CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-250s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs I
Division of Neurology Products

NDA/BLA #s:	NDA 022250
Products:	Ampyra (dalfampridine) Sustained Release Tablets, 10 mg
SPONSOR:	Acorda Therapeutics, Inc.
FROM:	Robert Temple, M.D.
DATE:	01/22/2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Ampyra (dalfampridine) to ensure that the benefits of the drug outweigh the risk of seizure. In reaching this determination, we considered the following:

A. Acorda seeks approval for the use of Ampyra (dalfampridine) to improve walking ability in patients with multiple sclerosis (MS). A review of published studies determined that the median prevalence of MS in North America was 2.0/1,000 persons (range 1.7-2.3)[1]. Impairment of the ability to walk is common among MS patients. In a group of 166 MS patients from Stockholm County, Sweden, testing revealed that only 8% (14/166) could walk at normal speed.[2] We do not have an estimate of the percentage of such patients who might be treated with Ampyra (dalfampridine).

B. MS is a chronic, often disabling disease that attacks the central nervous system (CNS.) In Western societies, MS is second only to trauma as a cause of

[1] Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohammed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurological disorders? Neurology 2007;68;326-337
[2] Einarsson U, Gottberg K, von Koch L, Fredrikson S, Ytterberg C, Jin YP, Andersson M, Holmqvist LW. Cognitive and motor function in people with multiple sclerosis in Stockholm County. Multiple Sclerosis 2006 June;12(3):340-53.

neurologic disability with onset in early to middle adulthood. MS can rapidly evolve to an incapacitating disease requiring profound lifestyle adjustments.[3] Impairment of the ability to walk is common among MS patients. In addition, MS patients have other symptoms including weakness of the limbs, visual symptoms including decreased acuity and visual blurring, sensory symptoms including tingling, ataxia, bladder dysfunction, memory loss and impaired attention, depression, and fatigue.

C. The efficacy of Ampyra (dalfampridine) for the improvement of walking speed in MS patients was studied in two phase 3 placebo-controlled studies. A significantly greater proportion of patients taking Ampyra (dalfampridine) had a consistent improvement in walking speed compared to patients taking placebo as measured by the Timed 25-foot Walk (approximately 35-43% vs 8-9%).

D. If approved, duration of treatment with Ampyra (dalfampridine) is expected to be chronic.

E. Ampyra (dalfampridine) causes seizures and the risk of seizures is believed to be related to its maximal plasma concentration. Increased incidence of seizures has been observed at 20 mg twice a day (b.i.d.) in controlled clinical studies of 9-14 weeks duration with Ampyra (dalfampridine) in patients with MS. There was one seizure seen in the placebo group at a dose of 10 mg b.i.d (0.25%), no seizures seen at 15 mg b.i.d., and 2 seizures (3.5%) seen at 20 mg b.i.d. In open label extension trials, the incidence of seizures during treatment with Ampyra 15 mg b.i.d. (1.7/100 person-years) was over 4 times higher than the incidence during treatment with 10 mg b.i.d. (0.4/100 person-years). In addition, plasma concentrations observed with a 15 mg b.i.d. dose overlap with those observed with a 10 mg dose. As Ampyra (dalfampridine) is eliminated through the kidneys primarily as unchanged drug, plasma concentrations in patients with renal impairment may reach exposure levels associated with greater seizure risk. Because patients with renal impairment would require a dose lower than 10 mg bid and no strength smaller than 10 mg is available, Ampyra (dalfampridine) is contraindicated in patients with moderate to severe renal impairment [Glomerular filtration rate (GFR) <50ml/min]. Ampyra (dalfampridine) must be used with caution in patients with mild renal impairment (GFR 51-80 ml/min), as the risk of seizure may be increased in these patients at the 10 mg twice daily recommended dose. Prescribers are warned in labeling that GFR should be estimated prior to initiating treatment with Ampyra if it is unknown.

Other adverse events occurring in ≥ 5% of patients in clinical trials at a dose of 10 mg b.i.d and more frequently compared to placebo patients include urinary tract infection, insomnia, dizziness, headache, asthenia, nausea, and balance disorder.

F. Ampyra (dalfampridine) is a new molecular entity.

[3] Harrrison's Principles of Internal Medicine-17th Ed. (2008)

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Ampyra (dalfampridine). 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 events. FDA has also determined that Ampyra (dalfampridine) 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).

