CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-250s000

OTHER REVIEW(S)

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 11, 2009

To: Russell, Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Lori A. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Pharmacologist

Subject: NDA-22-250 **fampridine-SR (4-aminopyridine)**
Indication: Improvement in walking ability in patients with multiple sclerosis
Dosage: 10 mg bid po
Company: Acorda Therapeutics, Inc.

Materials reviewed: NDA submission
\\CDSESUB1\EVSPROD\NDA022250\0007

Fampridine-SR clinical safety review by Gerard Boehm, MD, MPH.
DARRTS receipt date: 10/29/2009.

Fampridine-SR is a controlled release, orally administered form of 4-aminopyridine. Fampridine-SR is a new molecular entity and not marketed for human use in the United States. It is currently sold as an avicide under the trade name Avitrol. Fampridine acts primarily via blockade of potassium (K+) channels within the cell membrane. Fampridine is also used in basic scientific research to characterize diverse subtypes of potassium channels. Because 4-aminopyridine improves conduction in demyelinated nerve fibers, its use has been explored to improve symptoms in multiple sclerosis (MS) and spinal cord injury (SCI) patients. Because there are no marketed dosage forms of 4-aminopyridine, patients have depended on compounding pharmacies to obtain the drug.

The Division of Neurology Products requested CSS consultation on the abuse potential of fampridine-SR, although limited abuse potential information is available for review in the NDA.

CSS recommends that approval of fampridine-SR be contingent upon postmarketing requirements to perform preliminary assessments of the drug's abuse potential (see: RECOMMENDATIONS below).

I. Executive Summary

CONCLUSIONS

Fampridine-SR is a new molecular entity (NME). The Sponsor has not provided data to perform a complete assessment of the abuse potential of fampridine-SR. Standard abuse liability assessments (both clinical and preclinical) have not been performed and characterization of the abuse potential of fampridine-SR is lacking. In addition, the dependence liability of fampridine SR is unknown.

DISCUSSION

Although blockade of potassium channels is not a pharmacological mechanism of action traditionally recognized to be associated with known drugs of abuse, comprehensive receptor binding studies with fampridine-SR would establish whether activity at receptor sites associated with abused drugs exists. If receptor binding studies suggest that fampridine-SR has activity at receptors associated with abused drugs, it would be necessary to assess the behavioral effects of fampridine-SR using drug discrimination. Drug discrimination is a behavioral paradigm used to model the subjective effects of drugs, including drugs of abuse, in a non-verbal species. Drug discrimination data can be used to predict whether fampridine-SR will produce subjective effects similar to other drugs of abuse.

The ability of fampridine-SR to produce self-administration is also unknown. Among preclinical behavioral models used to evaluate the abuse potential of a drug, self-administration is often cited as the standard preclinical abuse potential assessment because of its face validity and predictive validity. Data from self-administration studies provide information about the likelihood that a drug will function as a reinforcer and be abused. Together, preclinical receptor binding, drug discrimination, and self-administration studies offer valuable information about fampridine-SR abuse potential.

Preliminary data including adverse event (AE) data from clinical trials and limited preclinical studies are inconclusive as to whether fampridine-SR has an abuse potential. The Sponsor did not assess AE terms related to abuse and misuse during clinical development. In addition, the Sponsor noted 3 reports of euphoric mood among 704 uncontrolled trial SCI patients and 2 reports in the non patient safety population (n=382). The Sponsor also found some cases of hallucination (4/1029 MS patients, 5/704 SCI patients, 1/384 non patient population). Lastly, the Sponsor reports that the overdose cases are mostly accidental. The Sponsor noted a few literature reports of attempted abuse of fampridine, but these were one-time events, based on uninformed exploratory behavior that produced acute negative side effects and did not lead to repeated attempts.

In fampridine-SR trials, investigators recorded AEs that occurred following discontinuation of study medication, allowing for an assessment of withdrawal effects. The AE data set included one study subject with an AE of drug withdrawal. This 53 year old male spinal cord injury patient participating in study SCI F201EXT experienced what was described as “excess sweating

–assoc. withdrawal symptom". This event was classified as severe but was not an SAE. The recorded outcome of this event was "resolved".

