Initial REMS Approval: 1/2010
Most Recent Modification: 7/2012

NDA 22-250 AMPYRA® (dalfampridine) EXTENDED RELEASE TABLETS

Acorda Therapeutics, Inc.
420 Saw Mill River Road
Ardsley, New York 10502

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

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.

II. REMS ELEMENTS

A. Communication Plan

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

- Dear Healthcare Professional Letters to prescribers and pharmacists. The initial letters will be distributed within 60 days of 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 the next three years.

The letters are described in greater detail below.

Dear Prescriber Letter

The Dear Prescriber 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 the following professionals:

- Prescribers who wrote at least one prescription for an immunomodulator drug approved for MS within the past 2 years
- Prescribers who have written a prescription for AMPYRA
- Specialists in Physical Medicine and Rehabilitation (PM&R) who have treated symptoms of multiple sclerosis based upon ICD9 codes.

The letter will describe the following key risk messages of the REMS:

- 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.
- The importance to counsel patients on the necessity to adhere to the prescribing guidelines and approved dosing schedule for Ampyra.
- Description of post-marketing seizure experience.
- 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. See Appendix A for a copy of the Dear Prescriber Letter.

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 Letter will be sent annually for three years, 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 or severe renal impairment. The mailing will also include a copy of the PI and the Medication Guide. See Appendix B for a copy of the Dear Pharmacist Letter.

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.

B. Timetable for Submission of Assessments

Acorda will submit REMS Assessments to FDA 18 months, 3 years and 7 years from the date of the initial approval of the AMPYRA REMS on January 22, 2010. 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: DEAR PRESCRIBER LETTER

IMPORTANT DRUG WARNING

Subject: Risk of Seizure with AMPYRA

Dear Healthcare Provider:

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 risk of seizures. AMPYRA (dalfampridine) has the same active ingredient as fampridine, 4-aminopyridine, or 4-AP.

Contraindication

AMPYRA is contraindicated in patients with:

- History of seizures
- Moderate or severe renal impairment (Creatinine clearance (CrCl) ≤50 mL/min)

Risk of Seizure

- **Clinical studies indicate doses greater than 10 mg twice daily increase the risk of seizure**.
- In patients with mild renal impairment (CrCl 51–80 mL/min), taking the recommended dose of AMPYRA 10mg twice daily, drug exposure may reach levels that have been associated with an increase in the risk of seizures.
- Estimated creatinine clearance (CrCl) should be known before initiating treatment with AMPYRA, and monitored at least annually during treatment with AMPYRA. CrCl can be estimated using the following equation (multiply by 0.85 for women):

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

- As mild renal impairment is more common after age 50, estimating CrCl is particularly important in these patients. The potential benefits of AMPYRA should be carefully weighed against the risk of seizures in these patients.

If the patient experiences a seizure, discontinue AMPYRA and promptly report the event to Acorda Therapeutics, Inc. at 1-800-367-5109 or to the FDA's MedWatch reporting system at 1-800-FDA-1088.

Post-Marketing Seizure Experience

In the first year of marketing ending March 31, 2011, 82 seizures were either reported or confirmed by a healthcare practitioner among 46,000 AMPYRA users. Because of various limitations in the quality of postmarketing data, and of potential underreporting of spontaneous adverse events, it is not possible to reliably estimate the rate of seizures with AMPYRA using post marketing reporting data, or to compare the reporting rate to that observed in clinical trials.

The majority of seizures reported postmarketing occurred at the recommended dose, within days to weeks of starting therapy, and in patients without a history of seizures. Seizure onset was on the first day of treatment with AMPYRA in 13 patients, and within a week of starting treatment in more than one third of patients (n=34). The median age of patients who experienced seizures in the postmarketing period is 52 years.

Dispensing/Prescribing Information

Prescriptions for AMPYRA are processed through the AMPYRA Patient Support Center and are dispensed via a closed pharmacy distribution network. AMPYRA is also dispensed through the Department of Veterans Affairs and through Kaiser Permanente for their patients. **AMPYRA is not available through retail pharmacies.**

- 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 (4-aminopyridine, 4-AP, fampridine) prior to initiating therapy with AMPYRA.
- It is important that a pharmacy-compounded formulation of the drug (4-aminopyridine, 4-AP, fampridine) 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.

Patient Counseling

Talk to your 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 and notifying you if a seizure occurs

Medication Guide
The patient Medication Guide provides detailed safety information written in easy-to-understand language and must be given to a patient every time a prescription for AMPYRA 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.

Reporting Adverse Events
To report any adverse events with the use of AMPYRA, contact:

- Acorda Therapeutics, Inc., Ardsley, NY 10502; 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/medwatch-online.htm)

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.
Sincerely,

Enrique Carrazana, MD
Chief Medical Officer

XX July 2012
2012V0.1

APPENDIX B: DEAR PHARMACIST LETTER

IMPORTANT DRUG WARNING

Subject: Risk of Seizure with AMPYRA

Dear Pharmacist:

There is important safety information you need to know about AMPYRA®.
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$$CrCl = \frac{(140 - age) \times weight(kg)}{SerumCr(mg/dl) \times 72}$$

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If the patient experiences a seizure, discontinue AMPYRA and promptly report the event to Acorda Therapeutics, Inc. at 1-800-367-5109 or to the FDA's MedWatch reporting system at 1-800-FDA-1088.

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- 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 (4-aminopyridine, 4-AP, fampridine) prior to initiating therapy with AMPYRA.
- It is important that a pharmacy-compounded formulation of the drug (4-aminopyridine, 4-AP, fampridine) 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).
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Medication Guide

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

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,

Enrique Carrazana, MD
Chief Medical Officer

XX July 2012
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS on behalf of RUSSELL G KATZ
07/20/2012