HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

11 April 2012

FAMPYRA 10 mg prolonged-release tablets
B/28 (CIP code: 219 395-4)
B/56 (CIP code: 219 396-0)

Applicant: BIOGEN IDEC FRANCE

fampridine
ATC code: N07XX (other central nervous system drug)

List I
Prescription restricted to neurology specialists

Date of Marketing Authorisation (centralised procedure): 20 July 2011

Conditional Marketing Authorisation with request for study (report expected by 30 June 2016)

Marketing Authorisation: FDA (22 January 2010), Australia (13 May 2011)
Refundable within the EU: Germany, UK

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Fampridine (4-aminopyridine)[1]

1.2. Indication

"FAMPYRA is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7)."

1.3. Dosage

"Treatment with FAMPYRA is restricted to prescription and supervision by physicians experienced in the management of MS."

Dosage

The recommended dose is one 10 mg tablet, twice daily, taken 12 hours apart (one tablet in the morning and one tablet in the evening). FAMPYRA should not be administered more frequently or at higher doses than recommended. The tablets should be taken without food.

Starting and evaluating Fampyra treatment

- Initial prescription should be limited to 2 weeks of therapy as clinical benefits should generally be identified within 2 weeks after starting FAMPYRA.
- A timed walking test, e.g. the Timed 25-Foot Walk (T25FW), is recommended to evaluate improvement after two weeks. If no improvement is observed, FAMPYRA should be discontinued.
- FAMPYRA should be discontinued if benefit is not reported by patients.

Re-evaluating FAMPYRA treatment

If decline in walking ability is observed physicians should consider an interruption to treatment in order to reassess the benefits of FAMPYRA (see above). The re-evaluation should include withdrawal of FAMPYRA and performing the walking test. FAMPYRA should be discontinued if patients no longer receive walking benefit.

[…]

1.4. Special warnings and precautions for use

Seizure risk

Treatment with fampridine increases seizure risk.
FAMPYRA should be administered with caution in the presence of any factors which may lower seizure threshold.

FAMPYRA should be discontinued in patients who experience a seizure while on treatment.

Renal impairment

FAMPYRA is primarily excreted unchanged by the kidneys. Patients with renal impairment have higher plasma concentrations which are associated with increased adverse reactions, in particular neurological effects. Determining renal function before treatment and its regular monitoring during treatment is recommended in all patients (particularly the elderly in whom renal function might be reduced). Creatinine clearance can be estimated using the Cockcroft-Gault formula.
FAMPYRA should not be administered to patients with renal impairment (creatinine clearance < 80 ml/min).

1 A voltage-gated potassium channel blocker

Caution is required when FAMPYRA is prescribed concurrently with medicinal products that are substrates of OCT2, for example, carvedilol, propranolol and metformin.

Other warnings and precautions

FAMPYRA should be administered with caution to patients with cardiovascular symptoms of rhythm and sinoatrial or atrioventricular conduction cardiac disorders (these effects are seen in overdose). There is limited safety information in these patients.

The increased incidence of dizziness and balance disorder seen with FAMPRYA in the first 4 to 8 weeks of treatment may result in an increased risk of falls. Patients who are using walking aids should continue to use these aids as needed.

In clinical studies low white blood cell counts were seen in 2.1% of FAMPRYA patients versus 1.9% of patients on placebo. Infections were seen in the clinical studies as stated below. An increased infection rate and impairment of the immune response cannot be excluded.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

N	Nervous system
N07	Other nervous system drugs
N07X	Other nervous system drugs
N07XX	Fampridine

2.2. Medicines in the same therapeutic category

Compounded 3,4-diaminopyridine (3,4-DAP) products are used in hospitals for fatigability associated with multiple sclerosis. The risk/benefit ratio of compounded 3,4-DAP is not judged to be favourable by AFSSAPS, which recommends that in the current state of knowledge it should not be used in this situation.