RECOMMENDATIONS

At this time, it is not clear that fampridine SR has abuse potential and that a complete characterization of the abuse potential including human studies is advisable. In order to resolve this issue, the Sponsor should provide the following:

1. Comprehensive receptor binding studies with fampridine-SR. This would include characterizing the affinity of fampridine-SR on dopamine, serotonin, GABA (gamma-amino-butyric-acid), opioid, NMDA, monoamine, sodium channel, calcium channel, and cannabinoid receptor sites.

   1a. Should the above receptor binding study show a mechanism of action similar to a known drug of abuse, CSS recommends that a rodent drug discrimination study be conducted evaluating fampridine-SR in animals trained to discriminate the known drug of abuse from saline.

2. Preclinical abuse potential assessment with a rodent self-administration study.

3. From clinical studies, assessment of adverse events related to abuse potential, with an emphasis on MedDRA terms that report incidents of euphoria-related behaviors; impaired attention, cognition, mood, and psychomotor events; and dissociative or psychotic behaviors (see below). Complete case report forms (CRF) should be provided for any individual who experiences overdose, psychiatric or neurological adverse events during a Phase 1, 2 or 3 study.

4. The Sponsor should report any postmarketing data on abuse, misuse, overdose and diversion of fampridine-SR that becomes available. In particular, the sponsor should evaluate any adverse events potentially related to abuse and report this information to FDA as serious adverse events..

The list below is a compilation of abuse-related adverse events terms, based on our experience to date. The list includes specific terms that are in the MedDRA dictionary and frequently used verbatim terms, words or phrases. Most terms are listed under General, Neurological, and Psychiatric Disorders High Level Groupings.

The presence of euphoria or other positive mood changes is a key observation that may influence a recommendation for scheduling. However, the overall behavioral profile and pharmacologic similarity to a scheduled drug is critical in determining whether scheduling will be recommended, and if so, into which schedule the drug will be recommended for placement.

Euphoria-related terms:

Euphoric mood: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high*, high* feeling, laughter. (* Exclude terms that clearly are not related or relevant such as "high blood pressure," etc.)

Elevated mood*:* mood elevated, elation.

Feeling abnormal: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey.

Feeling drunk: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged.

Feeling of relaxation: feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness.

Dizziness*:* dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy.

Thinking abnormal: abnormal thinking, thinking irrational, wandering thoughts.

Hallucination*:* (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted.

Inappropriate affect: elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laugher, inappropriate mood elevation.

Terms indicative of impaired attention, cognition, mood, and psychomotor events:

Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor.

Mood disorders and disturbances: mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional liability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability.

Mental impairment disorders: memory loss (exclude dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders.

Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

Dissociative/psychotic terms:

Psychosis: psychotic episode or disorder.

Aggressive: hostility, anger, paranoia.

Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity.

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/

CHAD REISSIG
12/11/2009

LORI A LOVE
12/14/2009

MICHAEL KLEIN
12/14/2009

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: November 30, 2009

To: James Reese, Ph.D.
Senior Regulatory Health Project Manager
Division of Neurology Products (DNP)

CC: Mary Dempsey
Project Management Officer
OSE, DRISK

Jessica M. Diaz, RN, BSN
Patient Product Information Reviewer
OSE, DRISK

From: Amy Toscano, Pharm.D., CPA
Regulatory Review Officer

Sharon Watson, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Drug: TRADENAME (fampridine) Extended Release Tablets
NDA: 22-250

DDMAC has reviewed the proposed October 16, 2009 PI and the November 24, 2009 Medication Guide (Med Guide) for TRADENAME (fampridine), including changes made by DRISK (to the Med Guide only), and we offer the following comments. DDMAC's comments are provided directly on the marked up version of this document, attached below.

Thank you for the opportunity to comment on this proposed labeling.

If you have any questions or concerns regarding these comments, please contact us.

29 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

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/

AMY TOSCANO
11/30/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	November 24, 2009
To:	Russell Katz, MD, Director **Division of Neurology Products (DNP)**
Through:	Mary Willy, PhD, Deputy Director **Division of Risk Management (DRISK)** LaShawn Griffiths, RN, MSHS-PH, BSN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Jessica M. Diaz, RN, BSN Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling Medication Guide
Drug Name(s):	TRADENAME (fampridine) Extended Release Tablets
Application Type/Number:	NDA 22-250
Applicant/sponsor:	ACORDA Therapeutics, Inc.
OSE RCM #:	2009-1018

1 INTRODUCTION

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Tradename (still to be determined) (fampridine). Please let us know if DNP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. DRISK's review of the proposed REMS will be provided to DNP under separate cover.