The elements of the REMS will be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

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

REMS Interim Review Comments

Drug Name:	**NDA:**	**Date:** 01/11/2010
Ampyra (dalfampridine)	#22-250	**Comment Set #2**
DRISK Scientific Lead: Kate Heinrich, Health Education Reviewer, DRISK through: Suzanne Robottom, Pharm. D., Team Leader DRISK		**Reviewers:** Suzanne Robottom, Pharm. D., Team Leader DRISK
RCM #: 2009-1018		

Materials Reviewed:

- REMS amendment received January 6, 2010.

Proposed REMS Comments for Sponsor:

We have reviewed the submission and have the following comments. Please be aware that we anticipate additional comments as your submission(s) undergo further review.

a. Please refer to the track changes provided for the REMS in appendix A.
b. We have no further comments on the content of the Pharmacy Letter and DHCP Letter at this time.
c. For the DHCP and Pharmacy mailings, please include that the letters will be revised based on any new (pertinent) safety information added to the label and that the dissemination plan for the letters will include any known new AMYPRYA prescribers/pharmacists. Refer to the track changes provided for the REMS.
   The proposed REMS states that the Pharmacist Letter will be mailed to a limited network of specialty pharmacies. The letter should be sent to all pharmacies, as any pharmacy is capable of compounding prescriptions and/or ordering aminopyridine. Thus, they should be aware of the safety issues with concomitant use. We also recommend including key pharmacy organizations such as the National Association of Boards of Pharmacy (NABP), International Academy of Compounding Pharmacists (IACP) and Pharmacy Compounding Accreditation Board (PCAB). Provide more detail about how the mailing list will be derived.
d. You state that the letters will be available through the product website.

We remind you that any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a direct link off the main website that includes REMS-specific materials. This link will direct users to a separate website that describes the REMS program and lists only approved REMS materials. The website should not be a means to promote Ampyra or any other Sponsor product. Only this separate website or link will be considered a component of the Communication Plan.

e. Regarding the website, we recommend a link off of the Ampyra homepage to a REMS landing page. For example, the link could state: "Important Safety Information and Risk Evaluation and Mitigation Strategy (REMS)", or "Healthcare Professionals click here for Risk Evaluation and Mitigation Strategy (REMS) information" Please submit the content of the REMS landing page for review, including the language used in the link to access the REMS landing page.

   For example, the link off the landing page could state, "Important Safety Information and Risk Evaluation and Mitigation Strategy (REMS)", or "Healthcare Professionals click here for Risk Evaluation and Mitigation Strategy (REMS) information."

   The landing page of the separate REMS link should then contain background information on the REMS, as well as safety information, along with the REMS communication materials. We recommend the following language as background information on the REMS landing page:

   > A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.
   >
   > In order for Acorda to communicate certain risks to ensure that Ampyra is prescribed and taken safely, Acorda has worked with the FDA to develop materials to communicate the following risks
   >
   > - drug-associated seizures
   > - Change in established name from fampridine to dalfampridine
   >
   > The REMS program is designed to inform health care providers and patients about the potential risks with Ampyra. To learn more about serious risks, read the important safety information provided in this link, including the Medication Guide, and discuss it with your patients.
   >
   > The goals of the Ampyra REMS are:
   >
   > - To inform healthcare providers about the risk of drug-associated seizures in patients treated with AMPYRA.
   > - To inform healthcare providers about the change of the established name from fampridine to dalfampridine.

- To inform patients about the serious risks associated with AMPYRA therapy.

f. Update the Supporting Document to be consistent with REMS.
g. Please present the data requested through the REMS assessment in bulleted format.

1. Information Needed For Assessment (REMS Assessment Plan):

A. Revise the Information Needed for Assessment (REMS Assessment Plan) in the REMS Supporting Document to include the following in bulleted format to clearly state the assessment points:

i. A summary of all reported seizures with analysis of adverse event reporting by prescriber type

ii. An evaluation of healthcare providers' understanding and patients' understanding of the serious risks of Ampriva

- 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.

iii. Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate.

iv. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

v. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

vi. 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.

2. General Comments:

A. Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Please provide a track changes and clean version of all revised materials and documents.

B. Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

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NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS

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/s/

KATE A HEINRICH
01/13/2010
DRISK Interim comments #2 on Ampyra.

