CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-250s000

SUMMARY REVIEW

MEMORANDUM

DATE: January 18, 2010

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-250

SUBJECT: Action Memo for NDA 22-250, for the use of Amaya (dalfampridine) for the treatment of patients with Multiple Sclerosis (MS) for the improvement of walking ability

NDA 22-250, for the use of Amaya (dalfampridine), also known as 4-aminopyridine, a potassium channel blocker believed to improve neuronal transmission, for the treatment of patients with Multiple Sclerosis (MS) for the improvement of walking ability, was submitted by Acorda Therapeutics on 4/22/09. The application contains the results of two definitive randomized placebo controlled studies, as well as the results of another, more preliminary controlled trial. The application also contains the requisite pharmacokinetic, chemistry, non-clinical, and other data.

The application has been reviewed by Dr. Kachikwu Illoh, medical officer, Dr. Sharon Yan, statistician, Dr. Gerard Boehm, safety team reviewer, Dr. Lyudmila Soldatova, chemist, Dr. Richard Houghtling, pharmacologist, Dr. Lois Freed, supervisory pharmacologist, Drs. Jagen Parepally and Joo-Yeon Lee, Office of Clinical Pharmacology, Dr. Lyudmila Soldatova, chemist, Drs. Chad Reissig and Lori Love, Controlled Substances Staff, Jeanine Best, Maternal Health Team, Todd Bridges, DMEPA, Laurie Kelley, Office of Surveillance and Epidemiology, Kate Henrich, Suzanne Robottom, and Amy Toscano, REMS, and Dr. Eric Bastings, deputy director. In this memo, I will briefly review the relevant data, and offer the division's recommendation for action on this application.

Effectiveness

As noted above, the sponsor has submitted the results of a preliminary dose finding study, and the results of two definitive controlled trials, in which fampridine 10 mg BID has been compared to placebo.

Study 203

This was 21 week study in which patients with MS of any kind with walking difficulties were randomized to receive fampridine 10 mg BID or placebo. The study consisted of a 1 week post-screening phase, a 2 week placebo, single blind phase, a 14 week double-blind randomized phase, and a 4 week post-treatment follow-up phase.

The primary outcome measure was based on the Timed 25 Foot Walk, which was assessed twice at each assessment (described in the next sentence), in seconds, using a stopwatch. In this study, this test (along with others) was performed at the screening visit, at the beginning of the single blind placebo phase, and then again at one week into the placebo phase. They were again assessed at week 2 of the placebo phase, and at that point randomized to double-blind treatment. The Timed Walk was assessed at 4 times during the 14 week treatment phase (including at the last double-blind visit), and then again at 2 and 4 weeks post-treatment. The score for each visit was the average of the two assessments at that visit.

The primary outcome was a comparison of the proportion of Responders in the treated compared to the placebo group. A Responder was defined as a patient with a faster walking speed at at least 3 of the 4 on-treatment assessments than any of the off-treatment assessments (the 4 pre-treatment assessments and the first post-treatment assessment).

In order to determine if the difference in proportion of responders on this novel endpoint measured a clinically meaningful outcome, the protocol also required that the Responders had to have done significantly better on the MSWS-12 score (Multiple Sclerosis Walking Scale). This is a 12 question instrument that asks patients to rate their disability during the previous 2 weeks on a 5 point scale (1=not at all to 5=extremely).

Finally, in order to assure that any treatment effect was not waning over time, the protocol required that responders would still have to show a significant improvement in walking speed compared to placebo at the last double-blind visit.

In effect, then, the primary outcome consisted of a three-part as described above.

Several other outcomes were assessed, including the Lower Extremity Manual Muscle Test (LEMMT), the Ashworth Spasticity Scale, CGI (clinician's global impression of change) and SGI (subject global impression of change).

The LEMMT rated 4 groups of lower extremity muscles, each from 0 (no movement) to 5 (normal). The Ashworth averaged spasticity ratings (0-4) for three muscle groups). The SGI asked patients to rate the effects of the medication over the previous 7 days on a scale from 0 (terrible) to 7 (delighted). Physicians who rated the CGI were also aware of the results on the primary outcome, and so the results on this scale do not provide an independent assessment of the patient's overall functioning.

Results

A total of 301 patients were randomized in a 3:1 ratio (229 on fampridine, 72 on placebo). A total of 17 patients withdrew from the fampridine group (11 AEs, 4 withdrew consent, 2 for "other" reasons), and one withdrew from the placebo group. A total of 5 fampridine patients withdrew prior to completing any double-blind walking tests, and were not included in the primary analysis of the ITT population.

A total of 78/224 (34.8%) fampridine treated patients met Responder criteria, compared to 6/72 (8.3%) of the placebo patients; p<0.0001.

The mean reduction from baseline in the MSWS-12 in the responders (N=84; 78 + 6) was 6.8, compared to an increase in the non-responders of 0.05; p=0.0002.