2 MATERIAL REVIEWED

- Draft TRADENAME (fampridine) Prescribing Information (PI) submitted September 16, 2009 and revised by the Review Division throughout the current review cycle.
- Draft TRADENAME (fampridine) Medication Guide submitted on October 20, 2009.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

MEDICATION GUIDE
[TRADENAME] ™ (phonetic spelling)
(fampridine)
Extended Release Tablets

Read this Medication Guide before you start taking [TRADENAME]and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about [TRADENAME]?

[TRADENAME] may cause seizures in people who do not have epilepsy.

- Your chance of having a seizure is higher if you take too much [TRADENAME] or if you have kidney problems.
  - Do not take [TRADENAME] if you have ever had a seizure.
  - Before taking [TRADENAME] tell your doctor if you have kidney problems.
  - Take [TRADENAME] exactly as prescribed by your doctor. See "How do I take TRADENAME?"

Stop taking [TRADENAME] and call your doctor right away if you have a seizure while taking [TRADENAME].

(b) (4)

What is [TRADENAME]?

[TRADENAME] is a prescription medicine used to help improve walking in adults with multiple sclerosis (MS). (b) (4)

It is not known if [TRADENAME] is safe or effective in children less than 18 years of age.

Who should not take [TRADENAME]?

Do not take [TRADENAME]if you have:

- ever had a seizure.

- certain types of kidney problems.*[DRISK Comment: Recommend using "certain types" (b) (4) because it may be interpreted differently by individual patients.]*

(b) (4)

What should I tell my doctor before taking [TRADENAME]?

Before you take [TRADENAME], tell your doctor if you:

- (b) (4)
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if [TRADENAME] will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if [TRADENAME] passes into your breast milk. You and your doctor should decide if you will take TRADENAME or breast-feed. You should not do both.

[DRISK Comment: The information regarding "head injury and medicines for depression" was deleted because it is not in the PI. For consistency this information needs to be added to the PI to be included in the MG.]

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

(b) (4)

How should I take [TRADENAME]?

- Take [TRADENAME] exactly as your doctor tells you to take it. Do not change your dose of [TRADENAME].
- (b) (4)

- Take [TRADENAME] 2 times each day at least 12 hours apart. Do not take more than 2 tablets of [TRADENAME] in a 24-hour period.
- Take [TRADENAME] tablets whole. Do not break, crush, chew or dissolve TRADENAME tablets before swallowing. If you cannot swallow [TRADENAME] tablets whole, tell your doctor. You may need a different medicine.
- [TRADENAME] is released slowly over time. If the tablet is broken, the medicine may be released too fast. This can raise your chance of having a seizure.

[DRISK Comment: The information in this section regarding taking tablets with any liquid was deleted because it is not listed in the PI. For consistency this information needs to be added to the PI to be included in the MG.

- **[TRADENAME] can be taken with or without food.**
- If you miss a dose of [TRADENAME], do not make up the missed dose. Do not take 2 doses at the same time . Take your next dose at your regular scheduled time.
- If you take too much [TRADENAME], call your doctor or go to the nearest hospital emergency room right away.

(b) (4)

What are the possible side effects of [TRADENAME]?

[TRADENAME] may cause serious side effects, including:

See "What is the most important information I should know about [TRADENAME]?"

[DRISK Comment: The information regarding "having a seizure while taking a TRADENAME" has been addressed in the section "What is the most important information I should know about [TRADENAME]?]

The most common side effects of [TRADENAME] include:*DRISK Comment: The Highlights section says "Most common adverse events (incidence ≥ 2% and a rate greater than the placebo rate) for [TRADENAME]" The list proposed in the MG does not include all adverse events ≥ 2%. For consistency the AEs have been added to the MG.]*

- (b) (4)
- trouble sleeping (insomnia)
- dizziness
- headache
- nausea
- (b) (4)
- back pain
- (b) (4)
- problems with balance
- multiple sclerosis relapse
- tingling or itching
- (b) (4)
- (b) (4) nose and throat (b) (4)
- constipation
- (b) (4)
- (b) (4)
- pain in your throat (b) (4)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of [TRADENAME]. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088. (b) (4)

(b) (4)

How should I store [TRADENAME]?

- Store [TRADENAME] at 59ºF to 86ºF (15ºC to 30ºC).
- Safely throw away [TRADENAME] that is out of date or no longer needed.

