

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-250s000

REMS

NDA 22-250

**AMPYRA™ (DALFAMPRIDINE)
EXTENDED RELEASE TABLETS**

**Acorda Therapeutics, Inc.
15 Skyline Drive
Hawthorne, New York 10532**

Contact Information:

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Executive Director, Regulatory Affairs and Drug Safety**

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

- 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.

II. REMS ELEMENTS

A. Medication Guide

In compliance with 21 CFR 208.24, Acorda Therapeutics, Inc. (“Acorda”) will institute the following measures:

- A Medication Guide will be dispensed with each AMPYRA prescription.
- AMPYRA is supplied as 10 mg tablets packaged in bottles of 60 tablets. A Medication Guide will be packaged with each bottle. In addition, a tear-off pad of Medication Guides will be provided with every shipment of AMPYRA to the pharmacies.
- AMPYRA packaging will contain a prominent notice to the pharmacist to include a Medication Guide with each filled prescription.
- The Medication Guide will be available through Acorda’s representatives, field-based Medical Affairs staff, the product website, and by request through the Acorda toll-free support line.

A copy of the Medication Guide is included in Appendix A.

B. Communication Plan

Acorda will implement a communication plan to support implementation of this REMS. This communication plan will comprise:

- Letters to prescribers and pharmacists. The initial letters will be distributed within 60 days of the approval of AMPYRA. Annual letters to both groups will be sent within 60 days of the anniversary date of approval for AMPYRA and every year for next three years.

The letters are described in greater detail below.

Dear Prescriber Introductory Letter

Within 60 days of approval of AMPYRA, an initial Dear Prescriber Introductory Letter will be sent by targeted mailing to educate prescribers about the proper distribution and safe use of AMPYRA. The mailing list will consist of professionals, of any specialty, who wrote at least one prescription for an immunomodulator drug approved for MS within the past 2 years. The letter will describe the key risk messages of the REMS. These include:

- The potential risk of seizure associated with AMPYRA. Clinical studies indicate doses greater than 10 mg twice daily may increase the risk of seizure.
- Selection of the appropriate patient population, specifically patients without a history of seizures and without moderate or severe renal impairment.
- AMPYRA (dalfampridine) has also been known as fampridine, 4-aminopyridine, or 4-AP.
- Appropriate prescribing, including the importance of discontinuing pharmacy-compounded formulations of the drug prior to initiating therapy with AMPYRA.
- Informing prescribers that a pharmacy-compounded formulation of the drug should not be substituted for AMPYRA due to the unknown pharmacokinetics of compounded formulations and the potential for overdose and increased risk of seizures.
- Informing prescribers not to take AMPYRA in addition to a compounded formulation of the drug (4-aminopyridine, 4-AP, fampridine).
- The importance of discontinuing AMPYRA and reporting the event promptly to Acorda should a patient experience a seizure.

The mailing will also include the Prescribing Information (PI) and the Medication Guide. The letter will urge HCPs to counsel patients about the risks and benefits of AMPYRA, the importance of taking AMPYRA as prescribed, and the need to notify their HCP of all medications they are taking.

19 January 2010

Additional PIs and Medication Guides will be available upon request through Acorda's toll free support line, the product website, or via Acorda's representatives and field-based Medical Affairs staff.

In order to ensure that HCPs remain informed of the AMPYRA REMS, the Dear Prescriber Introductory Letter will be sent annually, and revised appropriately to convey pertinent updated safety information included in the label. Any known new prescribers will also be targeted. The letter may be sent earlier if new safety information becomes available for AMPYRA. The annual mailing will include the current versions of the PI and the Medication Guide.

Dear Pharmacist Letter

A Dear Pharmacist Letter will be provided to all pharmacies and key pharmacy organizations. The letter will serve to educate these pharmacists about the potential risks associated with substituting AMPYRA with a compounded formulation of the drug and about the change in the established name from fampridine to dalfampridine. The letter will also inform pharmacists that AMPYRA is contraindicated in patients with moderate to severe renal impairment. The mailing will also include a copy of the PI and the Medication Guide.

Prescribing Information and additional Medication Guides will be made available via Acorda's toll free support line or the product website. In order to ensure that pharmacists remain informed of the AMPYRA REMS, the Dear Pharmacist Letter will be sent annually for three years from the approval of AMPYRA, and revised appropriately to convey pertinent updated safety information included in the label. The letter may be sent earlier if new safety information becomes available. All mailings will include the current versions of the PI and the Medication Guide.

C. Elements To Assure Safe Use

AMPYRA can be approved without any Elements to Assure Safe Use.

D. Implementation System

Because the REMS for AMPYRA does not include Elements to Assure Safe Use, an implementation system is not required.

E. Timetable for Submission of Assessments

Acorda will submit REMS Assessments to FDA 18 months, 3 years and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Acorda will submit each assessment-so that it will be received by the FDA on or before the due date.

APPENDIX A

The Medication Guide for AMPYRA™ (dalfampridine) Extended Release Tablets was updated on January 19, 2010 (Sequence 0048).

APPENDIX B

IMPORTANT DRUG WARNING

Dear Doctor:

There is important safety information you need to know before prescribing AMPYRA. The US Food and Drug Administration (FDA) has approved AMPYRA™ (dalfampridine) **Extended Release Tablets, 10 mg as a treatment to improve walking in patients with multiple sclerosis (MS) This was demonstrated by an increase in walking speed.** FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of AMPYRA outweigh the potential risk of seizure. AMPYRA (dalfampridine) has the same active ingredient as fampridine, 4-aminopyridine, or 4-AP.

AMPYRA is contraindicated in patients with:

- A history of seizure or
- Moderate or severe renal impairment.