2.3. Non-drug treatment

- Physiotherapy, rehabilitation, occupational therapy, equipment
- Neurosurgery, orthopaedic surgery

2.4. Medicines with a similar therapeutic aim

Primarily drug treatments for spasticity:

- baclofen, dantrolene, benzodiazepines
- treatments for the pain associated with spasticity
- botulinum toxin type A

3. ANALYSIS OF AVAILABLE DATA

3.1. Studies of Efficacy

The phase II study[1] (10, 15 and 20 mg b.d. vs. placebo) did not show any significant difference on the trial's primary efficacy endpoint: the changes in mean walking speed over a distance of 25 feet (Timed 25-Foot Walk[2,3]) observed on fampridine during the 12-week period of double-blind treatment were no different to those observed on placebo. The percentage of responder patients (with an increase of at least 20% in mean walking speed in comparison with initial speed) did not differ between fampridine and placebo. No dose-response relationship was demonstrated. Adverse effects and discontinuation of treatment were more frequent at dosages greater than 10 mg b.d. Only post-hoc analysis, with responder patients defined as those for whom at least 3 of the 4 walking speeds measured during treatment were greater than the maximum value obtained during the 5 pre- and post-treatment visits, was able to demonstrate a significant difference in efficacy between fampridine and placebo. The efficacy of the product at dosages below 10 mg b.d. was not studied.
Two placebo-controlled phase III studies were conducted in the USA and Canada: **MS-F203**[4] and **MS-F204.**[5]

3.1.1 Methodology of phase III studies

The MS-F203 and MS-F204 randomised double-blind superiority studies compared the efficacy and safety of fampridine 10 mg b.d. with those of placebo in patients with clinically defined MS according to the McDonald[6] criteria, selected for their ability to perform two walking tests over a distance of 25 feet (7.6 m) – Timed 25-Foot Walk – with a mean speed of between 8 and 45 seconds. The exclusion criteria were the occurrence of a relapse in the 2 months preceding inclusion, corticosteroid treatment or a change in the dosage of interferon, glatiramer acetate or natalizumab treatment in the 30 days preceding inclusion, and cyclophosphamide or mitoxantrone treatment in the 6 months preceding inclusion. Patients with a history of epilepsy or an electroencephalogram showing epileptiform activity were excluded.
The dosage of fampridine used was 10 mg twice daily.

The primary efficacy endpoint was the percentage of responders on the Timed 25-Foot Walk test. A responder patient was defined as having an increased walking speed on at least 3 of the 4 assessments conducted during the double-blind treatment period, in comparison with their maximum speed obtained during the 4 pre-treatment visits or the first post-treatment follow-up visit.

1 Goodman AD, Brown TR, Cohen JA et al. Dose comparison trial of sustained-release fampridine in multiple sclerosis. Neurology 2008; 71: 1134-1141.

2.This test forms part of the MSFC composite score. It measures the walking speed of the patient over a distance of 25 feet (7.6 metres). Mean walking speed is calculated from two walking tests performed with a maximum rest of 5 minutes between the two.

3 Fischer JS, Jak AJ, Kniker JE et al. Multiple sclerosis functional composite (MSFC). Administration and scoring manual. National Multiple Sclerosis Society. Revised October 2001.

4 Goodman AD, Brown TR et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet 2009; 373: 732-38.

5 Goodman AD, Brown TR et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. Ann Neurol 2010; 68: 494-502.

6 Mc Donald WI, Compston A et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol 2001; 50:121-127.

Amongst the secondary endpoints were evaluated the 12-Item MS Walking Scale[1] (MSWS-12), a self-reporting questionnaire assessing the impact of the disease on walking ability; the Lower Extremity Manual Muscle Testing score[2] (LEMMT), a manual test of muscle strength in the lower limbs; the Ashworth Spasticity Examination score[3], which tests muscle spasticity; and the SGI score.[4]

3.1.2 Results of phase III studies[5,6]

a. MS-203 study (14 weeks of treatment)

A total of 301 patients with a mean age of 51 years were randomised (ratio 3:1) to fampridine 10 mg B.D. (n=229) vs. placebo (n=72) after a single-blind period of 2 weeks on placebo. The patients had RRMS in 27 to 29% of cases, SPMS in 49 to 53% of cases and PPMS in 16 to 19% of cases.
Sixty-six to 69% of patients were taking immunomodulators (interferon or glatiramer acetate); 40 to 51% were taking baclofen.
The median duration of illness was 11.5 years. *The patients' median initial EDSS[7] score was 6 (2.5 to 7).*

Eighteen patients stopped treatment prematurely before the end of the double-blind period: 17 patients in the fampridine group (adverse events: 11, withdrawal of consent: 4, other: 2) and one patient in the placebo group (lost to follow-up).
In total, 296 patients were analysed on an intention-to-treat basis – patients who had received at least one dose of treatment and had had at least one assessment (T25FW or MSWS-12) on treatment.

