that further data is obtained to evaluate the validity of the criteria for identification of responders and the impact of fampridine on other important aspects of walking such as balance, endurance and walking distance.

6. Adverse effects include coordination abnormalities, anxiety, pain, insomnia and an increased risk of infections. The most frequent adverse events observed in

RCTs were falls and urinary tract infections. Fampridine is associated with an increased risk of seizure and as such is contraindicated in patients with a history of seizure and those with renal impairment

7. The estimated gross budget impact of fampridine reimbursement under the High-tech drug scheme is €1.3 million in year one increasing to €7.5 million in year five, assuming that 34.5% of patients respond to treatment and that the remainder of patients discontinue therapy after two to four weeks. An outcome-based responder-testing scheme, presented by Biogen Idec, proposes to restrict the number of patients who continue fampridine based on response to treatment at week two and four. In addition, under this scheme the company would incur the cost of fampridine treatment for the first four weeks of therapy, reducing the budget impact by €180,000 (2.4%) in year five.

8. Fampridine is a high-cost drug which requires intensive neurological assessments both initially and throughout longer-term follow-up. An assessment of the cost-effectiveness of fampridine has not been presented in the submission nor was any other evidence on the cost-effectiveness of fampridine found. It is as yet unknown what impact improvement in walking speed has on quality of life. Studies are ongoing to assess the wider impact of fampridine on both walking and quality of life. As the manufacturer is unable to demonstrate the cost-effectiveness of fampridine in the Irish healthcare setting we are unable to recommend reimbursement.