APPLICATION NUMBER:
22-250s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
EXCLUSIVITY SUMMARY

NDA # 022250     SUPPL #     HFD # 120

Trade Name   Ampyra
Generic Name   dalfampridine
Applicant Name   Acorda Therapeutics
Approval Date, If Known   January 22, 2010

PART I      IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  
      YES X  NO □

   If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

      505(b)(1)

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
      YES X  NO □

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
did the applicant request exclusivity?  

YES □ NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES □ NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES □ NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II  FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration?  Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.  Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES □ NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(#s).
2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of
summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:
(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>YES ☐ NO ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
<td>YES ☐ NO ☐</td>
</tr>
</tbody>
</table>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>YES ☐ NO ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
<td>YES ☐ NO ☐</td>
</tr>
</tbody>
</table>

If you have answered "yes" for one or more investigation, identify the NDA in which a
similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):  

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

   a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

   Investigation #1
   !
   !
   IND # YES □ ! NO □
   ! Explain:

   Investigation #2
   !
   !
   IND # YES □ ! NO □
   ! Explain:

   (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

   Investigation #1
   !
   !
Investigation #2

YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that
the applicant should not be credited with having "conducted or sponsored" the study?
(Purchased studies may not be used as the basis for exclusivity. However, if all rights to the
drug are purchased (not just studies on the drug), the applicant may be considered to have
sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ ! NO ☐

If yes, explain:

=================================================================
Name of person completing form: Robbin M. Nighswander, MS
Title: Chief, Regulatory Project Management Staff
Date: January 22, 2010

Name of Office/Division Director signing form: Russell Katz, MD
Title: Director, Division of Neurology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05
<table>
<thead>
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<th>Submitter Name</th>
<th>Product Name</th>
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<tr>
<td>NDA-22250</td>
<td>ORIG-1</td>
<td>ACORDA THERAPEUTICS INC</td>
<td>FAMPRIDINE TABLETS</td>
</tr>
</tbody>
</table>

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

/s/
ROBBIN M NIGHSWANDER
01/22/2010

RUSSELL G KATZ
01/22/2010
AMPYRA (dalfampridine) PMR/PMC Development Template: PMR 1582-1

PMR/PMC Description: Embryo-fetal development study in one non clinical species to qualify a drug product impurity with a specification limit that exceeds the qualification threshold.

PMR/PMC Schedule Milestones:  
Final protocol Submission Date: January 1, 2011  
Study/Clinical trial Completion Date: July 1, 2011  
Final Report Submission Date: January 1, 2012  
Other: ________________  
MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need  
- [ ] Life-threatening condition  
- [ ] Long-term data needed  
- [ ] Only feasible to conduct post-approval  
- [ ] Prior clinical experience indicates safety  
- [ ] Small subpopulation affected  
- [ ] Theoretical concern  
- [ ] Other

The sponsor proposes a specification limit that exceeds the qualification threshold for a drug product impurity. The intended patient population includes women of child-bearing potential. Assessing the potential for this impurity to adversely affect embryo-fetal development is important since an impurity does not contribute to clinical efficacy. This issue is appropriate for a PMR instead of a pre-approval requirement because of the unmet medical need for dalfampridine. The proposed label states that AMPYRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/cclinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Several nonclinical studies were conducted by the sponsor to qualify the impurity; however, an embryo-fetal development study was not one of these studies. Considering the number of women of child-bearing potential in the intended patient population, it is important to determine if this impurity has adverse effects on embryo-fetal development.
3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
   *If not a PMR, skip to 4.*
   
   **Which regulation?**
   - Accelerated Approval (subpart H/E)
   - Animal Efficacy Rule
   - Pediatric Research Equity Act
   - **FDAAA required safety study/clinical trial**

   **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
   - □ Assess a known serious risk related to the use of the drug?
   - □ Assess signals of serious risk related to the use of the drug?
   - □ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
   - □ Analysis of spontaneous postmarketing adverse events?  
     *Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk*

   - □ Analysis using pharmacovigilance system?  
     *Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk*

   - □ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
     *Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk*

   - □ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   **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.

   **Required**
   - □ Observational pharmacoepidemiologic study
   - □ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoeconomiclogic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
AM lyra (dalfampridine) PMR/PMC Development Template: PMC 1582-2

PMR/PMC Description: *In vitro* bacterial mutagenicity (Ames) assay for drug substance and drug product impurity, B(h)(4).

PMR/PMC Schedule Milestones: Final protocol Submission Date: July 28, 2010
Study/Clinical trial Completion Date: April 25, 2011
Final Report Submission Date: August 23, 2011
Other: ____________________________

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [X] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [ ] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

(b) (4) has been identified as a potentially genotoxic impurity based on SAR. The specification limit set by the sponsor allows for a daily dose of the (b) (4) that exceeds the maximum acceptable chronic daily dose for a genotoxic impurity (i.e., 1.5 μg/day); therefore, assessment of its genotoxic potential is needed. This issue is appropriate for a PMR instead of a pre-approval requirement because of the clinical importance of the drug.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

(b) (4) has been identified as a potentially genotoxic impurity based on SAR. The goal of the PMR is to obtain data to document the genotoxic potential of the (b) (4). A positive response in standard genetic toxicology studies suggests carcinogenic potential, information important for a drug product intended for chronic use.

3. If the study/clinical trial is a PMR, check the applicable regulation.
   *If not a PMR, skip to 4.*
   - Which regulation?
     - [ ] Accelerated Approval (subpart H/E)
     - [ ] Animal Efficacy Rule
     - [ ] Pediatric Research Equity Act
     - [X] FDAAA required safety study/clinical trial
- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
  □ Assess a known serious risk related to the use of the drug?
  □ Assess signals of serious risk related to the use of the drug?
  □ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
  □ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  □ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  □ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  □ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

| 1582-2: An in vitro bacterial mutagenicity (Ames) assay for impurity, | (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 | (in mouse or rat provides an adequate margin (≥25-fold) above the presumed plasma exposure in humans resulting from the presence of the | in the drug product, then the | would be considered qualified and the genetic toxicology study would not be needed. |

Required

□ Observational pharmacoepidemiologic study
□ Registry studies

Continuation of Question 4

□ Primary safety study or clinical trial
□ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
□ Thorough Q-T clinical trial
□ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
□ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
□ Pharmacokinetic studies or clinical trials
□ Drug interaction or bioavailability studies or clinical trials
□ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:
☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

__________________________
(signature line for BLAs)

1/21/2010
Ampyra (dalfampridine) PMR/PMC Development Template: 1582-3

PMR/PMC Description: *In vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay for drug substance and drug product impurity, [b](4)

PMR/PMC Schedule Milestones: Final protocol Submission Date: July 28, 2010
Study/Clinical trial Completion Date: April 25, 2011
Final Report Submission Date: August 23, 2011
Other: [b](4)

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [x] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [ ] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

(b)(4) has been identified as a potentially genotoxic impurity based on SAR. The specification limit set by the sponsor allows for a daily dose of the (b)(4) that exceeds the maximum acceptable chronic daily dose for a genotoxic impurity (i.e., 1.5 μg/day); therefore, assessment of its genotoxic potential is needed. This issue is appropriate for a PMR instead of a pre-approval requirement because of the clinical importance of the drug.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