1 Hobart JC, Riazi A et al. Measuring the impact of MS on walking ability: the 12-item MS walking scale (MSWS-12). Neurology 2003; 60: 31-36.
Twelve items assessing walking difficulties (function and quality), each rated on a scale of 1 to 5 to give a total score of 12 to 60, standardised as a score out of 100.

2 Paternostro-Sluga T J et al. Reliability and validity of the medical research council (MRC) scale and a modified scale for testing muscle strength in patients with radial palsy. J Rehabil Med 2008; 40: 665-671.

3 Bohannon, R. et al. (1987). Inter-rater reliability of a Modified Ashworth Scale of muscle spasticity. Physical Therapy 2011; 67: 206-207.

4 Subject's global impression – Effect of treatment in the past 7 days as assessed by the patient – scored from 1 (terrible) to 7 (delighted).

5 European Medicines Agency – FAMPYRA assessment report – 23 June 2011.

6 FDA – Clinical Review – Efficacy – Application number: 22-250.

7 Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33: 1444-52. A score from 0 to 10. Score from 0 to 3.5: no problems walking – Score of 4: able to walk 500 m unaided and without resting – Score of 6: constant or intermittent unilateral aid needed to walk around 100 m with or without intermediate rest – Score of 7: cannot walk more than 5 m with aid.

Results of the intention-to-treat analysis:

Endpoint	Fampridine 20 mg/day n=224		Placebo n=72	p
Initial walking speed (feet/sec)	2.02		2.04	
Mean change	0.30 (0.040)		0.11 (0.066)	
Difference from placebo*		0.19		0.01
% responders	**34.8%**		**8.3%**	
Difference from placebo (95% CI)	**26.5% (16.0;34.3)**			
OR (95% CI)**	**OR 6.77 (2.71; 16.92)**			**< 0.001**
% patients (improvement > 20%)	31.7%		11.1%	
Initial MSWS-12 score	70.98 (18.55)		68.48 (22.30)	
Mean change	-2.84 (0.878)		-0.08 (1.46)	
Difference from placebo*		2.76		ns
Initial LEMMT score	4.06 (0.586)		3.97 (0.737)	
Mean change	0.13 (0.014)		0.05 (0.024)	
Difference from placebo*		0.08		0.003
Initial Ashworth score	0.90 (0.713)		0.95 (0.670)	
Change	-0.18 (0.022)		-0.09 (0.037)	
Difference from placebo*		0.09		0.02

* Least square mean – ANOVA adjusted for centre; ** Logistic regression adjusted for centre

† Patients with missing data for a visit are considered to be non-responders at that visit

At 14 weeks of treatment, the mean times taken to walk the distance of 7.6 metres, corresponding to the walking speeds observed, were 10.8 seconds on fampridine versus 11.6 seconds on placebo.
SGI scores did not differ between the two treatment groups.

Analysis of changes in walking speed in the fampridine group showed increases of 0.51 feet/sec (25%) in responder patients (n=78) and 0.16 feet/sec (8%) in non-responder patients. The change was 0.10 feet/sec (5%) in the 6 responder patients in the placebo group. A reduction in MSWS-12 score of -6.84 in responder patients (n=84) and an increase of +0.05 in non-responders (n=212) were observed.

b. MS-204 study (9 weeks of treatment)

A total of 239 patients with a mean age of 51 years were randomised (ratio 1:1) to fampridine 10 mg b.d. (n=120) vs. placebo (n=119) after a single-blind period of 2 weeks on placebo. The patients had RRMS in 34 to 36% of cases, SPMS in 47 to 52% of cases and PPMS in 8 to 18% of cases.
59% of patients were taking immunomodulators (interferon or glatiramer acetate); 41 to 43% were taking baclofen.
The median duration of illness was 13 years. *The patients' median initial EDSS score was 6 (1.5 to 7.5).*

Twelve patients stopped treatment prematurely before the end of the double-blind period: 7 patients in the fampridine group (adverse events: 4, non-compliance: 2) and 5 patients in the placebo group (adverse events: 4, non-compliance: 1).

In total, 237 patients were analysed on an intention-to-treat basis – patients who had received at least one dose of treatment and had had at least one assessment (T25FW or MSWS-12) on treatment.