The mean change in walking speed from baseline to last double-blind visit was as follows for the respective groups:

Fampridine Responders	0.52 feet/sec
Fampridine Non-Responders	0.17 feet/sec
Placebo	0.10 feet/sec

The difference between the fampridine responders and placebo patients was significant (p<0.001). The difference between the fampridine Non-Responders and placebo patients was not significant (p=0.5), and the difference between fampridine Responders and fampridine Non-Responders was significant (p<0.001).

Agency reviewers conducted several additional analyses.

Of considerable importance was an analysis of the simple change in walking speed from baseline (last pre-treatment assessment) to last double-blind assessment for both treatment groups (independent of responder status). The following chart displays these results:

	Walking Speed (Ft/Sec)	
	Placebo (N=71)	Fampridine (N=222)
Baseline	2.11	2.13
Last On-Tx visit	2.16	2.34
Change	.05	.21
P-value		0.034

For the 25 foot Timed Walk, this difference translates to a total walking time of:

	Total Walking Time (Sec)	
	Placebo (N=71)	Fampridine (N=222)
Baseline	11.79	11.68
Last On-Tx visit	11.52	10.55

The difference between the change from baseline between the treatment groups was less than 1 sec.

The following chart displays the change in walking speed (baseline to last on-tx visit) for the responders and non-responders in each group:

	Walking Speed (Ft/Sec)			
	Pla Resp (N=6)	Pla NR (N=65)	Fam Res	Fam NR
Baseline	2.18	2.11	2.21	2.10
Last On-Tx visit	2.58	2.14	2.60	2.23
Change	.40	.03	.39	.13

Interestingly, the baseline walking speed for both the placebo and fampridine responders was faster than that for the placebo and fampridine non-responders.

The following chart displays the change in walking speed for the total Responders and Non-Responders:

	Walking Speed (Ft/Sec)	
	Responder (N=84)	Non-Responders (N=212)
Baseline	2.21	2.11
Last On-Tx visit	2.60	2.20
Change	.39	.09

Additional similar analyses were also performed for the MSWS-12.

The mean change from baseline to last on-treatment visit was -1.56 for the total fampridine group and +3.59 for the total placebo group (p=0.063).

The following chart displays the results for the Responder and Non-Responder groups within each treatment, and overall:

MSWS-12

	Pla Resp (N=6)	Pla NR (N=65)	Fam Res (n=77)	Fam NR (n=136)
Baseline	57.99	67.85	67.86	69.56
Last On-Tx visit	50.00	74.12	64.29	72.11
Change	-7.99	+6.27	-3.57	+2.55

MSWS-12

	Responder (N=84)	Non-Responders (N=212)
Baseline	67.15	69.03
Last On-Tx visit	63.25	72.75
Change	-3.90	+3.72

The following charts (taken from Dr. Yan's Table 4, page 14), displays the results for the LEMMT and Ashworth:

Mean Change from Baseline in LEMMT Scores

			Famp Responders	
	Placebo	Famp	Responders	Non-Responders
Baseline	3.97	4.06		
	0.04	0.13	0.18	0.11
		P=0.0029*	p=0.0002*	p=0.02*

* P-values based on comparison to Placebo group

Mean Change from Baseline in Ashworth Scores

			Famp Responders	
	Placebo	Famp	Responders	Non-Responders
Baseline	0.95	0.90		
	-0.07	-0.16	-0.13	-0.17
		P=0.02*	p=0.09*	p=0.02*

* P-values based on comparison to placebo group

Study 204

This was a study very similar in design to Study 203, with similar end-points, except the double-blind treatment period was only 9 weeks long and patients were randomized in a 1:1 ratio.

Results

A total of 239 patients were randomized to fampridine (N=120) and placebo (N=119) at 39 centers in the US and Canada. A total of 5 placebo patients and 7 fampridine patients withdrew prior to completing the study, and one patient from each group did not have any scheduled on-treatment assessments.

A total of 51/119 (43%) of fampridine patients met Responder criteria compared to 11/118 (9.3%) of placebo patients ($p<0.001$).

The mean reduction from baseline in the MSWS-12 in the responders (N=62; 51 + 11) was 6.04, compared to an increase in the non-responders of 0.85; $p<0.001$).

The mean change in walking speed from baseline to last double-blind visit was as follows for the respective groups:

Fampridine Responders	0.56 feet/sec
Fampridine Non-Responders	0.10 feet/sec
Placebo	0.19 feet/sec

The difference between the fampridine responders and placebo patients was significant ($p<0.001$). The difference between the fampridine Non-Responders

and placebo patients was not significant, and the difference between fampridine Responders and fampridine Non-Responders was significant ($p<0.001$).

Agency reviewers conducted several additional analyses.

Of considerable importance was an analysis of the simple change in walking speed from baseline (last pre-treatment assessment) to last double-blind assessment for both treatment groups (independent of responder status). The following chart displays these results:

	Walking Speed (Ft/Sec)	
	Placebo (N=118)	Fampridine (N=117)
Baseline	2.28	2.22
Last On-Tx visit	2.39	2.44
Change	.11	.22
P-value		0.034

For the 25 foot Timed Walk, this difference translates to a total walking time of:

	Total Walking Time (Sec)	
	Placebo (N=118)	Fampridine (N=117)
Baseline	10.96	11.31
Last On-Tx visit	10.42	10.25

The difference between the change from baseline between the treatment groups was less than 1 sec.