(b)(4) has been identified as a potentially genotoxic impurity based on SAR. The goal of the PMR is to obtain data to document the genotoxic potential of the (b)(4). A positive response in standard genetic toxicology studies suggests carcinogenic potential, information important for a drug product intended for chronic use.
3. If the study/clinical trial is a PMR, check the applicable regulation.  
   If not a PMR, skip to 4.
   - **Which regulation?**
     - Accelerated Approval (subpart H/E)
     - Animal Efficacy Rule
     - Pediatric Research Equity Act
     - FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - Assess a known serious risk related to the use of the drug?
     - Assess signals of serious risk related to the use of the drug?
     - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - Analysis of spontaneous postmarketing adverse events?  
       *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

     - Analysis using pharmacovigilance system?  
       *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
       *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

     - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   **1582-3:** In vitro chromosomal aberration assay in mammalian cells or an in vitro mouse lymphoma tk assay for the impurity, (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 in mouse or rat provides an adequate margin (≥25-fold) above the presumed plasma exposure in humans resulting from the presence of the in the drug product, then the would be considered qualified and the genetic toxicology study would not be needed.

   **Required**

   - Observational pharmacoepidemiologic study
   - Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:
☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [x] Unmet need
- [ ] Life-threatening condition
- [x] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [x] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [x] Theoretical concern
- [ ] Other

Fampridine fulfills an unmet medical need. Abuse potential is a theoretical concern, and prior clinical experience indicates safety. However, the abuse potential of the drug is part of the drug’s safety assessment. According to 21 CFR 314.50(d)(5)(vii), if the drug has a potential for abuse, the sponsor must submit a description and analysis of studies or information related to abuse of the drug. 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.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The NDA for fampridine-SR does not contain all of the information necessary for a complete evaluation of its abuse potential. The goal of this study is to provide information about the abuse potential of fampridine-SR. The ability of fampridine-SR to produce self-administration is 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 will provide information about the likelihood that fampridine-SR will function as a reinforcer and be abused.
3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   *If not a PMR, skip to 4.*

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - [ ] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [x] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - [ ] Analysis of spontaneous postmarketing adverse events?
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  - [ ] Analysis using pharmacovigilance system?
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

| 1582-4: A non-clinical self-administration study to assess the abuse potential of dalfampridine. |

**Required**
- [ ] Observational pharmacoepidemiologic study
- [ ] Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

- Is the PMR/PMC clear, feasible, and appropriate?
☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

______________________________
(signature line for BLAs)
Amprya (dalfampridine) PMR/PMC Development Template: 1582-5

PMR/PMC Description: Abuse potential assessment – receptor binding study

PMR/PMC Schedule Milestones: Final protocol Submission Date: 4/1/2010
Study/Clinical trial Completion Date: 11/1/2010
Final Report Submission Date: 1/1/2011
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [x] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

Amprya fulfills an unmet medical need. Prior clinical experience indicates safety, and abuse potential is a theoretical concern. However, the abuse potential of the drug is part of the drug’s safety assessment. According to 21 CFR 314.50(d)(5)(vii), if the drug has a potential for abuse, the sponsor must submit a description and analysis of studies or information related to abuse of the drug. Dalfampridine-SR is a new molecular entity (NME). The Sponsor has not provided data to perform a complete assessment of the abuse potential of dalfampridine-SR. Standard abuse liability assessments (both clinical and preclinical) have not been performed and characterization of the abuse potential of dalfampridine-SR is lacking. In addition, the dependence liability of dalfampridine SR is unknown.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The NDA for dalfampridine-SR does not contain all of the information necessary for a complete evaluation of its abuse potential. The goal of this study is to provide information about the abuse potential of dalfampridine-SR. 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 dalfampridine-SR would establish whether activity at receptor sites associated with abused drugs exists.
3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   *If not a PMR, skip to 4.*

   - **Which regulation?**
     - [ ] Accelerated Approval (subpart H/E)
     - [ ] Animal Efficacy Rule
     - [ ] Pediatric Research Equity Act
     - [X] FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - [ ] Assess a known serious risk related to the use of the drug?
     - [ ] Assess signals of serious risk related to the use of the drug?
     - [X] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - [ ] Analysis of spontaneous postmarketing adverse events?
       *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

     - [ ] Analysis using pharmacovigilance system?
       *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - [X] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

     - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   **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.

   **Required**
   - [ ] Observational pharmacoepidemiologic study
   - [ ] Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease,
background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition,
different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine
feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the
safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
PMR/PMC Description: Abuse potential assessment – assessment of adverse events from clinical trials

PMR/PMC Schedule Milestones:

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Final protocol Submission Date</td>
<td>4/1/2010</td>
</tr>
<tr>
<td>Study/Clinical trial Completion Date</td>
<td>1/1/2011</td>
</tr>
<tr>
<td>Final Report Submission Date</td>
<td>4/1/2011</td>
</tr>
<tr>
<td>Other:</td>
<td>MM/DD/YYYY</td>
</tr>
</tbody>
</table>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [x] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [x] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [x] Theoretical concern
- [ ] Other

Dalfampridine fulfills an unmet medical need. In addition, abuse potential is a theoretical concern. However, the abuse potential of the drug is part of the drug’s safety assessment. According to 21 CFR 314.50(d)(5)(vii), if the drug has a potential for abuse, the sponsor must submit a description and analysis of studies or information related to abuse of the drug. Dalfampridine-SR is a new molecular entity (NME). The Sponsor has not provided data to perform a complete assessment of the abuse potential of dalfampridine-SR. Standard abuse liability assessments (both clinical and preclinical) have not been performed and characterization of the abuse potential of dalfampridine-SR is lacking. In addition, the dependence liability of dalfampridine-SR is unknown.
2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The NDA for dalfampridine-SR does not contain all of the information necessary for a complete evaluation of its abuse potential. The goal of this study is to provide information about the abuse potential of dalfampridine-SR. Preliminary data including adverse event (AE) data from clinical trials and limited preclinical studies are inconclusive as to whether dalfampridine-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 spinal cord injury (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.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**
  
  - Accelerated Approval (subpart H/E)
  - Animal Efficacy Rule
  - Pediatric Research Equity Act
  - FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  - Analysis of spontaneous postmarketing adverse events?
    
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - Analysis using pharmacovigilance system?
    
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

| 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. 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.

**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, it 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 laughter, 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.

**Required**

- Observational pharmacoepidemiologic study
- Registry studies
  
  *Continuation of Question 4*

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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.