Results of the intention-to-treat analysis:

Endpoint	Fampridine 20 mg/day n=119	Placebo n=118	p
Initial walking speed (feet/sec)	2.12	2.21	
Mean change	0.31 (0.046)	0.18 (0.046)	
Difference from placebo*	0.13		0.038
% responders	**42.9%**	**9.3%**	
Difference from placebo (95% CI)	**33.5% (22.7;43.4)**		
OR (95% CI)**	**OR 9.22 (5.23; 16.27)**		**< 0.001**
% patients (improvement > 20%)	34.5%	15.3%	
Initial MSWS-12 score	73.80 (17.75)	67.68 (22.56)	
Mean change	-2.77 (1.20)	0.87 (1.22)	
Difference from placebo*	3.64		0.006
Initial LEMMT score	3.91 (0.603)	3.96 (0.580)	
Mean change	0.10 (0.024)	0.05 (0.024)	
Difference from placebo*	0.05		0.106
Initial Ashworth score	0.91 (0.611)	0.80 (0.672)	
Change	-0.17 (0.032)	-0.07 (0.033)	
Difference from placebo*	0.1		0.015

* Least square mean – ANOVA adjusted for centre; ** Logistic regression adjusted for centre
† Patients with missing data for a visit are considered to be non-responders at that visit

At 9 weeks of treatment, the mean times taken to walk the distance of 7.6 metres, corresponding to the walking speeds observed, were 10.3 seconds on fampridine versus 10.5 seconds on placebo.
SGI scores did not differ between the two treatment groups.

Analysis of changes in walking speed in the fampridine group showed increases of 0.51 feet/sec (25%) in responder patients (n=51) and 0.12 feet/sec (6%) in non-responder patients. The change was 0.17 feet/sec (8%) in the 11 responder patients in the placebo group. A reduction in MSWS-12 score of -6.04 in responder patients (n=62) and an increase of +0.85 in non-responders (n=175) were observed.

c. MS-F203 and MS-F204 extension studies (ECTRIMS poster 2011[1])

In total, 310 patients started or continued fampridine as an open-label treatment. A reduction in the difference between mean changes in walking speed observed in responders and non-responders can be noted during these follow-up studies. At 2 years, walking tests performed in 153/197 patients included in the MS-F203 study and 80/109 patients included in the MS-F204 study showed that this difference between the two groups was less than 10%; the low numbers of patients followed up in both groups means the results obtained during continuation of treatment cannot be interpreted.

3.1. Safety data

a. Data from phase II and III studies[2]

The product's safety profile has been established from data from 3 phase II and III clinical studies (MS-F202/203/204), including extension studies from these studies. A total of 507 patients were exposed to fampridine during the controlled periods of these studies (10 mg B.D..: n=400, 15 mg B.D.: n=50, 20 mg B.D.: n=57).

1 Goodman AD. Updated analysis of open-label extension studies of dalfampridine extended release tablets in multiple sclerosis. P 566 ECTRIMS 2011.

2 European Medicines Agency – FAMPYRA assessment report – 23 June 2011.

Safety data from patients treated with fampridine 10 mg b.d. during the MS-F202/203/204 placebo-controlled studies have been pooled together. Eighty-two percent of patients had at least one adverse event (AE) on fampridine versus 71% on placebo (n=238). The percentage of patients who stopped treatment due to AEs was 1.8% on fampridine and 0.4% on placebo. The percentage of patients who had a severe AE was 4.7% in the fampridine group and 1.7% in the placebo group.

The adverse events that occurred on fampridine 10 mg b.d. with a frequency at least double that observed on placebo were: vertigo (1% vs. 0.4%); gastrointestinal symptoms (18.5 vs. 16) including abdominal pain (1.3 vs. 0.4), dyspepsia (2 vs. 0.8), nausea (7 vs. 2.5) and vomiting (1.8 vs. 0.4); infections (31 vs. 24.8) including influenza (1.5 vs. 0), nasopharyngitis (3.5 vs. 1.7), pneumonia (1 vs. 0.4) and viral infection (1.5 vs. 0.4); back pain (5 vs. 2.1); balance disorder (4.8 vs. 1.3); sensory disorders (1 vs. 0.4); psychiatric disorders (12.3 vs. 5.5) including anxiety (1.5 vs. 0.4) and insomnia (8.8 vs. 3.8); pharyngolaryngeal pain (2 vs. 0.8); frequent urination (1.8 vs. 0.8); pruritus (1.5 vs. 0.4). AEs with a frequency greater than 5% on fampridine included: urinary tract infection (12% on fampridine vs. 8.4% on placebo), fatigue (6.8 vs. 3.8), dizziness (7.3 vs. 4.2) and headaches (7 vs. 3.8).
AEs were most common in the population of patients with impaired renal function.