The following chart displays the change in walking speed (baseline to last on-tx visit) for the responders and non-responders in each group:

Walking Speed (Ft/Sec)

	Pla Resp (N=11)	Pla NR (N=106)	Fam Res	Fam NR
Baseline	2.25	2.28	2.30	2.14
Last On-Tx visit	2.76	2.36	2.73	2.21
Change	.51	.08	.43	.07

The following chart displays the change in walking speed for the total Responders and Non-Responders:

Walking Speed (Ft/Sec)

	Responder (N=62)	Non-Responders (N=212)
Baseline	2.29	2.23
Last On-Tx visit	2.73	2.30
Change	.44	.07

Additional similar analyses were also performed for the MSWS-12.

The mean change from baseline to last on-treatment visit was -3.12 for the total fampridine group and +0.72 for the total placebo group (p=0.026).

The following chart displays the results for the Responder and Non-Responder groups within each treatment, and overall:

MSWS-12

	Pla Resp (N=11)	Pla NR (N=102)	Fam Res (n=51)	Fam NR (n=63)
Baseline	75.38	66.72	71.04	74.94
Last On-Tx visit	73.30	67.85	65.69	73.91
Change	-2.08	+1.13	-5.35	-1.03

	MSWS-12	
	Responder (N=62)	Non-Responders (N=165)
Baseline	71.81	69.93
Last On-Tx visit	67.04	70.16
Change	-4.77	+0.23

Mean Change from Baseline in LEMMT Scores

			Famp Responders	
	Placebo	Famp	Responders	Non-Responders
Baseline	3.96	3.91		
	0.04	0.09	0.14	0.05
		P=0.11*	p=0.028*	p=0.6*

* P-values based on comparison to placebo group

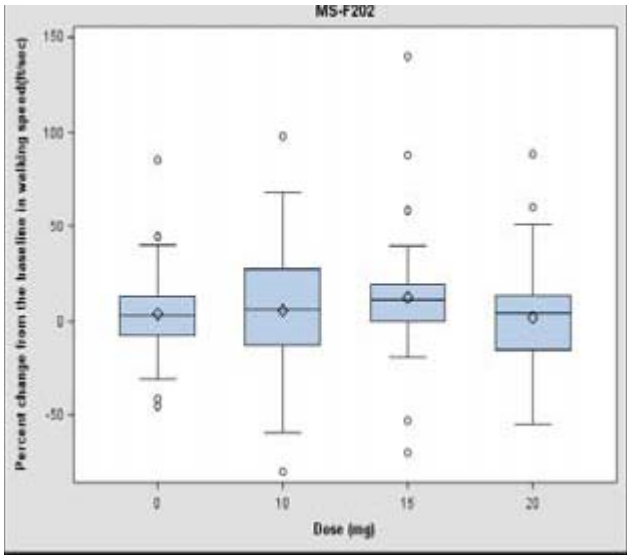
Mean Change from Baseline in Ashworth Scores

			Famp Responders	
	Placebo	Famp	Responders	Non-Responders
Baseline	0.8	0.91		
	-0.07	-0.16	-0.13	-0.17
		P=0.02*	p=0.09*	p=0.02*

* P-values based on comparison to placebo group

Study 202

As noted above, the sponsor also performed a study in which they compared fampridine 10, 15, and 20 mg BID in a similar population. The total study duration was 20 weeks, with a double blind phase of 15 weeks. In that study, the primary outcome was the change from baseline in the average Timed 25 Foot Walk. A total of 206 patients were randomized (fampridine 10 mg BID-52; fampridine 15 mg BID-50; fampridine 20 mg BID-57; placebo-47). There were no statistically significant differences between any dose and placebo. Independent analyses by Dr. Joo-Yeon Lee of Pharmacometrics has shown no dose response in the range studied for the percent change from baseline in walking speed (see her review, Figures 7 and 8, page 15):



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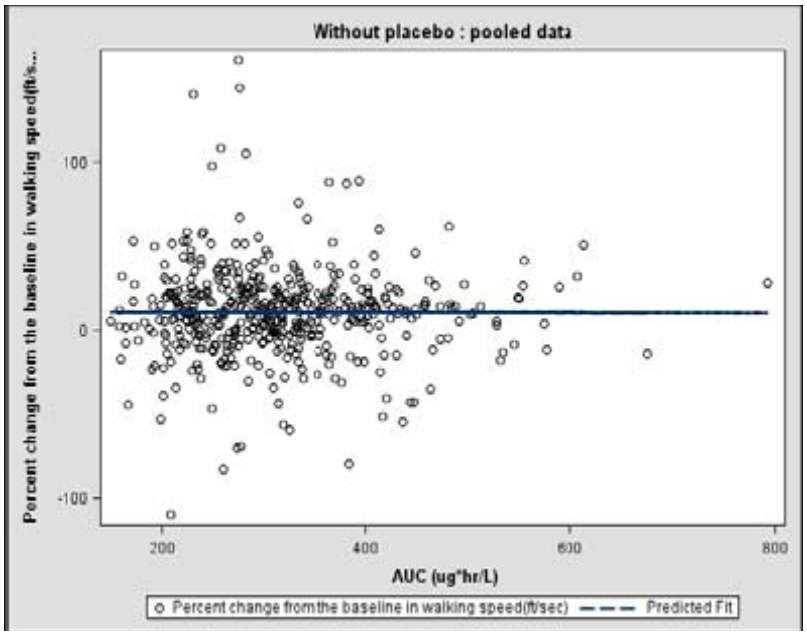