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
Ampyra (Dalfampridine) PMC Development Template: 1582-7

PMR/PMC Description: A Clinical Trial to Evaluate Efficacy of a 5 mg twice daily dose of Dalfampridine

PMR/PMC Schedule Milestones: Final protocol Submission Date: 5/1/2010
Study/Clinical trial Completion Date: 11/1/2012
Final Report Submission Date: 3/1/2013
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☑ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☑ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

Seizure risk from dalfampridine is thought to be dose-related, with increased risk above the 10 mg twice daily dose that will be approved. The label will address the dose-related seizure risk and will limit its use in patients with impaired renal function to those with mild renal impairment, warning that they could be at increased risk with a 10 mg dose. It will be contraindicated in patients with moderate to severe renal impairment as the dose that will be approved would result in excessive exposure in those patients and there is no smaller dosage available.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Seizure risk from dalfampridine is thought to be dose-related, with increased risk above the 10 mg twice daily dose that will be approved. There is significant overlap in concentrations following administration of 10 mg twice daily and 15 mg twice daily (the dose at which increased seizure risk is observed). The goal of the clinical trial will be to evaluate efficacy at a dose lower than 10 mg twice daily to identify a lower effective dose.
3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [ ] FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - [ ] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - [ ] Analysis of spontaneous postmarketing adverse events?
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

  - [ ] Analysis using pharmacovigilance system?
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - [ ] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

```
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.
```

- [ ] Required
  - [ ] Observational pharmacoepidemiologic study
  - [ ] Registry studies
Primary safety study or clinical trial
Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
Thorough Q-T clinical trial
Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
Pharmacokinetic studies or clinical trials
Drug interaction or bioavailability studies or clinical trials
Dosing trials
Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials
Immunogenicity as a marker of safety
Other (provide explanation)

Agreed upon:
Quality study without a safety endpoint (e.g., manufacturing, stability)
Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
Dose-response study or clinical trial performed for effectiveness
Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?
Are the objectives clear from the description of the PMR/PMC?
Has the applicant adequately justified the choice of schedule milestone dates?
Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
Ampyra (Dalfampridine) PMR/PMC Development Template: 1582-8

PMR/PMC Description: Develop a 7.5 mg tablet for patients with renal impairment

PMR/PMC Schedule Milestones:  
Final protocol Submission Date: 5/1/2010  
Study/Clinical trial Completion Date: 9/1/2011  
Final Report Submission Date: 12/1/2011  
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [x] Unmet need  
- [ ] Life-threatening condition  
- [ ] Long-term data needed  
- [ ] Only feasible to conduct post-approval  
- [ ] Prior clinical experience indicates safety  
- [ ] Small subpopulation affected  
- [ ] Theoretical concern  
- [x] Other

Seizure risk from dalfampridine is thought to be dose-related, with increased risk above the 10 mg twice daily dose that will be approved. The label will address the dose-related seizure risk and will limit its use in patients with impaired renal function to those with mild renal impairment, warning that they could be at increased risk with a 10 mg dose. Dalfampridine will be contraindicated in patients with moderate to severe renal impairment as the dose that will be approved would result in excessive exposure in those patients and there is no smaller dosage available. Development of a 7.5 mg SR formulation for patients with mild to moderate renal impairment can be done postmarketing because the drug fulfills an unmet need and because labeling will restrict its use until the lower strength is developed.
2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Seizure risk from dalfampridine is thought to be dose-related, with increased risk above the 10 mg twice daily dose that will be approved in patients with normal renal function. There is significant overlap in concentrations following administration of 10 mg twice daily and 15 mg twice daily (the dose at which increased seizure risk is observed). In patients with mild-moderate renal impairment a 60% increase in plasma concentrations is observed as a result of a decrease in dalfampridine clearance. Therefore, until a lower dose is available, dalfampridine will be contraindicated in these patients.

The goal of this PMR is to develop a 7.5 mg dosage strength that can be used safely in patients with mild to moderate renal impairment. The sponsor has conducted a clinical study in patients with renal impairment, and based on those study results and simulation, the 7.5 mg dose has been identified as appropriate in patients with moderate renal impairment.

3. If the study/clinical trial is a PMR, check the applicable regulation. 

If not a PMR, skip to 4.

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [ ] FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - [ ] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - [ ] Analysis of spontaneous postmarketing adverse events?
    
    *Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk*

  - [ ] Analysis using pharmacovigilance system?
    
    *Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk*

  - [ ] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    
    *Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk*
Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

1582-8: Support the addition of a 7.5 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.

Required
- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:
- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Development of a 7.5 mg dosage strength. Support for this may include an evaluation of the pharmacokinetics of the 7.5 mg dose.

5. Is the PMR/PMC clear, feasible, and appropriate?
☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
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/s/

SALLY U YASUDA
01/21/2010
PMR/PMC development template
Brian,

"Here is a preliminary list of PMR/PMCs. We have one more PMR (PMR #1) that will be communicated to you later.

Please comment as to whether the timetable for these PMRs/PMCs appears reasonable to you, and also provide your commitment for the PMC.

POSTMARKETING REQUIREMENTS UNDER 505(o)
1. [To be communicated later].

2. Embryo-fetal development study in one non clinical species to qualify a drug product impurity with a specification limit that exceeds the qualification threshold. The study protocol should be submitted to the Division for comment prior to study initiation.

Final Protocol Submission: by April 1, 2010
Study Completion Date: by September 1, 2010
Final Report Submission: by December 31, 2010

3. An in vitro bacterial mutagenicity (Ames) assay for drug substance and drug product impurity, 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 in mouse or rat provides an adequate margin (≥25-fold) above the presumed plasma exposure in humans resulting from the presence of the in the drug product, then the would be considered qualified and the genetic toxicology study would not be needed. The study protocol should be submitted to the Division for comment prior to study initiation.

Final protocol Submission: by June 1, 2010
Study Completion Date: by August 1, 2010
4. In vitro chromosomal aberration assay in mammalian cells or an in vitro mouse lymphoma tk assay for drug substance and drug product impurity, 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 in mouse or rat provides an adequate margin (≥25-fold) above the presumed plasma exposure in humans resulting from the presence of in the drug product, then the would be considered qualified and the genetic toxicology study would not be needed. The study protocol should be submitted to the Division for comment prior to study initiation.

Final protocol Submission: by June 1, 2010
Study Completion Date: by September 1, 2010
Final Report Submission: by November 1, 2010

5. A non-clinical self-administration study to assess the abuse potential of dalfampridine. The study protocol should be submitted to the Division for comment prior to study initiation.

Final Protocol Submission: by March 22, 2010
Study Completion Date: by January 22, 2011
Final Report Submission: by March 22, 2011

6. A receptor binding study (dopamine, serotonin, GABA [gamma-aminobutyric-acid], opioid, NMDA, monoamine, sodium channel, calcium channel, and cannabinoid receptor sites) to assess the abuse potential of dalfampridine. The study protocol should be submitted to the Division for comment prior to study initiation.

Final Protocol Submission: by April 1, 2010
Study Completion Date: by September 1, 2010
Final Report Submission: by December 31, 2010

7. 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 the Appendix to this letter Appendix B.

Final Protocol Submission: by March 22, 2010
Study Completion Date: by July 22, 2010
Final Report Submission: by October 22, 2010

The terms for abuse potential will be included in the approval letter.

**POSTMARKETING COMMITMENTS**

1. A randomized prospective placebo controlled trial to evaluate the efficacy of dalfampridine SR 5 mg twice daily and 7.5 mg twice daily in patients with multiple sclerosis; the study 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 study 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 study should be submitted to the FDA for special protocol assessment.