Severe adverse events

In the phase II study, the percentage of patients who had at least one severe AE increased with the dose of fampridine: 17.3%, 24.0% and 29.58% on 10, 15 and 20 mg b.d. respectively versus 14.9% in the placebo group.
Some severe AEs were reported in the 10 mg b.d. group: diarrhoea (3.8%), asthenia (5.8%), fatigue (5.8%), urinary tract infection (1.9%) and falls/contusions (1.9%). Severe neurological disorders seemed to increase with the dose (confusion, balance disorder, delirium, seizure, abnormal coordination, headaches, hypoaesthesia, paraesthesia, migraine, MS relapse, transitory ischaemia).
The pooled data from the MS-F202/203/204 studies showed that the frequency of severe AEs such as anxiety (0.3%), asthenia (1.8%), balance disorder (0.5%), dizziness (0.3%), headache (0.8%) and urinary tract infection (1.0%) occurring on fampridine 10 mg b.d. was greater than that observed on placebo.

Treatment-related adverse events

In the phase II study, the incidence of treatment-related AEs was 42.3% in the fampridine 10 mg b.d. group and 36.2% in the placebo group; this incidence increased with the dose (48.0% and 54.4% for 15 mg and 20 mg b.d. respectively).
The pooled data from the MS-F202/203/204 studies showed that these adverse events had a frequency of 27.8% on fampridine 10 mg b.d. and 21.4% on placebo. Some adverse effects occurred twice as frequently on fampridine as on placebo: nausea (3.3% vs. 1.3%), asthenia (2.8% vs. 1.3%), balance disorder (2.3% vs. 0.4%), headache (2.8% vs. 0.8%) and paraesthesia (2.8% vs. 0.8%).

Serious adverse events – Death – Other significant events

The frequency of serious adverse events (SAEs) observed during the phase II study increased with the dose: 4.3% (placebo), 0.0% (10 mg b.d.), 8.0% (15 mg b.d.) and 12.3% (20 mg b.d.). The most common type of SAE was neurological: 0% (placebo), 0% (10 mg b.d.), 4% (15 mg b.d.) and 10.5% (20 mg b.d.).
Pooled data from the MS-F202/203/204 studies showed that SAEs were more frequent in the fampridine group (5.5%) than in the placebo group: infections (2.3% vs. 0.8%) including pyelonephritis, influenza, pneumonia, sepsis, urinary tract infection, viral infection; neurological disorders; injuries/poisoning/medical or surgical complications.
Eight deaths considered not to be treatment-related were reported during the extension studies: 7 patients receiving fampridine 10 mg b.d. and one patient receiving fampridine 15 mg b.d.: suicide (2), accidental oxycodone overdose (1), intracranial haemorrhage (2), cerebral

aneurysm (1), aortic dissection (1), ischaemic heart disease (1), unknown cause (1). For the last two events and the depression that led to the suicides, a link with the use of fampridine cannot be ruled out. One patient died 5 weeks after the last dose.

Cardiovascular disorders were slightly more common on fampridine (3.0%) than on placebo (1.3%). Bundle branch block, tachycardia and palpitations were reported slightly more frequently on fampridine than on placebo.

MS-F202, MS-F203 and MS-F204 extension studies

In total, 660 patients started or continued open-label treatment with fampridine 10 mg b.d.; 464 were receiving treatment at the time of data analysis (30 November 2008) and 303 had been taking fampridine for at least 2 years.

The incidence of AEs was 83% in the first 6 months of follow-up and 40 to 67% between 6 and 54 months. The incidence of SAEs varied between 1.6% and 9.6%. Nausea, asthenia, back pain, headaches, dizziness and insomnia were more frequent during the first 6 months. The incidence of urinary tract infections (31%) remained relatively stable during the follow-up period. Thirty-four SAEs were reported, including massive pulmonary embolism, tuberculosis, splenic rupture, septic shock, acute kidney failure, accidental overdose and suicide. Cardiovascular disorders were reported in 2% of patients in the first 6 months and was still observed after 48 weeks of treatment.