SAFETY

Fampridine has been studied in numerous formulations, including immediate release formulations, and controlled release formulations, including the to-be-marketed SR formulation.

A total of 1922 subjects/patients received at least one dose of some formulation of fampridine. A total of 1510 patients with either MS or Spinal Cord Injury (SCI) received at least one dose of some formulation (N=917 with MS and 583 with SCI), and a total of 1621 subjects/patients were exposed to at least one dose of fampridine SR, the formulation of interest. Of these, 807 had MS.

A total of 780 patients received fampridine SR for at least 6 months (601 with MS) and 444 patients received fampridine SR for at least one year (405 with MS).

A total of 200 patients were exposed to 10 mg BID for between 24 and 48 weeks (all with MS), and a total of 329 patients were exposed to 10 mg BID for at least 96 weeks (all with MS).

Deaths

There were a total of 7 deaths that occurred either while on treatment or within 30 days of discontinuation of treatment (6 MS, 1 SCI). The MS deaths all occurred during open-label extension treatment.

Dr. Boehm describes these deaths in detail in his review (see pages 16-18). In brief:

1) a 57 year old woman on 10 mg BID for about 3 years found in bed lethargic and then unresponsive. Autopsy demonstrated death due to accidental oxycodone overdose.
2) A 58 year old woman who discontinued fampridine 15 mg BID after 3 weeks with neck pain. She died of a ruptured aortic dissection.
3) 65 year old man on 10 mg BID committed suicide.
4) A 45 year old woman treated with 10 mg BID for over 2 years found dead in bed. She was on multiple medicines, but no autopsy was performed, and no cause of death was noted.
5) A 51 year old man treated with 10 mg BID for over one year who was brought to the ER after a single dose of alprotadil for impotence. He was shown to have had a major CNS hemorrhage.
6) A 68 year old woman treated with 10 mg BID for over 4 years died of an intracranial hemorrhage.

A single death occurred in a 57 year old man with SCI who had been treated with 40 mg BID. He was found dead on the floor, having fallen out of his wheelchair and been the victim of a compressed airway and positional asphyxia.

There was a death in a fampridine treated patients 5 weeks after his last dose (52 year old man; cause of death ischemic heart disease), and in a single placebo patient (cause of death morphine intoxication).

Serious Adverse Events (SAE)

A total of 33/507 (6.5%) of fampridine-treated MS patients experienced at least one SAE in controlled trials compared to 5/238 (2.1%) of placebo MS patients. MS Relapse was the only SAE that occurred in more than 2 fampridine-treated patients (N=4 [1.4%]; 0 placebo patients).

In MS controlled and uncontrolled studies, 177/917 (19.3%) of patients experienced at least one SAE. Events experienced by more than 3 patients were MS Relapse (N=38 [4.1%]), convulsion, UTI (N=13 each [1.4%]), cellulitis (N=11 [1.2%]), pneumonia (N=10 [1.1%]), and sepsis (N=7 [0.8%]). A total of 3 (0.3$) patients experienced complex partial seizures. The occurrence of seizures will be discussed separately.

In MS and SCI controlled and uncontrolled trials, 228/1510 (15.1%) of patients experienced at least one SAE. The most frequent was MS Relapse (N=38 [2.5%]), followed by Convulsion (N=19 [1.3%]), UTI (1.2%), and Cellulitis (1.1%). See Dr. Boehm's Table on page 19 of his review for a more complete listing of SAEs seen in this population.

As he notes, two patients experienced an SAE of potential interest:

1) a 45 year old man with SCI treated with fampridine for 2 months was noted to have a WBC of 3.45 k/mm3 (baseline 7.48), hemoglobin of 12.8 g/dL (baseline 14.4), and a platelet count of 193 k/mm3 (baseline 202). The drug was stopped and the patient was diagnosed with pancytopenia (preceded by a GI illness with diarrhea). Repeat labs one week later showed values returned to baseline.
2) A 47 year old man diagnosed with acute pancreatitis secondary to cholelithiasis. He underwent a cholecystectomy and the event resolved and the drug was discontinued.

Three patients were reported to have experienced encephalopathy, but, as described by Dr. Boehm (page 20) none can reasonably be considered to have been related to treatment with fampridine.