Risk of Seizure with AMPYRA

- **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 AMPYRA.
- If the patient experiences a seizure, discontinue AMPYRA and promptly report the event to Acorda Therapeutics, Inc. at 1-800-367-5109.

Renal Impairment

AMPYRA is eliminated through the kidneys primarily as unchanged drug. Patients with renal impairment may require a dose lower than 10 mg bid. AMPYRA is available only as a 10 mg tablet which cannot be divided. Therefore, AMPYRA is contraindicated in patients with moderate or severe renal impairment, as defined by creatinine clearance 50 mL/min or less. The following formula can be used to estimate creatinine clearance (multiply by 0.85 for women):

$$CrCl = \frac{(140 - age) \times weight(kg)}{SerumCr(mg / dl) \times 72}$$

Because elderly patients are likely to have decreased renal function, it is particularly important to know the estimated creatinine clearance in these patients before initiating AMPYRA treatment.

AMPYRA Dosing/Prescribing Information

Prescriptions for AMPYRA will be processed through the AMPYRA Patient Support Center. AMPYRA will be dispensed only through specialty pharmacies and one highly controlled HMO system (Kaiser Permanente).

- The approved dose of AMPYRA 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 discontinuations were more frequent at higher doses.

- It is important to discontinue pharmacy-compounded formulations of the drug prior to initiating therapy with AMPYRA.
- It is important that a pharmacy-compounded formulation of the drug (4-aminopyridine, 4-AP, fampridine) should not be substituted for AMPYRA due to the unknown pharmacokinetics of compounded formulations and the potential for overdose and increased risk of seizures.
- It is important that AMPYRA not be taken in addition to a compounded formulation of the drug (4-aminopyridine, 4-AP, fampridine).
- AMPYRA 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 fluids.

You should counsel the patients about:

- The risks and benefits of AMPYRA;
- The importance of taking AMPYRA as prescribed and in particular not to double-dose if a dose is missed;
- The need for patients to notify you about all medications they are taking;
- The importance of immediately discontinuing AMPYRA if a seizure occurs and reporting the event to Acorda at 1-800-367-5109.

Please carefully review the enclosed AMPYRA Prescribing Information and the Medication Guide with particular attention to the safety and prescribing information.

The patient Medication Guide provides detailed safety information written in easy to understand language and is to be given to a patient every time an AMPYRA prescription is filled. The Medication Guide can be used to counsel your patients about the safe use of AMPYRA.

All of the enclosed materials are also available for download from www.AMPYRA.com and from your 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 AMPYRA use. Complete information about the use of AMPYRA can be found in the accompanying AMPYRA Prescribing Information.

Health care professionals should report any adverse events suspected to be associated with AMPYRA use to one of the following:

- 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,

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Acorda Therapeutics, Inc.

APPENDIX C

IMPORTANT DRUG WARNING

Dear Pharmacist:

There is important safety information you need to know before dispensing AMPYRA. The US Food and Drug Administration (FDA) has approved AMPYRA™ (dalfampridine) Extended Release Tablets, 10 mg *as a treatment to improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase walking speed.* FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of AMPYRA outweigh the potential risk of seizure. AMPYRA (dalfampridine) has the same active ingredient as fampridine, 4-aminopyridine, or 4-AP.

AMPYRA is contraindicated in patients with:

- A history of seizure or
- Moderate or severe renal impairment.

Risk of Seizure with AMPYRA

- **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 AMPYRA.

Renal Impairment

AMPYRA is eliminated through the kidneys primarily as unchanged drug. Patients with renal impairment may require a dose lower than 10 mg bid. AMPYRA is available only as a 10 mg tablet which cannot be divided. Therefore, AMPYRA is contraindicated in patients with moderate or severe renal impairment, defined by creatinine clearance 50 mL/min or less. Because elderly patients are likely to have decreased renal function, it is particularly important to know the estimated creatinine clearance in these patients before initiating AMPYRA treatment.

Prescriptions for AMPYRA will be processed through the AMPYRA Patient Support Center. AMPYRA is only available through a limited network of specialty pharmacies and Kaiser Permanente.

AMPYRA Dosing/Prescribing Information

- The approved dose of AMPYRA 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.**
- It is important to discontinue pharmacy-compounded formulations of the drug prior to initiating therapy with AMPYRA.

- It is important that a pharmacy-compounded formulation of the drug (4-aminopyridine, 4-AP, fampridine) should not be substituted for AMPYRA due to the unknown pharmacokinetics of compounded formulations and the potential for overdose and increased risk of seizures.
- It is important that AMPYRA not be taken in addition to a compounded formulation of the drug (4-aminopyridine, 4-AP, fampridine).
- AMPYRA 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 fluids.

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

- A Medication Guide is included with each 60-count bottle of AMPYRA, and tear-off pads of Medication Guides will be provided with each AMPYRA shipment.
- In addition to the Medication Guide included with each bottle of AMPYRA, a separate copy of the Medication Guide, whether from the tear-off pad or printed on demand at the pharmacy, must be included with each fill.
- It is important that you counsel the patients about:
 - The risks and benefits of AMPYRA;
 - The importance of taking AMPYRA as prescribed and in particular not to double-dose if a dose is missed;
 - The need for patients to notify their prescribing physician and you about all medications they are taking;
 - The importance of immediately discontinuing AMPYRA if a seizure occurs and reporting the event to Acorda at 1-800-367-5109.

This letter is not intended to describe all important information associated with AMPYRA use. **Please carefully review the enclosed AMPYRA Prescribing Information and the Medication Guide with particular attention to the safety and prescribing information.**

All of the enclosed materials are also available for download from www.AMPYRA.com and from your 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.

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Sincerely,

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Acorda Therapeutics, Inc.

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/

ROBERT TEMPLE

01/22/2010