During these extension studies, 3 patients in the MS-F202 study receiving fampridine 15 mg b.d. (2 patients) and fampridine 10 mg b.d. (1 patient) and 4 patients in the MS-F203 study receiving fampridine 10 mg b.d. had convulsions. Four of the five patients treated with fampridine 10 mg b.d. had a generalised seizure.

Gastrointestinal symptoms (constipation, diarrhoea and nausea), fatigue and asthenia were common in the first 6 months of treatment.

Infections, primarily upper respiratory and urinary tract infections, were also frequently observed. Likewise, falls, dizziness and balance disorders were relatively common. Paraesthesia, tremor, hypoaesthesia and headaches were noted. Insomnia frequently developed in the first 6 months of treatment.

Laboratory parameters

During the controlled studies and extension studies, low values of some haematology parameters were observed: haematocrit (6.6%), haemoglobin (4.0%), lymphocytes (5.2%) and white blood cells (3.4%). Lymphocytopaenia was reported more frequently on fampridine (4.5%) than on placebo (2.2%).

b. Pharmacovigilance data (USA, Germany)[1]

This product was marketed in the USA under the name AMPYRA (dalfampridine) in March 2010. On 22 October 2011, the population exposed to the drug was estimated to be 47,800 patients, or around 26,700 patient-years. In Europe, around 3,000 patients have been exposed to the product since its launch in Germany in September 2011. In total, 12,331 adverse events have been reported. The 507 serious cases reported included 1,212 events.

Ninety-five cases of seizures were reported by healthcare professionals. Concomitant treatment that could lower the seizure threshold was reported in 50 of these cases. The incidence was estimated to be 3.5/1,000 patient-years. The events most frequently reported by healthcare professionals were: dizziness, balance disorders, seizures, insomnia, nausea, headaches, fatigue and walking difficulties.

1 Data provided by the pharmaceutical company

3.2. Conclusion

a. Efficacy

Two randomised double-blind trials compared fampridine (10 mg b.d.) to placebo for a period of 14 weeks in the MS-F203 study (n=301) and 9 weeks in the MS-F204 study (n=239) in patients with clinically defined MS according to the McDonald criteria, who had not had a relapse in the 2 months preceding inclusion or any change to their disease-modifying treatment in the 30 days preceding inclusion. Patients with a history of epilepsy were excluded.

The median EDSS score of these patients on inclusion was 6. Sixty to 70% of patients were taking immunomodulators (INF or glatiramer acetate). No information was provided about the impairments causing walking disability, or physiotherapy and associated measures that could affect patients' ability to walk.

The primary efficacy endpoint of these two phase III studies was the percentage of responder patients on the Timed 25-Foot Walk, a timed walking test over a distance of 25 feet (7.6 m); a responder patient was defined as one with an increased walking speed on at least 3 of the 4 assessments performed during the double-blind treatment period, in comparison with the maximum speed obtained during the 4 pre-treatment visits or the first post-treatment follow-up visit.

The percentage of responder patients was higher on fampridine than on placebo: 34.8% versus 8.3%, i.e. a difference of 26.5% (16.0; 34.3) in the MS-F203 study; 42.9% versus 9.3%, i.e. a difference of 33.5% (22.7; 43.3) in the MS-F204 study. The increase in walking speed over 25 feet observed on fampridine (0.3 feet/sec) was greater than that observed on placebo (0.1 to 0.2 feet/sec), but the gain was minimal and was only observed in a sub-group of patients; the identification of these patients as "responder" after 2 weeks of treatment has yet to be validated. The changes observed in secondary endpoints (MSWS-12, LEMMT, Ashworth Spasticity Examination) were not clinically relevant.

The clinical relevance of the primary efficacy endpoint of these two studies is debatable. An improvement in walking speed over the limited distance of 25 feet is not sufficient to demonstrate an improvement in walking disability. Other locomotor aspects, in particular balance, endurance and walking distance, contribute to patients' walking ability and were not measured; it is not always desirable to increase patients' walking speed, especially if certain impairments are present, such as cerebellar syndrome. The impact of fampridine treatment on walking disability measured using other quantitative scales that assess locomotor function, as well as on limitations of daily living activities, has yet to be studied.