Dr. Boehm also discusses three patients reported to have had anemia. One had a significant drop in hemoglobin (from previous on-treatment values of about 12 g/dL after at least 119 days on drug to about 5.9 g/dL, which was attributed to a GI bleed. The anemia reported for the two other patients was not reasonably related to treatment with fampridine.

Discontinuations

MS Controlled Trials

A total of 17/507 (3.4%) of fampridine-treated MS patients and 5/238 (2.1%) of placebo patients discontinued treatment in MS controlled trials due to an AE. As described by Dr. Boehm, events that occurred in at least 2 fampridine-treated patients and more frequently than in the placebo group were as follows:

Event	Fampridine (N=507)	Placebo (N=238)
Headache	0.8%	0
Balance Disorder	0.6%	0
Dizziness	0.6%	0
Confusional state	0.4%	0

One fampridine patient (0 Placebo) discontinued because of convulsions.

MS Controlled and Uncontrolled Trials

A total of 102/917 (11%) of MS patients discontinued due to one or more AEs.

The following chart displays those events that occurred in at least 3 MS fampridine-treated patients:

Event	Fampridine (N=917)
Convulsion	13 (1.4%)
Balance Disorder	8 (0.9%)
Dizziness	7 (0.8%)
Asthenia	6 (0.7%)
Paresthesia	5 (0.5%)
Trigeminal Neuralgia	5 (0.5%)
Headache	5 (0.5%)
Confusional state	5 (0.5%)
MS Relapse	4 (0.4%)
Fatigue	4 (0.4%)
Nausea	4 (0.4%)
Anxiety	4 (0.4%)

Three patients discontinued because of complex partial seizures.

Dr. Boehm's Table on pages 23-4 lists those events that resulted in discontinuation of treatment in the combined MS and SCI controlled and uncontrolled populations (N=1510). Those events that occurred in at least 1% of patients were:

Event	Pooled MS and SCI patients (N=1510)
Dizziness	38 (2.5%)
Insomnia	22 (1.5%)
Convulsion	19 (1.3%)
Asthenia	19 (1.3%)
Nausea	17 (1.1%)
Anxiety	17 (1.1%)

Dr. Boehm describes several patients who had AEs of interest that led to discontinuation of treatment:

1) A 48 year old man discontinued fampridine because of a macular rash on his forehead. According to the narrative, at 13 months of treatment he developed a macular rash on his forehead, and then about 8 months later he was treated with topical hydrocortisone for 3 months, and the rash persisted

2) A 33 year old man who was reported to have discontinued due to rib pain and "increased hypersensitivity" that the investigator rated as Moderate in intensity. It resolved on follow-up.

3) a 69 year old man about 2 months after starting treatment was reported to have had "toxic erythema" on his hands and trunk. Two days later he developed peeling skin on his hands. The drug was stopped, he was treated with corticosteroids, and it resolved a few days later.

Common Adverse Events

The following adverse events were reported in controlled trials of patients with MS that occurred in at least 2% of fampridine treated patients and at least twice as often as in the placebo group. See Dr. Boehm's table, pages 56-7, for a more complete list of common adverse events. Most of the events in the table below were dose related.

Event	Fampridine (N=507)	Placebo (N=238)
Insomnia	10.5%	3.8%
Dizziness	9.5%	4.2%
Headache	8.9%	4.2%
Asthenia	8.7%	4.2%
Nausea	7.7%	2.5%
Balance dis.	6.3%	1.3%
Back pain	5.3%	2.1%
Difficulty walking	2.8%	1.3%
Pharyngeal pain	2.6%	0.8%
Pollakiuria	2.4%	0.8%
Vomiting	2.4%	0.4%
Pyrexia	2.2%	0.8%
Anxiety	2.0%	0.4%
Tremor	2.0%	0%

Dr. Boehm has conducted extensive investigations into several of these adverse events. In particular, a detailed examination of events coded as "dizziness" did not reveal any relationship to changes in blood pressure (as he notes, most of the verbatim terms which were coded to "dizziness" were "dizziness" and "lightheadedness"), the events were transient, there was no increased incidence of syncope, and no clear relationship of falls or balance disorders to events reported as dizziness.

Laboratory Tests

There were no important differences between fampridine and placebo treated

patients in mean laboratory values or in the incidence of outliers on routine laboratory tests. This is true for urinalyses as well (urinary leukocytes), despite the increase in the incidence of UTIs in fampridine, compared to placebo, treated patients.

Vital Signs

There were no systematic differences in vital signs between fampridine and placebo treated patients.

EKG

There were no systematic differences in EKG measures between fampridine and placebo treated patients. A thorough QT study that examined fampridine SR doses up to 30 mg did not reveal any differences between fampridine and placebo patients for which the upper bound of the 90% CI reached 10 msec.

Seizures

As noted earlier, various investigations of different formulations have been studied. Early work with an immediate release formulation in MS patients revealed 6/178 (3.3%) patients had seizures. According to Dr. Boehm, the following events occurred:

One seizure occurred in a patient 22 months after starting 12.5 mg BID.