CLAUDIA B KARWOSKI
01/19/2010
concur

REMS Interim Review Comments

Drug Name:	NDA:	Date: 12/14/2009
Ampriva (fampridine)	#22-250	**Comment Set # 1**
DRISK Scientific Lead: Kate Heinrich, Health Education Reviewer, DRISK		**Reviewers:** Suzanne Robottom, Pharm. D., Team Leader DRISK Amy Toscano, Regulatory Review Officer, DDMAC
RCM #: 2009-1018		

Materials Reviewed:

- Proposed REMS amendment, received October 20, 2009.
- Amendment received December 2, 2009, concerning the possible name change for fampridine and distribution through specialty pharmacies.

Introduction:

The comments below are OSE's preliminary review of the proposed REMS for Ampriva (fampridine). Please request the Sponsor respond to these comments.

Attached to this review is an edited (with track changes) Dear Healthcare Professional Letter and Dear Pharmacist Letter.

Please note that we have included language for DNP to put into the Approval Letter.

Comments for DNP:

The sponsor proposes a safety questionnaire to collect information when an adverse event is reported about a seizure. Information regarding dose, regimen, concomitant medications, detailed demographics and disease type and related clinical chemistry data will be collected. The actual questionnaire was not included in the Supporting Document. If DNP would like to review this questionnaire, please include this request in your comments to the sponsor.

Provided are proposed information for assessments. If there is additional information that is needed, please contact DRISK.

Please include the following in the Approval Letter for Ampriva:

1. Information Needed for Assessment (REMS Assessment Plan) will include, but is not limited to the following:

i. A summary of all reported seizures with analysis of adverse event reporting by prescriber type

ii. An evaluation of healthcare providers' understanding and patients' understanding of the serious risks of Ampriva

- 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.

iii. Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate.

iv. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

v. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

vi. 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.

2. In the approval letter, consider including the requiring the sponsor to submit seizure adverse events as expedited reports.

Proposed REMS Comments for Sponsor:

We have reviewed the submission and have the following comments. Please be aware that we anticipate additional comments as your submission(s) undergo further review.

Revise your REMS document based on recommended changes provided.

1. REMS Goals:
Revise REMS goals as follows:

To inform healthcare providers about the risk of drug-associated seizures in patients treated with Ampriva

To inform healthcare providers about the change of the established name from fampridine to (new established name here).

To inform patients about the serious risks associated with Ampriva therapy

2. Communication Plan:

Revise the Communication Plan as follows:

1 Page has been Withheld in Full following this page as B4 (TS)

(b) (4)

3. **Information Needed For Assessment (REMS Assessment Plan):**
   A. Revise the Information Needed for Assessment (REMS Assessment Plan) in the REMS Supporting Document to include the following:
      i. A summary of all reported seizures with analysis of adverse event reporting by prescriber type
      ii. An evaluation of healthcare providers' understanding and patients' understanding of the serious risks of Ampriva
         - 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.
      iii. Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate.
      iv. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
      v. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
      vi. 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.
   B. You state that the Medication Guide is packaged with each 60 count bottle. However, the distribution of Ampriva is not unit-of-use. Therefore you must include a report of the periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

4. **General Comments:**

   A. Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Please provide a track changes and clean version of all revised materials and documents.

   B. Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

C. We remind you to submit the healthcare provider and patient surveys and methodology at least 3 months before it is administered to patients and prescribers.

APPENDIX A

IMPORTANT DRUG WARNING

Dear Doctor:

(b) (4)

Ampriva is contraindicated in (b) (4)

- History of Seizure
- Moderate or severe renal impairment

Risk of Seizure with AMPRIVA

- **Clinical studies indicate doses greater than 10 mg twice daily increase the risk of seizure.**
- Patients with a history of seizure should not be prescribed AMPRIVA.

(b) (4)

Renal Impairment

- Ampriva is eliminated through the kidneys primarily as unchanged drug.

(b) (4)

AMPRIVA Dosing/Prescribing Information

- The approved dose of AMPRIVA is **10 mg twice daily**, approximately 12 hours apart, with or without food. This dose should not be exceeded.
  No additional benefit was demonstrated at doses greater than 10 mg twice daily and adverse events and discontinuation were more frequent at higher doses.
- (b) (4)
- AMPRIVA is available in 10 mg strength extended release tablets.
- Tablets should be taken whole. They should not be scored, divided, crushed , chewed or dissolved in (b) (4).