The CHMP felt that additional efficacy data were necessary to assess the benefit of fampridine on walking ability and that the validity of the criteria proposed for identifying responder patients had not been demonstrated. The CHMP therefore asked the pharmaceutical company to conduct a new double-blind, placebo-controlled study in order to assess the long-term efficacy and safety of the product using the most relevant clinical criteria in terms of walking ability, and also to identify treatment responders early so that treatment may be continued (report expected by 30 June 2016).

b. Safety

During placebo-controlled studies, the percentages of treatment discontinuation due to adverse events (1.8% vs. 0.4%), patients who had at least one AE (82% vs. 71%) and patients who had an SAE (4.7% vs. 1.7%) were higher on fampridine 10 mg B.D.. than on placebo; this was also the case for neurological (28.8% vs. 21.4%) and psychiatric (12.3% vs. 5.5%) adverse effects, infections (31% vs. 24.8%), in particular urinary tract infections (12% vs. 8.4%), and gastrointestinal symptoms (18.5% vs. 16%), in particular nausea (7% vs. 2.5%).

Neurological and psychiatric adverse effects (headaches, balance disorders, insomnia, asthenia, paraesthesia) were the most common adverse effects observed on fampridine. The

risk of seizures is the most worrying. This dose-dependent adverse effect, with an estimated incidence of 3.5/1,000 patient-years, reduces the product's therapeutic index.

Studies are being arranged through the EU Risk Management Plan to assess fampridine's safety, in particular to quantify the risk of seizures and to clarify the effects of the product in patients with cardiovascular disease or renal impairment. A register of pregnancies occurring on treatment is planned to be created.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Multiple sclerosis is a disabling, progressive, chronic neurological disorder. It causes multiple impairments that vary according to the course of the disease and between individuals: motor and sensory disorders, sensory impairments, bladder and sphincter dysfunction, sexual dysfunction, cognitive and mood disorders. These may considerably reduce patients' independence and affect their quality of life. The severity of the disease varies greatly, from benign forms that are not very disabling to severe forms leading to significant handicap within a few years.

FAMPYRA is intended as symptomatic treatment for walking disability in patients with MS.

The efficacy/safety ratio for this medicinal product is yet to be established.

Treatments (drugs or other therapy) intended to reduce spasticity, pain and/or fatigue can contribute to improving the limited walking ability of patients with MS.

Public health benefit:

Multiple sclerosis (MS) currently affects between 70,000 and 90,000 patients in France, with a probable annual incidence of 4 to 6 per 100,000 inhabitants[1], and is the leading non-traumatic cause of severe acquired disability in young people. The severity of the disease lies in the disabilities it causes, their effect on quality of life and their socioeconomic impact. The public health burden of MS is considered to be moderate, including the subpopulation of patients for whom FAMPYRA is indicated.

Reducing the functional limitations caused by multiple sclerosis, and improving the quality of life of patients with the disease, is a public health need which is an established priority (objective 65 of the Law of 9 August 2004 on public health policy, *Plan sur l'amélioration de la qualité de vie des patients atteints de maladies chroniques* [Plan for improving the quality of life of patients with chronic illness] 2007-2011).

Taking into account the results of two phase III, randomised, double-blind, placebo-controlled studies, with an endpoint based on speed in a walking test over a very limited distance of uncertain clinical relevance, the impact of FAMPYRA on the quality of life of patients treated and on reducing their level of disability (especially as regards walking ability) has not been demonstrated. FAMPYRA has no impact on healthcare organization.

Furthermore, the applicability of these results in current practice is uncertain, in particular because patients included in the trials were selected according to their ability to perform two walking tests with a mean speed of 8 to 45 seconds, because of the exclusion criteria used and because compliance may not be optimal especially as a result of safety.

FAMPYRA therefore does not meet an identified public health need.

Consequently, FAMPYRA is not expected to benefit public health in this indication.

1 *Guide affection longue durée* [Long-Term Illness Guide] – HAS – September 2006

Despite the insufficiency of the efficacy data presented, the actual benefit of FAMPYRA is low, taking into account the limitations of oral symptomatic treatments used in this indication. This is a conditional actual benefit, subject to reassessment of the efficacy/safety ratio of the product by the Committee in 12 months (from the date of inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use), especially as regards pharmacovigilance data for the proprietary medicinal product.

4.2. Improvement in actual benefit (IAB)

Taking into account the weak efficacy data for fampridine and the product's narrow therapeutic index, the Transparency Committee considers that FAMPYRA offers no improvement in actual benefit (IAB V) in the treatment of walking disability in patients with MS.