Final Protocol Submission: by April 1, 2010
Study Completion date: by December 1, 2011
Final Report Submission: by June 1, 2012

Jim

James H. Reese, Ph.D., RAC
Senior Regulatory Health Project Manager
DNP\ODE1\CDER\FDA
T: 301-796-1136
F: 301-796-9842
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/s/

JAMES H REESE
12/23/2009
Brian,

We have these comments re. fampridine.

We have reviewed your response of July 21, 2009 to potential nonclinical deficiencies conveyed in the Agency’s Information Request Letter dated July 2, 2009: (1) identification of potentially genotoxic impurities and (2) lack of sufficient data to support the specification limit of for the impurity.

Regarding the issue of genotoxic impurities, it continues to be your position that none of the impurities has genotoxic potential and that no further testing is necessary. Your conclusion is based upon the absence of structural alerts for mutagenicity, genotoxicity, or carcinogenicity predicted by Derek for Windows. However, as we previously stated, we do not consider a negative result in a Derek report definitive for regulatory purposes. Our computational toxicology analyses have identified two of these impurities— and as positive for genotoxicity; the remaining impurities— , and are equivocal for genotoxicity.

Therefore, each of the remaining impurities identified as potentially genotoxic would need to be either reduced to a maximum daily intake of ≤ 1.5 μg/day or determined to be negative when tested directly in in vitro genotoxicity assays (i.e., an in vitro bacterial reverse mutation assay and either an in vitro cytogenetic assay in mammalian cells or an mouse lymphoma tk assay (with colony sizing)) (cf., Guidance for Industry Q3A Impurities in New Drug Substances [February 2003, ICH, Revision 1], and Guidance for Industry Q3B(R2) Impurities in New Drug Products [July 2006, ICH, Revision 2]).

Regarding the qualification of the impurity, we acknowledge our previous communication and will take it into consideration when reviewing the data. The adequacy of the data remains a matter of review.
James H. Reese, Ph.D., RAC
Senior Regulatory Health Project Manager
DNP\ODE\CDER\FDA
T: 301-796-1136
F: 301-796-9842
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/s/

JAMES H REESE
12/23/2009
NDA 22-250

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fampridine oral tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Update the drug substance specifications to include limits for \underline{(b) (4)} impurities that correspond to acceptable daily exposure to potentially genotoxic impurities.

\underline{(b) (4)} holder of DMF \underline{(b)} have been requested to update their specifications, accordingly.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

\{See appended electronic signature page\}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research
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/s/

MARTHA R HEIMANN
10/28/2009
Signed for Ramesh Sood
Dear Dr. Walter:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fampridine sustained-release (SR) tablets, 10 mg.

On October 20, 2009, we received your October 20, 2009, major amendment (solicited) to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 22, 2010.

In addition, we are establishing a new timeline for communication of feedback on proposed labeling and postmarketing commitments in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES - FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 6, 2010.

If you have any questions, call James H. Reese, Ph.D., RAC, Senior Regulatory Health Project Manager, at 301-796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
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/s/

RUSSELL G KATZ
10/21/2009
INFORMATION REQUEST

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fampridine oral tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The (b) (4) DMF # (b) (4) that you are referencing for (b) (4) is currently deficient. A Deficiency Letter dated July 10, 2009 was sent to DMF holder. In order to have an approval of the submitted NDA, the DMF # (b) (4) should receive an adequate status.

2. Provide the mass-spectrum of (b) (4) Lot No 120308 to confirm the structure of this impurity.

3. Three potentially genotoxic impurities in the drug substance and potentially genotoxic impurities in the drug product have been identified as outlined in the Filing Letter dated 7/2/2009. In case you choose to control the levels of these potentially genotoxic impurities in the drug substance and drug product specifications at the limits acceptable for daily exposure to potentially genotoxic impurities, you should provide appropriate validation data to demonstrate that the analytical procedure is capable of quantifying these impurities at the respective level.

4. Provide Certificate of Analysis of the drug product batches manufactured at (b) (4) after the (b) (4) and the representative updated executed batch record for such drug product (refer to the Amendment dated (b) (4)

5. Add “film-coated” and “non-scored” to the description of the tablets in the Appearance section of the drug product specification.

6. Provide confirmation that all excipients of the drug product comply with the USP<467> for residual solvent.

7. The resolution of the impurity at (b) (4) from fampridine peak on the resolution chromatogram for the Assay and Related Substances Method 1 is not satisfactory. Clarify how the impurity at (b) (4) is quantified.
8. Provide data to confirm that the in-process testing of the Appearance of the fampridine tablets guarantees that on the tablets. Confirm that commercial Amaya (fampridine) tablets are free from this defect on the tablet surface.

9. Please confirm that you intend to market the product in bottles. If so, revise your post-approval stability protocol to include the drug product packaged in HDPE bottles since stability data demonstrates difference in the level of impurities in the drug product packaged in bottles.

10. Include a NDC code on the container labels for 14 count and 60 count labels for HDPE bottles. Change the font for the established name, fampridine, to the more prominent font that is commensurate with that of the proprietary name. Provide label for bulk tablet containers.

11. Change the description of the fampridine tablets in the How supplied/ Storage and Handling section of the Package Insert to that provided in the Appearance section of the proposed drug product specification. Add the “film-coated” and “non-scored” to the description of the tablets in the same section of the Package Insert.

12. List the components of the Opadry white film coat instead of including the name in the Description Section of the Package Insert and in the description of the Inactive Ingredients in the Medical Guide.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research
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/s/

RAMESH K SOOD
08/13/2009
The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #22-250

Drug Name: AMAYA (fampridine)

Sponsor: Acorda Therapeutics, Inc.

Background: AMAYA (fampridine) is a potassium channel (\(I_{Kv}\)) blocker indicated as a treatment to improve walking ability in patients with multiple sclerosis (MS).

The test article was negative in a full battery of \textit{in vitro} (Ames test, chromosomal aberration assay in CHO cells, and \(tk^+/-\) mouse lymphoma assay) and \textit{in vivo} (rat and mouse micronucleus assay) genotoxicity assays.

ECAC concurrence was not requested for either of the 2-year carcinogenicity studies.

Mouse Carcinogenicity Study

CD-1/Crl mice were administered fampridine at doses of 0, 0, 2.0, 12.5, and 80 mg/kg/day via dietary admixture for up to 104 weeks. The HDM and HDF had a reduced survival rate compared to Controls; the effect was statistically significant only in HDF. HDF were euthanized at week 100 due to low survival; however, this sacrifice did not compromise the outcome of this study. Decreased body weight for HD groups was observed (M, -11.6% and F, -12.3%) compared to controls. HD groups exhibited an increased incidence of convulsions, which is considered part of the pharmacological effect of fampridine. No other significant adverse effects were observed. No drug-related increases of any tumor type were found in this study.

Rat Carcinogenicity Study

CD\(^8\)BR (VAF/Plus)/Crl rats were administered fampridine at doses of 0, 0, 2, 6, and 18 mg/kg/day via dietary admixture for 104 weeks. Mean body weights for HDM and HDF were decreased throughout the entire dosing period; final mean body weights were significantly decreased (-18.1 and -21.4%, respectively) compared to Controls. Mean body weights for LD and MD groups were not significantly affected. Initially, histopathological evaluation was conducted only for the Control and HD groups. Histopathological evaluation for the LD and MD groups were subsequently conducted, at
the Agency’s request, because of the magnitude of the body weight effects at the HD. No
drug-related increase of any tumor type was observed in males; however, a statistically
significant increase in the incidence of uterine polyps was observed in females at the HD.