(b) (4)

Keep [TRADENAME] and all medicines out of the reach of children.

General Information about the safe and effective use of [TRADENAME]

Medicines are sometimes prescribed for purpose other than those listed in a Medication Guide. Do not use [TRADENAME] for a condition for which it was not prescribed. Do not give [TRADENAME] to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about [TRADENAME]. If you would like more information talk with your doctor. You can ask your pharmacist or doctor for information about [TRADENAME] that is written for health professionals.

For more information, go to www.TRADENAME.com or call 1-xxx-xxx-xxxx. *[DRISK Comment: The Applicant should add their web address and toll-free number, if available, here.]*

What are the ingredients in [TRADENAME]?

Active ingredient: fampridine
Inactive ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, macrogol, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

Distributed by: Acorda Therapeutics, Inc.
Hawthorne, NY 10532

Issued Month DD, YYYY

This Medication Guide has been approved by the U.S. Food and Drug Administration.

[TRADENAME] is a trademark of Acorda Therapeutics, Inc.
Manufactured under license from Élan Pharma International Ltd. (EPIL), Ireland utilizing EPIL's MXDAS™ Technology
MXDAS™ is a registered trademark of Elan Pharmaceutical International Ltd.
U.S. Patent Nos.: US 5,540,938 and 5,370,879

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/

JESSICA M DIAZ
11/24/2009

MARY E WILLY
11/24/2009
I concur

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Maternal Health Team Review

Date: November 20, 2009 **Date Consulted:** October 30, 2009

From: Jeanine Best, MSN, RN, PNP
Clinical Analyst, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D.
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Neurology Products (DNP)

Drug: [redacted] (b) (4) Tablets for oral use, NDA 22-250

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Fampridine [redacted] (b) (4) Tablets for oral use labeling dated April 22, 2009

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of Fampridine [redacted] (b) (4) Tablets for oral use labeling.

INTRODUCTION

Acorda Therapeutics, Inc. submitted an original NDA (22-250) on January 30, 2009 (resubmitted April 22, 2009, after a refuse-to-file issued for e-CTD formatting and missing data issues), for Fampridine (b) (4) Tablets for oral use for the treatment of patients with Multiple Sclerosis (MS) for improvement in walking ability. Orphan Drug Designation was granted to Fampridine (b) (4) Tablets for oral use on September 15, 1998.

The Division of Neurology Products consulted the Maternal Health team (MHT) to review the Pregnancy and Nursing Mothers subsections of fampridine labeling.

BACKGROUND

Fampridine

Fampridine is a form of 4- aminopyridine which is a selective potassium channel blocker. In animal studies, fampridine has been shown to increase conduction of action potentials in demyelinated and non-myelinated axons through inhibition of potassium channels. 4-aminopyridone is also used as a bird poison (Avitrol 200 and Avitroland) and is classified by the EPA as a restricted use pesticide. 4-aminopyridone has also been used as a research tool to characterize potassium channels. To date, MS patients have had to rely on compounding pharmacies to obtain a therapeutic dosage form of 4-aminopyridone and compounding errors have resulted in drug toxicity with seizures as the most common occurring toxic adverse event. (b) (4) Fampridine Tablets for oral use has been developed to provide an available dosgage form of 4-aminopyridone to limit drug toxicity. A dose-dependent increase in seizures was noted in clinical trials with fampridine and dosing of fampridine will be limited to 10 mg twice daily.

Multiple Sclerosis (MS): Pregnancy and Lactation

Pregnancy does not appear to have an effect on the long-term prognosis of MS and MS has not been shown to affect a pregnancy or fetal outcomes. MS symptoms usually stabilize during pregnancy because of the natural immune suppression that occurs in a woman's body during pregnancy. However, many women (about 70 %) with MS experience a relapse in symptoms in the first six months postpartum, sometimes affecting their ability to adequately care for their infant. Clinicians and patients must carefully weigh the risks and benefits of drug therapies to treat MS symptoms during a pregnancy and lactation as many therapies are associated with adverse effects to the developing fetus during a pregnancy and to a human milk fed infant.[1]

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal

[1] Ferrero S, Pretto S, Ragni N. Multiple sclerosis: management issues during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2004 Jul 15;115(1):3-9

data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes describing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. This review provides MHT's suggested revisions to the Sponsor's proposed Pregnancy and Nursing Mothers subsections of Fampridine [redacted] (b) (4) Tablets for oral use labeling.