One event occurred after a second dose of 40 mg BID.

One event occurred after the third dose of 12.5 mg given Q6H.

One event occurred after a dose of 25 mg, given 9 hours after a dose of 12.5 mg that was preceded by a dose of 12.5 mg (total of 3 doses of fampridine).

One event occurred about 10 hours after a dose of 12.5 mg (given BID).

One event occurred about 7 hours after a dose of 17.5 mg (given BID).

Study 201, performed by Acorda, examined doses of 10, 15, 20, 25, 20, 35, and 40 mg BID of the SR formulation. In this study (total N=36), there were a total of 2 convulsions: one at 30 mg BID, and one at 35 mg BID. An inspection of Dr. Boehm's review of these two patients suggests that in neither patient was the evidence strong that a seizure occurred.

In Study 202, 2/57 patients who received 20 mg BID (the highest dose in that study) were reported to have had seizures: one who took an overdose, and had a

complex partial seizure about 8.5 hours after a single dose of 40 mg, and one patient who had a tonic-clonic seizure. The latter seizure occurred about 7.5 hours after dose of 20 mg.

In all controlled trials of MS patients excluding Study 201 (Studies 202, 203, and 204), the following incidence of seizures was reported, as taken from Dr. Boehm's table, page 31 of his review:

Study	Pla	Fam 10	Fam 15	Fam 20	Fam Total
202	0/47	0/52	0/50	3.5% (2/57)	1.3% (2/159)
203	0/72	0.4% (1/228)	----	----	0.4% (1/228)
204	0.8% (1/119)	0/120	----	----	0/120
Total	0.4% (1/238)	0.3% (1/400)	0/50	3.5% (2/57)	0.6% (3/507)
Patient-yrs	1.6/100	0.9/100	0/100	11.8/100	2.1/100

A few points need to be made about these data.

The incidence of seizures at 10 mg BID (the sponsor's proposed dose) is overall the same as for placebo patients (0.3% vs 0.4%, respectively), and the rate at 10 mg BID is less than in the placebo patients (0.9/100 pt-yrs vs 1.6/100 pt-yrs, respectively). The zero rate at 15 mg BID is based on extremely minimal exposure to that dose, and the rate of 11.8/100 pt-yrs at 20 mg BID is also based on very small numbers, and is somewhat misleading, given that one of these seizures occurred after a single dose of 40 mg.

In controlled trials of patients with SCI, there was one fampridine treated patient (0.27%; 1/372) who had a seizure, compared to 0/324 placebo patients. The seizure occurred in a patient receiving 40 mg BID (4.3%; 1/23). No seizures occurred in the other patients in that study: 0/29 at 17.5 mg BID, 0/66 at 20 mg BID, and 0/245 at 25 mg BID.

In open-label MS studies, the following seizure events were reported (taken from Dr. Boehm's table, page 33):

	Fam 10 BID	Fam 15 BID
# of Patients	660	175
Patient-Years	1060	115
Number of patients		
With seizures	5	2
%	0.76%	1.4%
Inc/100 pt-yrs (95% CI)	0.47 (0.15,1.10)	1.7% (0.21, 6.28)

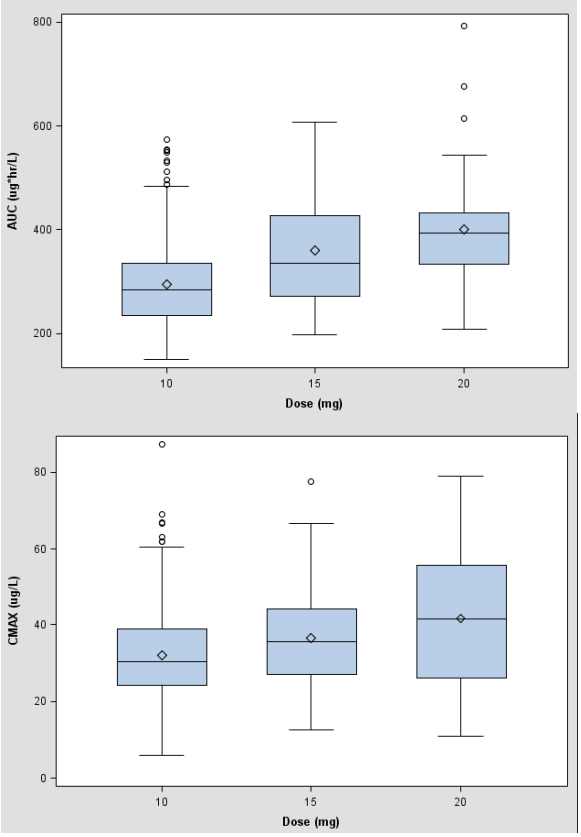
One of the 15 mg BID patients had an EEG that suggested a recent CVA, and an MRI with stable MS lesions and "…2 foci of enhancement with volume loss in the left hemisphere.", according to Dr. Boehm.