4.3. Therapeutic use

Multiple sclerosis is a disabling, progressive, chronic neurological disorder. Its general course and prognosis vary and are considered to be unpredictable.
In 85% of cases, the disease starts with a relapse followed by remission (relapsing-remitting forms), and it progresses gradually with or without additional relapses in the remaining 15% of cases (primary progressive forms). The median time to onset of secondary progression after an initial relapsing-remitting form is estimated to be between 15 and 19 years, depending on the series.
High-dose corticosteroids can speed up recovery from a relapse. The existing disease-modifying treatments (immunomodulators, immunosuppressants) are essentially active on inflammatory phenomena and can reduce the frequency of relapses. These aim to stabilise the disease and slow the progression of disability. Symptomatic treatment of the disease is usually based on specific and multidisciplinary management (physiotherapy, functional rehabilitation, psychological support, occupational therapy, nursing care, etc.) combining medicinal products and rehabilitation techniques that can improve the patient's quality of life by limiting complications from the disease.

Motor disorders are related to pyramidal damage with loss of muscle strength and spasticity. This can affect the lower and/or upper limbs. Progressive spastic paraparesis, corresponding clinically to the progressive onset of walking disability, is common. This motor difficulty may be accompanied by loss of deep sensation in the lower limbs, as well as by coordination problems with ataxia. The whole range of symptoms is often aggravated by the existence of chronic fatigue. Loss of superficial sensation and the presence of paraesthesia/dysaesthesia or even pain may be associated with these motor disorders.

Deterioration in walking ability is one of the main limitations of activity observed in patients and has an impact on independence and daily living. It is one of the main indicators that the disease has progressed, and its impact on functioning is a major criterion in the EDSS.

The main treatment for walking disability is rehabilitative treatment, especially individual physiotherapy, in response to a detailed analysis of the impairments causing locomotor disability. Different physiotherapy techniques (isokinetic muscle-strengthening exercises, combined exercises for strengthening muscles against resistance, balancing and improving aerobic capacity, functional electrical stimulation of the foot levator muscles, specific programmes for improving walking pattern or even computer-assisted training, etc.) have been shown to be of value, including in terms of improving walking speed.
Irritative spines that could aggravate spasticity need to be prevented and treated. Cold physiotherapy may be offered to patients who are sensitive to heat.
Walking disability in MS can also benefit from drug treatments. Oral anti-spasticity drugs may be prescribed. Botulinum toxin injections, intrathecal baclofen pump implantation or neurosurgery may be indicated in cases of severe spasticity. The prescription of an analgesic may be required.

Treatment with FAMPYRA should only be considered in association with an appropriate rehabilitation programme, which should be implemented without delay, as well as physical walking aids or specific treatments such as anti–spasticity drugs.

4.4. Target population[1]

The prevalence of patients with MS, assessed in several regions of France, is currently more than 100/100,000 inhabitants, i.e. 60,000 to 65,000 patients.
In large series of patients, it is estimated that half of patients will have some difficulty walking after 8 years of the disease, requiring a walking stick after 15 years and a wheelchair after 30 years. So-called "benign" forms, defined as those where there is no disability after 15 years of the disease, affect 25% of patients. However, these initially favourable forms may worsen later. In contrast to these benign forms, very severe MS leading to rapid disability occurs in 10% of cases.

In June 2010, 1,664 patients in the EDMUS database[2] had received a clinical assessment in the last 24 months. Sixty-one percent of these patients had an EDSS between 4 and 7. According to these data and the product's indication, the number of patients who could receive this treatment for at least 2 weeks is around 39,000.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

In view of the conditional actual benefit of FAMPYRA, the Transparency Committee wishes to have access to additional data allowing the efficacy/safety ratio of FAMPYRA to be reassessed in 12 months, and in particular pharmacovigilance data for the proprietary medicinal product.

4.5.1 Packaging

Appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 15%

1 *Livre blanc de la Sclérose en plaques* [White paper on multiple sclerosis] – *Comité de Pilotage des Etats Généraux de la Sclérose en plaques* [Steering Committee of the General Assembly for Multiple Sclerosis] – April 2006

2 Via the EDMUS (European Database for Multiple Sclerosis) software developed at the EDMUS Coordination Centre in Lyons