SUMBMITTED LABELING
Proposed Pregnancy and Nursing Mothers Labeling (April 22, 2009 version)

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: based on animal data, may cause fetal harm (8.1)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C
Administration of fampridine to animals during pregnancy and lactation resulted in decreased offspring viability and growth at doses similar to the maximum recommended human dose (MRHD) of 20 mg/day. There are no adequate and well-controlled studies of fampridine in pregnant women. [Tradename] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In developmental toxicity studies in rats and rabbits, fampridine was administered orally at doses of up to 10 and 5 mg/kg/day, respectively, during the period of organogenesis. These doses are approximately 5 times the MRHD on a body surface area (mg/m^2) basis**.** No evidence of developmental toxicity was found in either species at the highest doses tested, which were maternally toxic. Oral administration of fampridine (1, 3, and 9/6 mg/kg/day) to rats throughout the pregnancy and lactation periods resulted in decreased offspring survival and growth. The no-effect dose for pre- and postnatal developmental toxicity in rats (1 mg/kg) is approximately 0.5 times the MRHD on a mg/m^2 basis.

8.2 Labor and delivery
The effect of tradename on labor and delivery in humans is unknown.

8.3 Nursing Mothers
It is not known whether fampridine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fampridine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

17.4 FDA-Approved Patient Labeling/Medication Guide

What should I tell my doctor before taking [TRADENAME]?

Tell your doctor about all your health problems. Tell your doctor if you:

- (b) (4)
- (b) (4)
- Are pregnant or (b) (4). It is not known if [TRADENAME] will harm your unborn baby. You and your doctor (b) (4)
- Are breast-feeding. It is not known if [TRADENAME] passes into your breast milk. (b) (4)].

DISCUSSION AND CONCLUSIONS

The MHT is structuring the Pregnancy and Nursing Mothers label information in a way that complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

Most drug therapies used in the treatment of Multiple Sclerosis are not recommended for use during lactation because of potential serious adverse events in human milk fed infants. Because multiple sclerosis commonly occurs in women of childbearing potential, MHT considered requesting a milk-only lactation trial for fampridine to provide information regarding the presence of drug in milk, the concentration of the drug in milk, and the calculated infant dose could better inform labeling to assist clinicians and their patients in making informed decisions regarding the risks and benefits of human milk feeding while on specific therapies for Multiple Sclerosis. The transport of drugs into human milk is largely a function of their physio-chemical structures and the concentration in maternal plasma. Factors that tend to produce higher breast milk levels of drug include: higher maternal plasma concentration, higher lipid solubility, higher pKa, lower protein binding, and lower molecular weight.[2] Based on physio-chemical characteristics, we expect fampridine to be excreted into human milk; however, due to the drug's potential toxicity to a human milk-fed infant, enrollment in a lactation trial would be difficult as the study could only ethically include women who were starting fampridine therapy and stopping lactation concurrently.

MHT's recommended pregnancy and nursing mothers labeling revisions for fampridine are provided below on pages 5-6 of this review. Appendix A of this review also provides a track changes version of labeling.

[2] From guidance in clearance: Guidance for Industry: Clinical Lactation Trials – Trial Design, Data Analysis, and Recommendations for Labeling

MATERNAL HEALTH TEAM LABELING RECOMMENDATIONS

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)

Reviewer Comment: Required regulatory language for Nursing Mothers added to Highlights of Prescribing Information.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of fampridine in pregnant women. Administration of fampridine to animals during pregnancy and lactation resulted in decreased offspring viability and growth at doses similar to the maximum recommended human dose (MRHD) of 20 mg/day. [Tradename] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In developmental toxicity studies in rats and rabbits, fampridine was administered orally during organogenesis at doses up to 10 and 5 mg/kg/day, respectively which are approximately 5 times the MRHD based on body surface area (mg/m^2)**.** No evidence of developmental toxicity was found in either species at the highest doses tested, which were maternally toxic. Oral administration of fampridine at doses of 1, 3, and 9/6 mg/kg/day which are approximately 0.5 to 4.5/3 times the MRHD based on body surface area (mg/m^2) to rats throughout the pregnancy and lactation periods resulted in decreased offspring survival and growth. The no-effect dose for pre- and postnatal developmental toxicity in rats (1 mg/kg) is approximately 0.5 times the MRHD based on body surface area (mg/m^2).