Executive CAC Recommendations and Conclusions:

Mouse:

- Although prior concurrence of the exec-CAC was not obtained, the Committee
  agreed that the dose selection for the study was adequate, based on reduced body
  weight at the high dose.

- The Committee concluded that the study was negative for drug related neoplasms.

Rat:

- Although prior concurrence of the exec-CAC was not obtained, the Committee
  agreed that the dose selection for the study was adequate, based on reduced body
  weight at the high dose.

- The Committee concurred that the study was negative for drug related neoplasms
  in males, but positive in females with a statistically significant increase in the
  incidence of uterine endometrial polyps at the HD, which was above the historical
  incidence range.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:
/Division File, DNP
Freed/Supervisor, DNP
Houghtling/Reviewer, DNP
Reese/CSO/PM, DNP
/ASefried, OND IO
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/s/

ADELE S SEIFRIED  
08/12/2009

DAVID JACOBSON KRAM  
08/12/2009
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, for fampridine Sustained-Release (SR) tablets, 10 mg.

We also refer to your submissions dated May 8, 15, 20, and 28, and June 22 and 24, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process.

If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 1, 2008.

During our filing review of your application, we identified the following potential review issues:

NONCLINICAL

1. potentially genotoxic impurities in the drug substance and/or drug product have been identified:

We acknowledge that you have submitted in vitro genotoxicity assays (Ames, chromosomal aberration in CHO cells) for , and that these assays adequately address the genotoxic potential of this impurity. We also acknowledge that you have provided in Amendment No012 (June 22, 2009) Derek for Windows reports for five of the impurities listed, including However, since we do not consider a negative result in a
Derek report definitive for regulatory purposes, these reports do not adequately address our concern regarding the genotoxic potential of the \( \text{(b)(4)} \) other impurities assessed.

Therefore, each of the remaining \( \text{(b)(4)} \) impurities identified as potentially genotoxic would need to be either reduced to a maximum daily intake of \( \leq 1.5 \, \mu g/\text{day} \) or determined to be negative when tested directly in \textit{in vitro} genotoxicity assays (i.e., an \textit{in vitro} bacterial reverse mutation assay and either an \textit{in vitro} cytogenetic assay in mammalian cells or an \textit{in vitro} mouse lymphoma tk assay (with colony sizing)) (cf., Guidance for Industry—Q3A Impurities in New Drug Substances [February 2003, ICH, Revision 1], and Guidance for Industry—Q3B(R) Impurities in New Drug Products [November 2003, ICH, Revision 1]).

2. You have not provided sufficient data to support your proposed specification limit of \( \text{(b)(4)} \) for the \( \text{(b)(4)} \) impurity. The specification limit of \( \text{(b)(4)} \) exceeds the 0.5% qualification threshold (cf. Guidance for Industry—Q3B(R) Impurities in New Drug Products [November 2003, ICH, Revision 1]). As noted, the \textit{in vitro} genotoxicity assays adequately address the genotoxic potential of this impurity; however, to qualify an impurity in a drug product intended for chronic use we generally also require a 3-month repeat-dose toxicity study and an embryofetal study, each in a single species.

SAFETY

1. Please explain how you defined abnormal renal function for your analysis of AEs that is summarized in ISS table 32.2.2.4.

1. A search of the AE data set identified one pregnancy during fampridine trials. Did you identify any other pregnancies in fampridine trials? If so, please provide details for these events.

2. In the Summary of Clinical Safety you state that no indications have been found of abuse potential of fampridine. How did you assess the abuse potential of fampridine?

3. Please provide additional details of the overdose for patient #10 from study SCI-F301. You should include how much fampridine the patient took, describe the circumstances surrounding the event (why the overdose occurred), report the duration of associated symptoms, and report any other pertinent information about the event.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at...
The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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 fampridine for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call James H. Reese, Ph.D., RAC, Senior Regulatory Health Project Manager, at 301-796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
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/s/
---------------------
Russell Katz
7/2/2009 03:05:38 PM
NDA 22-250

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

Dear Dr. Walter:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our March 30, 2009, refusal to file letter for the following:

Name of Drug Product: Fampridine

Review Priority Classification: Priority

Date of Application: April 22, 2009

Date of Receipt: April 22, 2009

Our Reference Number: NDA 22-250

We have filed the application in accordance with 21 CFR 314.101(a). The user fee goal date will be October 22, 2009.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. After the review, we will notify you whether we have waived the pediatric study requirement for this application.
Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltville, MD 20705-1266

If you have any questions, call James H. Reese, Ph.D., RAC, Regulatory Project Manager, at 301-796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
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/s/

Russell Katz
5/5/2009 10:30:02 AM
NDA 22-250

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 January 30, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fampridine SR.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. Format issues for eCTD
   a. The current eCTD submission only has study numbers without study titles. You must include the study titles for all studies under Modules 4 and 5 in the eCTD submission.
   b. The current tabular listing of studies does not have a complete listing of all clinical pharmacology studies. You must include all the clinical pharmacology studies included in Module 5 of the submission in the tabular listing of studies under Module 5.

   For eCTD format issues you may find it helpful to contact the Agency at esub@fda.hhs.gov.

2. Missing analytical reports
   a. Analytical validation reports are missing for some studies. You must submit analytical reports for studies BE10F-SR022004, RD10F-SR012004, and 0194-002.
   b. The quality control summary is not included in the analytical report of study BE10-25F-SR10OS12003. You must provide the missing pages (pages 19-21) of the analytical report for study BE10-25F-SR10OS12003, as well as any other missing information related to the quality control summary.
3. Missing pharmacokinetic information
   
a. The study entitled “Pharmacokinetic and Tolerability Evaluation of Single Dose Fampridine SR Tablets Under Fed and Fasted Conditions, Single Dose Fampridine SR Capsules Under Fasted Conditions, and Multiple Dose Fampridine SR Tablets in Patients with Multiple Sclerosis [Tolerability Evaluation] (0195-001US)” does not provide any pharmacokinetic information in the study report. You must submit pharmacokinetic information from this study as pharmacokinetic samples were taken during the conduct of this study.

Additional Issues Not Related to the Refuse to File Decision

Although the following deficiencies cannot serve as the basis for refusing to file the application, we cannot perform an adequate independent review of your application until they are addressed.

Statistical Issues

1. Walking speed data are inadequately presented in the efficacy dataset of study F-204.
   Walking speed data at screening and at visits 0 and 1 are missing. Walking speed data for visits 2, 3, 4, 5, and 6 are given as an average of the 2 separate walking speed evaluations. Walking speed data for visit 7 are either missing or mislabeled. Therefore, we are not able to independently verify the primary efficacy endpoint.