You should counsel the patients about:

- The risks and benefits of AMPRIVA;

- The importance of taking AMPRIVA as prescribed (b) (4) not double-dosing if a dose is missed);
- The need for patients to notify you about all medications they are taking;
- The importance of immediately discontinuing AMPRIVA if a seizure occurs and reporting the event to Acorda at 1-800-367-5109.

Please carefully review the enclosed safety and prescribing information, including the AMPRIVA Prescribing Information and the Medication Guide. The Medication Guide provides detailed safety information in lay language for patients and is provided to a patient every time an AMPRIVA prescription is filled. The Medication Guide can be used to counsel your patients about the safe use of AMPRIVA.

All of the enclosed materials are also available for download from www.Ampriva.com and from you Acorda Therapeutics representative or field-based Medical Affairs staff. If you have any questions, please contact Acorda Therapeutics Medical Information Services at 1-800-367-5109.

This letter is not intended to describe all important information associated with AMPRIVA use. Complete information about the use of AMPRIVA can be found in the accompanying AMPRIVA prescribing Information.

Health care professional should report any adverse events suspected to be associated with AMPRIVA use to:

- Acorda Therapeutics, Inc., Hawthorne NY 10532; 1-800-367-5109.
- FDA's MedWatch reporting system
  - By phone (1-800—FDA-1088)
  - By facsimile (1-800-FDA-0178)
  - Online (https://www.accessdata.fda.gov/scripts/medwatch/)
  - By mail (using the MedWatch Voluntary Reporting form 3500 to the FDA Safety Information and Adverse Event Reporting Program: Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787).

Sincerely,

XXXX
Acorda Therapeutics, Inc.

APPENDIX B

IMPORTANT DRUG WARNING

Dear Pharmacist:

(b) (4)

Ampriva is contraindicated in the following conditions:

- History of Seizure
- Moderate or severe renal impairment

(b) (4)

AMPRIVA Dosing/Prescribing Information

- The approved dose of AMPRIVA is 10 mg twice daily, approximately 12 hours apart, with or without food. This dose should not be exceeded.
  No additional benefit was demonstrated at doses greater than 10 mg twice daily and adverse events and discontinuation were more frequent at higher doses.
- **In the event that more than 10 mg twice daily is prescribed, you should contact the prescriber to verify the dosage and reinforce the dosage administration recommendation.**
- (b) (4)
- AMPRIVA is available in 10 mg strength extended release tablets.
- Tablets should be taken whole. They should not be scored, divided, crushed , chewed or dissolved in water.

Risk of Seizure with AMPRIVA

- **Clinical studies indicate doses greater than 10 mg twice daily increase the risk of seizure.**
- Patients with a history of seizures should not be prescribed AMPRIVA.
- (b) (4)
-

A Medication Guide must be given to the patient with each prescription of AMPRIVA.

- (b) (4)
- It is important that you counsel the patients about:

- The risks and benefits of AMPRIVA;
- The importance of taking AMPRIVA as prescribed (b) (4) not double-dosing if a dose is missed);
- The need for patients to notify their (b) (4) about all medications they are taking;
- The importance of immediately discontinuing AMPRIVA if a seizure occurs and reporting the event to Acorda at 1-800-367-5109.

(b) (4)

All of the enclosed materials are also available for download from www.Ampriva.com and from you Acorda Therapeutics representative or field-based Medical Affairs staff. If you have any questions, please contact Acorda Therapeutics Medical Information Services at 1-800-367-5109.

This letter is not intended to describe all important information associated with AMPRIVA use. (b) (4)

Health care professionals should report any adverse events suspected to be associated with AMPRIVA use to:

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- FDA's MedWatch reporting system
  - By phone (1-800—FDA-1088)
  - By facsimile (1-800-FDA-0178)
  - Online (https://www.accessdata.fda.gov/scripts/medwatch/)
  - By mail (using the Medwatch Voluntary Reporting form 3500 to the FDA Safety Information and Adverse Event Reporting Program: Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787).

Sincerely,

XXXX
Acorda Therapeutics, Inc.

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/s/

KATE A HEINRICH
12/14/2009
OSE interim REMS review for Ampriva

CLAUDIA B KARWOSKI
12/15/2009
concur