Reviewer Comment: The P/T reviewer should confirm the multiples of human exposures used in the animal studies throughout pregnancy and lactation periods.

8.2 Labor and delivery

The effect of [Tradename] on labor and delivery in humans is unknown.

Reviewer Comment: There is no data presented in this subsection so MHT leaves it up to the Sponsor whether to keep or delete this subsection.

8.3 Nursing Mothers

It is not known whether fampridine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fampridine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer Comment: MHT concurs with the proposed language. We searched the Drugs and Lactation database (LactMed)[3] and found no human lactation data for fampridine. Infants could suffer serious adverse reactions if fampridine were excreted in human milk in an appreciable amount and then absorbed by an infant.

17.4 FDA-Approved Patient Labeling/Medication Guide

(b) (4)

12 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

Appendix A - MHT Tracked-Changes Labeling Revisions

[3] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT

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

/s/

JEANINE A BEST

12/22/2009

Corrected version to delete suggested PMR for lactation trial

Karen B FEIBUS

12/22/2009

I agree with the recommended labeling revisions and the decision to NOT request a clinical lactation study for logistical and ethical reasons.

LISA L MATHIS

12/22/2009

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 2, 2009

TO: James Reese, Ph. D. Regulatory Health Project Manager
Kachikwu Illoh, M.D., Medical Officer
Division of Neurology Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-250

APPLICANT: Acorda Therapeutic, Inc.

DRUG: Fampridine-SR Tablets

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of patients with multiple sclerosis for the improvement of walking ability. .

CONSULTATION REQUEST DATE: March 19, 2009

DIVISION ACTION GOAL DATE: July 30, 2009

PDUFA DATE: July 30, 2009

I. BACKGROUND:

The sponsor, Acorda Therapeutic, Inc., has submitted a New Molecular Entity NDA 22-250 using oral fampridine–SR (10 mg b.i.d) in subjects with multiple sclerosis. The sponsor submitted the following two protocols in support of their application: Protocol MS-F203, a 21-week study, and protocol MS-F204, a 14-week study. The review division requested inspection of three clinical investigator sites to cover the two protocols. Because the test article is a new molecular entity, the sponsor, Acorda Therapeutic, Inc., was also inspected.

The primary objective of the study protocol MS-F203 was to assess the efficacy and safety of fampridine 10 mg b.i.d. in a double–blind, placebo-controlled, parallel group study of subjects diagnosed with multiple sclerosis. The primary measure of efficacy was based on changes in walking (in feet per second) as measured by the timed 25-foot walk from the Multiple Sclerosis Functional Score. The primary objective of the study protocol MS-F204 was to assess whether the proportion of subjects who experienced consistent improvements in walking speed while on drug would be greater in the fampridine-SR treated group compared to placebo.

The inspection targeted three domestic clinical investigators who enrolled a relatively large number of subjects. The goals of the inspection included validation of submitted data and compliance of study activities with FDA regulations. The records inspected included, but not limited to, 100% informed consent forms, source documents, drug accountability records, protocol inclusion/exclusion criteria, randomization procedures, efficacy end points and documentation of adverse events.

II. RESULTS (by protocol/site):

Name of CI, or Sponsor site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Jonathan Calkwood, M.D. c/o Randall Shapiro, M.D. Minneapolis, MN 55422	MS-F203 15 subjects	5/5-7/09	NAI
Andrew Goodman, M.D. c/o Steven Schwid, M.D. Rochester, NY 14642	MS-F203 and MS-F204 20 and 18 subjects	4/7-21/09	NAI
Keith Edwards, M.D Bennington, VT 05201	MS-F203 and MS-F204 15 and 18 subjects	5/15-22/09	Pending. Preliminary classification NAI
Acorda Therapeutic, Inc.(Sponsor) Hawthorne, NY 10532-21522	MS-F203	3/18-27/09	NAI

Key to Classifications
NAI = No deviation from regulations
VAI = deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocols MS-F203 and MS-F204

1. Jonathan C. Calkwood, M.D.
   Minneapolis Clinic of neurology
   4225 Golden Valley Road
   Minneapolis, MN 55422

   At this site, a total of 15 subjects were screened, 15 subjects were randomized, and 15 subjects completed the study. Informed consent for all 15 subjects was reviewed to verify that subjects signed informed consent prior to screening and randomization into the study.