Clinical Pharmacology Issues

1. Data Sets
   
a. Analysis data sets are not included for studies BE10-25F-SR10OS12003, 0494-006, 1194-002, 0497-010, 0792-001, 0193-002, RD10F-SR012004, 1194-001US, and 0194-002. (Note that you should provide analysis data for all studies throughout your submission in order to promote an efficient review of your application.)

b. You have only presented concentration time data for some relative bioavailability studies. You have not provided any pharmacokinetic parameters for studies BE10F-SR022004 or BE25F-SR022004. You should submit pharmacokinetic data as an xpt file for studies BE10F-SR022004 and BE25F-SR022004 with pharmacokinetic parameters in this format: “Subject, Period, Sequence, Treatment, AUCinf, AUCt, Cmax”.

2. Additional Information
   
a. We could not locate formulation information for the SR capsule in your submission. If already provided, please indicate its location in the submission. Also, please clarify whether the SR capsule is different from the capsule. If they are different, you should provide the formulations and dosage strengths of each of these formulations.
Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference.

If you have any questions, call James H. Reese, Ph.D., RAC, Regulatory Project Manager, at 301-796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
3/30/2009 04:19:47 PM
Acorda Therapeutics, Inc.
Attention: Brian A. Walter, Ph.D.
Senior Director, Regulatory Affairs
15 Skyline Drive
Hawthorne, NY 10532

Dear Dr. Walter:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Fampridine-SR Tablets
Date of Application: January 30, 2009
Date of Receipt: January 30, 2009
Our Reference Number: NDA 22-250

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 31, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266
All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call James H. Reese, PhD, RAC, Regulatory Project Manager, at (301) 796-1136.

Sincerely,

{See appended electronic signature page}

James H. Reese, PhD, RAC
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
James Reese
2/19/2009 03:05:55 PM
## ACTION PACKAGE CHECKLIST

### APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>22-250</th>
<th>NDA Supplement #</th>
<th>N/A</th>
<th>BLA STN #</th>
<th>If NDA, Efficacy Supplement Type:</th>
<th>N/A</th>
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<tbody>
<tr>
<td>Proprietary Name:</td>
<td>Ampyra</td>
<td>Applicant:</td>
<td>Acorda Pharmaceuticals, Inc.</td>
<td>Agent for Applicant (if applicable):</td>
<td>N/A</td>
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<tr>
<td>Established/Proper Name:</td>
<td>dalfampridine</td>
<td>Dosage Form:</td>
<td>Extended Release Tablets</td>
<td>RPM:</td>
<td>Hamet Toué, PharmD</td>
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<tr>
<td>Division:</td>
<td>Neurology Products</td>
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</tbody>
</table>

### NDAs:

- **NDA Application Type:**
  - X 505(b)(1)
  - [ ] 505(b)(2)

- **Efficacy Supplement:**
  - [ ] 505(b)(1)
  - [ ] 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

### 505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

- Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):
  - N/A

- Provide a brief explanation of how this product is different from the listed drug:
  - N/A

- [ ] If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

- [ ] No changes
- [ ] Updated

Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

**On the day of approval**, check the Orange Book again for any new patents or pediatric exclusivity.

### Actions

- Proposed action
- User Fee Goal Date is January 22, 2010
- Previous actions *(specify type and date for each action taken)*

<table>
<thead>
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<th>Date</th>
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<td>TA</td>
</tr>
<tr>
<td>None</td>
<td>Refuse to File</td>
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<tr>
<td>March 30, 2009</td>
<td></td>
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</tbody>
</table>

---

1 The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Version: 12/4/09
If accelerated approval, were promotional materials received?
Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain______

<table>
<thead>
<tr>
<th>Application Characteristics²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review priority:</td>
</tr>
<tr>
<td>Chemical classification (new NDAs only):</td>
</tr>
<tr>
<td>□ Fast Track</td>
</tr>
<tr>
<td>□ Rolling Review</td>
</tr>
<tr>
<td>X Orphan drug designation</td>
</tr>
<tr>
<td>NDAs: Subpart H</td>
</tr>
<tr>
<td>□ Accelerated approval (21 CFR 314.510)</td>
</tr>
<tr>
<td>□ Restricted distribution (21 CFR 314.520)</td>
</tr>
<tr>
<td>Subpart I</td>
</tr>
<tr>
<td>□ Approval based on animal studies</td>
</tr>
</tbody>
</table>

Comments:

| BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only) | □ Yes, date |
| BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only) | □ Yes □ No |
| Public communications (approvals only) | X Yes □ No |
| • Office of Executive Programs (OEP) liaison has been notified of action | X Yes □ No |
| • Press Office notified of action (by OEP) | □ None |
| • Indicate what types (if any) of information dissemination are anticipated |
| □ HHS Press Release |
| □ FDA Talk Paper |
| □ CDER Q&As |
| □ Other |

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.
### Exclusivity

- Is approval of this application blocked by any type of exclusivity?  
  - X No  □ Yes

- NDAs and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.  
  - X No  □ Yes  
    If yes, NDA/BLA # and date exclusivity expires:

- (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)  
  - □ No  □ Yes  
    If yes, NDA # and date exclusivity expires:

- (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)  
  - □ No  □ Yes  
    If yes, NDA # and date exclusivity expires:

- (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)  
  - □ No  □ Yes  
    If yes, NDA # and date exclusivity expires:

- NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)  
  - X No  □ Yes  
    If yes, NDA # and date 10-year limitation expires:

### Patent Information (NDAs only)

- Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.  
  - X Verified  □ Not applicable because drug is an old antibiotic

- Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.  
  - 21 CFR 314.50(i)(1)(i)(A)  □ Verified  
  - 21 CFR 314.50(i)(1)  □ (ii) □ (iii)

- [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).  
  - □ No paragraph III certification  
    Date patent will expire

- [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).  
  - □ N/A (no paragraph IV certification)  □ Verified

Version: 12/4/09
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

(1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

If “Yes,” skip to question (4) below. If “No,” continue with question (2).

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If “No,” continue with question (3).

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “No,” continue with question (5).
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner’s receipt of the applicant’s notice of certification?

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If “No,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “Yes,” a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.

### VOLUME 1 CONTENTS OF ACTION PACKAGE

- Copy of this Action Package Checklist\(^3\)  
  Included as Package Cover

### VOLUME 1 Officer/Employee List

- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)  
  X Included

- Documentation of consent/non-consent by officers/employees  
  X Included

### VOLUME 1 Action Letters

- Copies of all action letters (including approval letter with final labeling)  
  Action(s) and date(s)  
  Refuse to File March 30, 2009  
  Approval Letter: January 22, 2009

### VOLUME 1 Labeling

- Package Insert (write submission/communication date at upper right of first page of PI)  
  - Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.  
  - Original applicant-proposed labeling  
  - Example of class labeling, if applicable

\(^3\) Fill in blanks with dates of reviews, letters, etc.