Of the 10 mg BID patients, one (a 60 year old woman) was taking concomitant Detrol-LA (tolterodine) 12 mg BID (presumably a high dose) and experienced what appears to have been a generalized tonic clonic seizure. Both drugs were discontinued, and the patients were ultimately re-started on Detrol, after which she experienced another generalized tonic clonic seizure.

The descriptions of the other events suggest that these were seizures, and did not reveal any other obvious causes for seizures.

In open-label SCI studies, 5/354 (1.4%) patients were reported to have experienced a seizure**.** One seizure presumably occurred at a dose of 25 mg BID, one occurred at 30 mg BID, one at 35 mg BID, and 2 at 40 mg BID.

The following charts (taken from Dr. Parapelli's review, page 14/24) display the comparison of the AUC's and Cmax's at 10, 15, and 20 mg BID:



As Drs. Bastings and Boehm note, attempts have been made to correlate seizure occurrence with plasma levels, in particular Cmax. As can be seen in the chart above, the mean Cmax at 10 mg BID is about 30 mcg/ml, at 15 mg BID about 35 mcg/ml, and at 20 mg BID, about 40 mcg/ml, although it is clear that there is considerable overlap in the levels that can be achieved at any of these doses.

Of all of the patients who had seizures, there were only 7 who had plasma levels evaluated, and there were 5 patients who had a seizure in controlled trials in whom plasma level data were obtained. Levels in these patients ranged from 35.5 ng/ml to 117 ng/ml. However, in most of these cases, although the time after dosing was noted, it is not clear what the level was at the time of the seizure, given that the seizure often occurred on a different day than the day on which the level was drawn, it is not known with certainty what dose was actually taken, etc. For these reasons, it is difficult to assess what the plasma levels were at the time of the seizures.

Advisory Committee Meeting

The NDA was presented to the Peripheral and Central Nervous Systems (PCNS) Advisory Committee at a meeting on October 14, 2009. The Committee voted 12-1 that the data provide substantial evidence of effectiveness for fampridine as a treatment to improve walking in patients with MS. Further, they voted 12-1 that the sponsor should evaluate the effectiveness of doses lower than 10 mg BID in controlled trial(s), but voted 11-2 that these studies should not be required prior to approval.

The Committee also voted 10-2 that the sponsor had identified conditions under which the drug could be considered safe, and in the ensuing discussion recommended that the drug should be contraindicated in patients with moderate or severe renal impairment, because these patients would achieve plasma levels associated with a risk for seizures. The Committee also recommended that patients need not be screened with EEG prior to initiating treatment, despite the fact that patients enrolled in the trials were screened with an EEG, and those with evidence of possible seizures were excluded.

Trade name

Late in the review process, it became clear that the established name "fampridine" was very similar (especially in appearance when hand written) to the established name for "famotidine", and that therefore there was a risk for medication errors involving these two drugs. Although famotidine is an over-the-counter (OTC) drug at low doses, higher doses that overlap with the fampridine dose are available by prescription.

For this reason, we asked the sponsor to propose another established name. They have done so, proposing "dalfampridine", which we find acceptable. The sponsor will apply to (b) (4) for the new name to be adopted (although "fampridine" already has USAN approval and is accepted world-wide). The Agency has the authority to adopt a new established name prior to USAN approval, and even in the face of an alternative USAN approved name (as is the case here), if we feel that the USAN approved name poses safety concerns. Given that we do believe the established name "fampridine" does pose a risk for serious medication errors, we will exercise our authority to approve an alternative name (in this case "dalfampridine") in this case.

Pharmacology/Toxicology

As noted by Dr. Freed, Dr. Houghtling recommends that the application not be approved for the following reasons"

1) a potentially genotoxic impurity, (b) (4), has not be adequately evaluated,

2) an impurity, (b) (4), has not been adequately qualified, and
3) the embryo-fetal study in the rat is inadequate

Dr. Freed has addressed these concerns in her cover memo.

In brief, Dr. Freed notes that the sponsor has presented evidence that the (b) (4) impurity is, in fact, a metabolite, but in her view the data are not adequate to address the genotoxic potential of this compound. She therefore recommends that the sponsor test this impurity directly in appropriate in vitro or in vivo genotoxicity assays, or demonstrate that the (b) (4) occurs in either rat or mouse at at least 25 times the human AUC for this moiety. She recommends, however, that this data be acquired post-marketing, given her understanding of the medical utility of this product.

Similarly, she agrees that the evaluation of the potential toxicity of the (b) (4) impurity has not been adequately addressed, though she disagrees with Dr. Houghtling about the specific studies necessary to provide this evaluation. Specifically, she does not agree that a 3 month general toxicity study is needed (the sponsor performed a 28 day study spiked with this impurity and saw no new toxicities). She does believe that an embryofetal study evaluating this impurity should be performed, but that it can be done in Phase 4. Finally, if the sponsor includes a high dose fampridine in this embryo-fetal study in the rat, this will address Dr. Houghtling's third concern.