The medical records for 15 subjects enrolled were reviewed in depth including drug accountability records, IRB records, diaries, and laboratory results. Source documents were compared to case report forms and data listings for primary efficacy end points and adverse events. Adverse events experienced by study subjects were reported to the sponsor and IRB within the required timeframes.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

2. Andrew Goodman, M.D.
601 Elmwood Ave.
Box 605
Rochester, NY 14642-0001

Protocol MS-F203

At this site, 26 subjects were screened, 5 subjects were reported as screen failures, 21 subjects were randomized, and 20 subjects completed the study. Informed consent for all 21 subjects was verified to be signed by subjects prior to enrollment.

Protocol MS-F204

At this site, a total of 21 subjects were screened, 3 subjects were reported as screen failures, and 3 subjects were terminated early and the reasons documented. Eighteen subjects were enrolled, and 15 subjects completed the study. Informed consent for all subjects were reviewed and verified to be signed by subjects prior to enrollment.

The medical records/source documents for all subjects randomized were reviewed in depth including drug accountability, IRB records, and laboratory results. Source documents were compared to case report forms and to the data listings, including primary efficacy endpoints and adverse events for the majority of the subjects.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the study, records reviewed were accurate in terms of data entries and reporting of adverse events. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

3. Keith Edwards, M.D.
   140 Hospital Drive, Suite 210
   Bennington, VT 05201

   Observations noted below are based on an e-mail summary statement from the field investigator; the EIR for this inspection is currently pending. An inspection addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

   Protocol MS-F203

   At this site, a total of 18 subjects were screened, 3 subjects were reported as screen failures, 15 subjects were randomized, and 14 subjects completed the study. Informed consent for all subjects was verified. There were no subjects enrolled prior to IRB approval of the protocol and informed consent.

   The medical records/source data for 15 subjects were reviewed in depth including drug accountability records, and source data were compared to case report forms and data listings for primary efficacy measures and adverse events.

   Protocol MS-F204

   At this site, a total of 20 subjects were screened, one subject was reported as a screen failure, 19 subjects were randomized, and 18 subjects completed the study. Informed consent for all subjects was verified to be completed by subjects prior to enrollment.

   The medical records/source data for 20 subjects were reviewed in depth including drug accountability records, and source data were compared to case report forms and data listings for primary efficacy endpoint and adverse events.

   The medical records reviewed for both protocols disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the study records were found to be in order and verifiable. There were no known limitations to this inspection.

   The data appear acceptable in support of the pending application.

4. Acorda Therapeutics, Inc.(Sponsor)
   15 Skyline Drive
   Hawthorne, NY 10532-2152

   The inspection audited Protocols MS-F203 and MS F204 and focused on the following clinical investigators: Drs. Shapiro, Schwid and Edwards during the course of this sponsor monitor inspection.

The inspection reviewed the following: company history and Officers responsibilities, training program, manufacturing/design operations, selection of clinical investigators, quality assurance, study monitoring procedures, data review and reports, concomitant therapy, protocol adherence, data safety monitoring board documentation, participating clinical investigators, IRB documentation, CRFs, data collection, and study drug accountability. The investigator also compared selected subject CRFs with the firm's data listings.

The inspection found that the sponsor adhered to their SOPs regarding proper monitoring of their clinical investigators. The activities included, but not limited to, trial drug accountability records, laboratory samples, case report forms/source documents and adverse events reporting.

The sponsor's monitoring procedures appears to have been conducted adequately and the data submitted by the sponsor may be used in support of the respective indication.
In general, the data generated from the above three sites appear acceptable in support of the pending application. There were no limitations to this inspection.

The data appear acceptable in support of the pending application

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

There was sufficient documentation to assure that all audited subjects at the sites of Drs. Shapiro, Schwid, and Edwards did exist, fulfilled the eligibility criteria, received the assigned study medication and had their primary efficacy endpoint captured as specified in the protocol. Overall, the inspections of the above clinical investigators revealed no significant problems that would adversely impact data acceptability. The data generated and submitted by the sponsor from the above three inspected sites are acceptable in support of the pending application.

{*See appended electronic signature page}*

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{*See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/

Antoine El-Hage
7/10/2009 06:16:01 AM
PHARMACOLOGIST

Constance Lewin
7/10/2009 10:09:09 AM
MEDICAL OFFICER