Version: 12/4/09
| Medication Guide/Patient Package Insert/Instructions for Use (write submission/communication date at upper right of first page of each piece) | Medication Guide | X | None |
| --- | --- | --- | --- | --- |
| • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | None |
| • Original applicant-proposed labeling | Included |
| • Example of class labeling, if applicable | N/A |
| Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission) | Included |
| • Most-recent draft labeling | January 6, 2010 |
| Proprietary Name | | | |
| • Acceptability/non-acceptability letter(s) (indicate date(s)) | Letters: |
| • Review(s) (indicate date(s)) | August 6, 2009 (conditional OK) |
| | December 11, 2009 (withdrawn) |
| | December 18, 2009 (granted) |
| | Reviews: |
| | August 4, 2009 |
| | November 24, 2009 |
| | December 18, 2009 |
| Labels: | | | |
| | August 14, 2009 |
| | November 20, 2009 |
| | X DMEPA |
| | X DRISK |
| | November 24, 2009 |
| | X DDMAC | November 30, 2009 |
| | CSS |
| | X Other reviews: |
| | Maternal Health Team: |
| | December 22, 2009 |

VOLUME 1

Administrative / Regulatory Documents

<table>
<thead>
<tr>
<th>Administrative Reviews (e.g., RPM Filing Review(^4)/Memo of Filing Meeting) (indicate date of each review)</th>
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<tbody>
<tr>
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<td>X January 22, 2010</td>
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<td>Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></td>
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<tr>
<td>• Applicant in on the AIP</td>
<td>Yes X No</td>
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<tr>
<td>• This application is on the AIP</td>
<td>Yes X No</td>
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<tr>
<td>o If yes, Center Director's Exception for Review memo (indicate date)</td>
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<tr>
<td>o If yes, OC clearance for approval (indicate date of clearance communication)</td>
<td></td>
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<tr>
<td></td>
<td>Not an AP action</td>
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</table>

\(^4\) Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Version: 12/4/09
### Pediatrics (approvals only)
- Date reviewed by PeRC ______
  - If PeRC review not necessary, explain: ______
- Pediatric Page (approvals only, must be reviewed by PERC before finalized)

<table>
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### Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)

<table>
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<th>Verified, statement is acceptable</th>
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<td>TCon: February 6, 2008</td>
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<tr>
<td>Email: March 7, 2008</td>
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<tr>
<td>Ack Letter: May 5, 2009</td>
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<tr>
<td>74-day Ltr: July 2, 2009</td>
</tr>
<tr>
<td>Email Req: August 7, 2009</td>
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<tr>
<td>CMC IR Ltr: August 13, 2009</td>
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<tr>
<td>CMC IR Ltr: October 28, 2009</td>
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### Outgoing communications (letters (except action letters), emails, faxes, telecons)

### Internal memoranda, telecons, etc.

### Minutes of Meetings

- Pre-Approval Safety Conference (indicate date of mtg; approvals only)
  - X Not applicable
- Regulatory Briefing (indicate date of mtg)
  - X No mtg
- If not the first review cycle, any end-of-review meeting (indicate date of mtg)
  - X N/A or no mtg
- Pre-NDA/BLA meeting (indicate date of mtg)
  - Pre-NDA Mtg: December 7, 2006
  - Pre-NDA Mtg: October 31, 2007
  - Pre-NDA Mtg: October 27, 2008
- EOP2 meeting (indicate date of mtg)
  - December 20, 2004
- Other milestone meetings (e.g., EOP2a, CMC pilot programs) (indicates dates)
  - SPA Minutes: April 8, 2005

### Advisory Committee Meeting(s)

- Date(s) of Meeting(s)
  - October 14, 2009
- 48-hour alert or minutes, if available (do not include transcript)
  - Included

### VOLUME 2 Decisional and Summary Memos

- Office Director Decisional Memo (indicate date for each review)
  - January 22, 2010
- Division Director Summary Review (indicate date for each review)
  - January 21, 2010
- Cross-Discipline Team Leader Review (indicate date for each review)
  - January 20, 2010
- PMR/PMC Development Templates (indicate total number)
  - January 21, 2010

### VOLUME 2 Clinical Information

- Clinical Reviews
  - Clinical Team Leader Review(s) (indicate date for each review)
    - November 30, 2009 (Safety)
    - January 20, 2010 (CDTL Rev)
  - Clinical review(s) (indicate date for each review)
    - October 26, 2009 (Safety)
    - December 24, 2009
  - Social scientist review(s) (if OTC drug) (indicate date for each review)
    - X None

---

5 Filing reviews should be filed with the discipline reviews.

Version: 12/4/09
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<td>Financial Disclosure review(s) or location/date if addressed in another</td>
<td>See Clinical Review dated December 24, 2009 (page 12)</td>
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<tr>
<td>review OR</td>
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<td>a review/memo explaining why not (indicate date of review/memo)</td>
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<td>Clinical reviews from immunology and other clinical areas/divisions/Centers</td>
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<td>(indicate date of each review)</td>
<td>Scheduling Recommendation: None at this time.</td>
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<td>Controlled Substance Staff review(s) and Scheduling Recommendation</td>
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<td>(indicate date of each review)</td>
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<td>Risk Management</td>
<td>December 15, 2009</td>
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<tr>
<td>- REMS Document and Supporting Statement (indicate date(s) of submission(s)</td>
<td>January 19, 2010</td>
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<td>- REMS Memo (indicate date)</td>
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<td>- Risk management review(s) and recommendations (including those by OSE and</td>
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<td>CSS) (indicate date of each review and indicate location/date if</td>
<td></td>
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<tr>
<td>incorporated into another review)</td>
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<tr>
<td>DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters</td>
<td>DSI Letters:</td>
</tr>
<tr>
<td>to investigators)</td>
<td>June 11, 2009 (2 letters)</td>
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<tr>
<td></td>
<td>June 25, 2009</td>
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<td>Clinical Microbiology</td>
<td>July 10, 2009</td>
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<tr>
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<td>VOLUME 3</td>
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<td>letters)</td>
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<td>VOLUME 3</td>
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<td>each review)</td>
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<tr>
<td>Statistical review(s) of carcinogenicity studies (indicate date for each</td>
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</tr>
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</tr>
<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>Included in P/T review, page 252</td>
</tr>
<tr>
<td>DSI Nonclinical Inspection Review Summary (include copies of DSI letters)</td>
<td>X None requested</td>
</tr>
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**VOLUME 3  Product Quality**

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<td>NDAs: Microbiology reviews (sterility &amp; pyrogenicity) (OPS/NDMS) (indicate date of each review)</td>
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<tr>
<td>BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)</td>
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| Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review) | X None |

| Environmental Assessment (check one) (original and supplemental applications) |  |
| Categorical Exclusion (indicate review date) (all original applications and all efficacy supplements that could increase the patient population) | September 14, 2009 page 81 | December 14, 2009 page 6 |
| Review & FONSI (indicate date of review) |  |
| Review & Environmental Impact Statement (indicate date of each review) |  |

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<tr>
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<td>Date completed: July 31, 2009</td>
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<tr>
<td>EER/EES Printout in September 14, 2009 review (pages 84-86)</td>
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<td>BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date)</td>
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<td>X Not needed</td>
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Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

1. It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
2. Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
3. Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean any reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

1. The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
2. And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
3. And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

1. Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
2. Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
3. Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.
IND 17,627

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Fampridine-SR Tablets.

We also refer to the meeting between representatives of your firm and the FDA on October 27, 2008.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call James H. Reese, Regulatory Project Manager, at 301-796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes
MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 27, 2008
TIME: 9:00-10:00 AM EST
LOCATION: CDER WO Room 1309
APPLICATION: IND 17,627
DRUG NAME: Fampidine-SR Tablets
TYPE OF MEETING: Type B/preNDA meeting

MEETING CHAIR: Russell Katz, M.D.

