CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-250s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA APPROVAL

NDA 022250

Acorda Therapeutics, Inc.
Attention: Brian A. Walter, Ph.D.
Senior Director, Regulatory Affairs
15 Skyline Drive
Hawthorne, NY 10532

Dear Dr. Walter:

Please refer to your new drug application (NDA) dated April 22, 2009, received April 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for AMPYRA (dalfampridine) Extended Release Tablets.

We also acknowledge receipt of the following amendments and correspondence dated:

May 8, 2009	August 5, 2009	November 23, 2009
May 15, 2009	August 12, 2009	November 25, 2009
May 20, 2009	August 14, 2009	December 2, 2009
May 28, 2009	August 20, 2009	December 8, 2009
June 22, 2009	September 4, 2009	December 15, 2009 (3)
June 24, 2009	September 8, 2009	December 29, 2009
June 30, 2009	September 14, 2009	January 6, 2010 (2)
July 14, 2009	September 16, 2009 (2)	January 8, 2010
July 21, 2009	September 18, 2009	January 14, 2010
July 22, 2009	September 21, 2009 (2)	January 19, 2010 (4)
July 24, 2009	October 20, 2009	January 20, 2010 (2)
August 4, 2009	October 28, 2009	January 21, 2010

This new drug application provides for the use of AMPYRA (dalfampridine) to improve walking, as demonstrated in walking speed, in individuals with multiple sclerosis (MS).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide). For administrative purposes, please designate this submission, "**SPL for approved NDA 022250**"

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the draft carton and immediate container labels submitted on January 6, 2010 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled
Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).
Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022250**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for AMPYRA (dalfampridine) to ensure the benefits of the drug outweigh the risk of seizures.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that AMPYRA (dalfampridine) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of AMPYRA (dalfampridine). FDA has determined that AMPYRA (dalfampridine) is a product for which patient labeling could help prevent serious adverse effects and that has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use AMPYRA (dalfampridine). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed AMPYRA (dalfampridine).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on January 15, 2010 and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. A summary of all reported seizures with analysis of adverse event reporting by prescriber type
b. An evaluation of healthcare providers' (HCPs) understanding and patients' understanding of the serious risks of AMPYRA (dalfampridine)
    - The survey instruments and methodologies will be provided to FDA for review and comment at least 3 months before it is administered to patients and prescribers.
c. Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate.
d. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
e. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
f. Based on the information submitted, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

We request that you submit all adverse reports of seizures as expedited reports.

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022250
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022250
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022250
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the following potential serious risks: the potential for the impurity, (b) (4), to adversely affect embryo-fetal development, the abuse potential of dalfampridine, or the potential of genotoxicity related to the impurity, (b) (4).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1582-1:

Embryo-fetal development study in one non clinical species (the rat) to qualify (b) (4), a drug product impurity with a specification limit that

exceeds the qualification threshold. This study may be conducted on dalfampridine spiked with the impurity up to a level that provides a safety margin compared to the specification limit proposed, and include a group receiving a high dose of dalfampridine alone. The timetable you submitted on January 21, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	by January 1, 2011
Study Completion Date:	by July 1, 2011
Final Report Submission:	by January 1, 2012

PMR 1582-2:

An in vitro bacterial mutagenicity (Ames) assay for impurity, (b) (4), (tested directly) that has been identified as a potentially genotoxic impurity based on SAR. If data can be provided to document that plasma exposure (AUC) to the (b) (4) in mouse or rat provides an adequate margin (≥25-fold) above the presumed plasma exposure in humans resulting from the presence of the (b) (4) in the drug product, then the (b) (4) would be considered qualified and the genetic toxicology study would not be needed. The timetable you submitted on January 14, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	by July 28, 2010
Study Completion Date:	by April 25, 2011
Final Report Submission:	by August 23, 2011

PMR 1582-3:

In vitro chromosomal aberration assay in mammalian cells or an in vitro mouse lymphoma tk assay for the impurity, (b) (4), (tested directly) that has been identified as a potentially genotoxic impurity based on SAR. If data can be provided to document that plasma exposure (AUC) to the (b) (4) in mouse or rat provides an adequate margin (≥25-fold) above the presumed plasma exposure in humans resulting from the presence of the (b) (4) in the drug product, then the (b) (4) would be considered qualified and the genetic toxicology study would not be needed. The timetable you submitted on January 14, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	by July 28, 2010
Study Completion Date:	by April 25, 2011
Final Report Submission:	by August 23, 2011

PMR 1582-4:

A non-clinical self-administration study to assess the abuse potential of dalfampridine. The timetable you submitted on January 14, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: by April 1, 2010
Study Completion Date: by April 1, 2011
Final Report Submission: by June 1, 2011

PMR 1582-5:

A receptor binding study (dopamine, serotonin, GABA [gamma-amino-butyric-acid], opioid, NMDA, monoamine, sodium channel, calcium channel, and cannabinoid receptor sites) to assess the abuse potential of dalfampridine. The timetable you submitted on January 14, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: by April 1, 2010
Study Completion Date: by November 1, 2010
Final Report Submission: by January 1, 2011

PMR 1582-6:

Assessment of adverse events related to abuse potential from clinical studies and clinical trials. MedDRA terms that report incidents of euphoria-related behaviors should be emphasized: 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 or psychiatric or neurological adverse events during a Phase 1, 2 or 3 study or clinical trial. A compilation of abuse-related adverse events terms, which is based on our experience to date, is included in Appendix 2 of this letter.

The timetable you submitted on December 19, 2009 states that you will conduct this study according to the following schedule:

Final Protocol Submission: by April 1, 2010
Study Completion Date: by January 1, 2011
Final Report Submission: by April 1, 2011

Submit the protocols to your IND, with a cross-reference letter to this NDA . Submit all final reports to NDA 022250. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a

safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS OF SECTION 506B

We remind you of your postmarketing commitments in your submissions dated January 19 & 20, 2010. These commitments are listed below.

PMC 1582-7:

A randomized prospective placebo controlled trial to evaluate the efficacy of dalfampridine SR 5 mg twice daily in patients with multiple sclerosis; the trial should include a 10 mg twice daily arm. The primary outcome measure should be the improvement in walking speed as measured by the Timed 25-Foot Walk during the treatment period of 4 weeks. The trial should not exclude patients with EEG abnormalities who do not have a history of seizures. The trial should incorporate testing to assess the risk for urinary tract infections. The trial should be submitted to the FDA for special protocol assessment.

Final Protocol Submission:	by May 1, 2010
Trial Completion date:	by November 1, 2012
Final Report Submission:	by March 1, 2013

PMC 1582-8:

Support the addition of a7.5 mg dosage strength, for use in patients with mild or moderate renal impairment, a population at risk for drug accumulation. Such support may include an evaluation of the pharmacokinetics of the 7.5 mg dose. The proposal should be submitted to the Division for comment prior to study initiation.

Final Protocol Submission:	by May 1, 2010
Study Completion date:	by September 1, 2011
Final Report Submission:	by December 1, 2011

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for studies or clinical trials, the number of patients entered into each study or trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."

CHEMISTRY, MANUFACTURING AND CONTROLS

A shelf-life of 36 months is granted for AMPYRA (dalfampridine) Tablets packaged in 60-count, 60 cc HDPE round bottles, and physician samples packaged in 14-count in 30 cc HDPE round bottles.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05

5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). Please note that any seizure case and any serious liver injury case must be submitted as 15-day reports. We also request that assessment of adverse events related to abuse potential be compiled in PSURs 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).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Hamet Touré, PharmD, Regulatory Health Project Manager, at 301-796-7534.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures
Appendix 1: Content of Labeling (Package Insert, MedGuide)
Appendix 2: Abuse-Related Adverse Event Terms
Appendix 3: REMS

Appendix 2 Abuse-Related Adverse Event Terms

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

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/s/

ROBERT TEMPLE
01/22/2010