It should also be noted briefly that originally the division was concerned about the genotoxic potential of 7 impurities, based upon structural alerts. However, as noted by Dr. Freed, the CMC reviewers have determined that for 6 of these impurities (all except the (b) (4) discussed above) the structural alert was based on a moiety shared by all 6 as well as the parent compound itself. Given that fampridine itself was negative in a battery of genotoxicity assays, it is reasonable to conclude that these 6 impurities pose no additional genotoxicity risk.

Comments

In my view, the sponsor has submitted two adequate and well-controlled clinical trials that establish substantial evidence for dalfampridine as a treatment to improve some aspect of walking in patients with MS; the PCNS AC agreed overwhelmingly with this conclusion. Although the mean absolute increase in walking speed was quite small, ancillary evidence suggests that these changes were useful to the patients, including changes in the MSWS-12 (as evidenced by large differences between responders and non-responders, and nominally significant, or near-significant differences between fampridine and placebo responders, although it needs to be noted that these latter comparisons are not based on analyses of randomized groups), LEMMT, and Ashworth scores. Further, an examination of the percent of patients with various percentages of improvement (compared to baseline) on walking speed shows significant

differences between dalfampridine and placebo patients for differences up to 30% change from baseline (see Dr. Bastings's figure 4, page 14 of his memo).

Exactly what aspect of walking has been shown to have been improved, however, is not entirely obvious. The sponsor wishes to indicate dalfampridine to improve walking generally, although the primary data speak directly only to a benefit in walking speed. This issue will be discussed below.

It is also important to point out that the available data establish that there is no evidence that doses greater than 10 mg BID provide any additional benefit. This raises the question, of course, that doses lower than 10 mg BID might be effective; the AC recommended that this question be evaluated in Phase 4, and I believe that this is critical, especially in light of the safety issue described above, and below.

The sponsor has also provided sufficient safety data to support approval; the PCNS AC also clearly agreed with this conclusion.

The primary safety issue, as discussed by the review team, is the potential of dalfampridine to cause seizures. As discussed above and by Drs. Bastings and Boehm, the data suggest that there is no increased risk of seizures at the proposed dose of 10 mg BID, but that the risk does appear, and appear to be dose-related, at doses above 10 mg BID, including at 15 and 10 mg BID. For this reason, the AC recommended that the drug be contraindicated in patients with moderate or severe renal disease, because plasma levels of drug in these patients will be similar to those in normal patients receiving doses greater than 10 mg BID (a lower strength than 10 mg is not available at this time, making dosage adjustment in any population difficult, if not impossible).

I agree, although it should be noted that patients with mild renal impairment are likely to achieve plasma drug levels approximating those associated with 15 mg BID, and associated with an increased risk of seizures. Nonetheless, the AC clearly felt that such patients could be treated with dalfampridine, and in this context it is worth noting that many patients who would otherwise be candidates for treatment with dalfampridine may have some degree of renal impairment, so excluding patients with mild renal impairment could markedly decrease the number of patients who could benefit from treatment.

Regarding the potential for patients to experience seizures, it should also be noted that patients in these studies were screened with EEGs, and those with "evidence" of seizures were excluded. For this reason, it is not known if such patients are at an increased risk for dalfampridine induced seizures compared to "normal" patients. The AC recommended that patients not be screened with EEG before they may be treated with dalfampridine.

A total of about 2-4% of patients screened in the development program were excluded based on EEG findings. I agree that prospective treatment candidates need not be screened with EEG (it can be difficult to know if any changes on EEG are, in fact, seizure-related or artifact), although labeling, of course, should note this.

Recommendations

For the reasons cited above, I believe the NDA should be approved.

I recognize that Dr. Illoh recommends that the application not be approved because he is unconvinced about the clinical meaning of the changes seen on the primary study outcomes. Although I note that these changes were small, on average, for the reasons stated above, I believe that the sponsor has provided evidence that the changes seen were clinically meaningful. Further, I agree with Dr. Freed that the issues raised by Dr. Houghtling can be addressed as she described, and in Phase 4.

We have agreed with the sponsor on product labeling. In particular, as discussed above, the issue of the specific indication was a matter of discussion. We have ultimately agreed with the sponsor that the indication can be described in two sentences. The first will state that the drug is approved to improve "walking" in patients with MS, and the second will state that this was demonstrated on the basis of an effect on "walking speed" in controlled trials. Further, labeling will contain no explicit statement that an effect on walking ability, etc., was shown.

The application will be approved with a Risk Evaluation and Mitigation Strategy (REMS), the primary elements of which are a Medication Guide and a Communication Plan consisting of annually issued Dear Prescriber and Dear Pharmacist letters.

The following studies will be provided in Phase 4:

Embryo-fetal study to evaluate dalfampridine and (b) (4)
Genotoxicity evaluation of (b) (4)
Non-clinical self-administration study to assess the abuse potential of dalfampridine.
Receptor binding studies to further assess the abuse potential of dalfampridine.
Analyses of clinical data to assess the abuse potential of dalfampridine.
A controlled trial evaluating lower doses of dalfampridine.

Russell Katz, M.D.

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
01/21/2010