MEETING RECORDERS: James Reese, Ph.D.
Stephanie N. Keefe

FDA ATTENDEES:

Russell Katz, MD, Division Director, DNP
Eric Basting, MD, Deputy Division Director & Clinical Team Leader, DNP
Billy Dunn, MD, Clinical Team Leader, DNP
Rob Harris, MD, Clinical Reviewer, DNP
Jagan Parepally, PhD, Clinical Pharmacology Reviewer, DNP
Sharon Yan, PhD, Biostatistics Reviewer, DNP
James Reese, PhD, Regulatory Project Manager, DNP
Stephanie N. Keefe, Consumer Safety Officer, DNP
Hiren Patel, FDA Student Intern, DNP

ACORDA THERAPEUTICS, INC. ATTENDEES:

Clinical:
Andrew Blight, Ph.D.
Patricia Snyder, MPH
Ron Cohen, M.D.

Statistics:
Lawrence Marinucci, M.S.

Regulatory Affairs:
Brian Walter, Ph.D.
Susan Way, Ph.D.
Susi Antoniuk, M.S.
IND 17,627
Page 3

BACKGROUND:

Acorda Therapeutics, Inc. requested a Type B/preNDA meeting, on June 19, 2008, to
discuss the clinical results of their second Phase 3 study as well as the clinical content and format
for the proposed NDA for Fampridine-SR tablets. A separate Type B/preNDA meeting was held
on October 30, 2007, to discuss the non-clinical and CMC information to be provided in the
NDA for Fampridine-SR tablets. Minutes from the October 30, 2007 meeting, with the Agency,
were provided to Acorda Therapeutics on January 10, 2008.

QUESTIONS FOR PRE-NDA MEETING

Clinical Efficacy:

Acorda has completed 3 well-controlled studies that demonstrate the efficacy of Fampridine-SR
10 mg, b.i.d. In all three studies, there was a statistically significant increase in the proportion of
patients who met a defined criterion for an improvement in walking speed. Secondary efficacy
variables (leg strength, the 12-Item MS Walking Scale (MSWS-12), Subject Global Impression
(SGI) and Clinician Global Impression (CGI) were consistent across studies and demonstrated
benefit across all four types of MS and independent of concomitant treatment with
immunomodulator drugs. A description of the statistical analyses performed in each of the three
studies, as well as the Statistical Analysis Plan (SAP) for the ISE are included in the Briefing
Package.

1) Does the Division agree that all appropriate analyses that are planned demonstrate
efficacy of Fampridine-SR? [See Section 7.3 Efficacy of Fampridine: Plans for the ISE]

FDA preliminary response:
This will ultimately depend on detailed review of the data. On face, the analyses
appear appropriate.

Meeting Discussion:
The briefing document included plan for analyses of ISE. We are more interested in
efficacy analysis for individual studies. We have previously requested endpoint analyses
of walking speed and MSWS-12 for F204, which should be performed with last
observation carry forward (LOCF) and observed cases (OC).

2) Acorda proposes to market 10 mg BID for Fampridine-SR. Is the proposed dosage and
administration supported by the available data in the MS-F203 and MS-F204 studies?
[See Section 7.3.2 ISE Overview]

FDA preliminary response:
On face, yes, but it will depend on the detailed analysis of the data in the NDA.

Meeting Discussion:
No additional comments.
3) Does the Division have any additional requests with respect to the analyses or data presentations planned for the ISE? [See Section 7.3.2 ISE Overview]

**FDA preliminary response:**

Please present secondary efficacy variable analyses for all patients randomized (i.e. not limited to responders).

**Meeting Discussion:**

FDA requested as a secondary efficacy analysis the change from baseline at each double-blind visit and at the last visit. FDA stressed the importance of preserving type I error in secondary comparisons. FDA asked Acorda to provide analyses not only of patients identified as responders, but also of entire treatment groups (i.e. drug vs. placebo).

4.) Acorda proposes the following indication for Fampridine-SR package insert based upon the clinical program. While Acorda appreciates that labeling content is a review issue, does FDA agree, in principle, that the proposed wording would be appropriate, based on the primary endpoint measure and its validation with the MSWS-12? [See Section 6.1.2 Proposed Indication Statement]

*Fampridine-SR is indicated for the treatment of walking disability in people with Multiple Sclerosis*  
(b) (4)

**FDA preliminary response:**

No. Any claim must be supported by independent substantiation of an effect on a relevant and valid endpoint. You appear to have demonstrated an effect on walking speed in at least 2 independent clinical trials. To support any additional claim (i.e. disability, strength), you would need to show an effect on relevant endpoints in the entire randomized population (i.e. limiting that analysis to only the subgroup of responders would not be valid). One way to proceed may be to design a study where you first identify responders, and then re-randomize these patients to active drug or placebo, prospectively conducting the primary analysis on the disability and leg strength endpoints.
Meeting Discussion:

FDA commented that the MSWS-12 walking scale has not been fully validated to support a disability claim, and that a full validation would be required, in collaboration with the FDA patient-reported outcome (PRO) review group.

FDA will determine whether any of this information will be recorded in the indication section or in the clinical trial section of the label.

5) Acorda plans to request a Priority Review for Fampridine-SR. Does the Division concur that such a request would be appropriate for Fampridine-SR? [See Section 6.1.3 Justification for Priority Review]

FDA preliminary response:

No. We acknowledge that fampridine may become the first oral agent approved for an MS-related indication, but others products approved were showed to have a lasting (i.e. at least 2 years) effect on disability. Your product not only does not appear to have shown an effect on disability, but also appears to have demonstrated an effect sustained for no more than 4 months.

Meeting Discussion:

Acorda argued that other drugs decrease relapse rate, but that fampridine improves walking change today/next week, which Acorda considers a significant difference. FDA asked Acorda to make a case for a difference from marketed products when they apply for priority review. Acorda requested that FDA refers to a July 28 letter.

Clinical Safety

The Statistical Analysis Plan (SAP) for the Integrated Summary of Safety (ISS) describes the statistical methods to be used for the analysis of the integrated safety data from all clinical trials and formulations of fampridine completed by Acorda or by previous Investigational New Drug (IND) holders. Particular emphasis will be placed on the safety of the proposed commercial formulation and dose (Fampridine-SR 10 mg b.i.d) in the target population (patients with MS). A total of 55 studies will be included in the safety assessment. A description of the statistical analyses to be performed as well as the Statistical Analysis Plan (SAP) for the ISS is included in the Briefing Package.
IND 17,627
Page 6

The Briefing Package contain plans for the analysis of additional key safety information, including the recently completed thorough QTc study, seizure data, and other uncommon but potentially significant adverse events.

6) Are the plans for analyzing and presenting the safety information adequate? [See Section 7.4 Safety of Pampridine Planned for the ISS]

**FDA preliminary response:**

On face, yes. Please insure the coding dictionary with a list of all investigator verbatim terms and the preferred terms to which they were matched is submitted as an SAS transport file.

**Meeting Discussion:**

FDA reiterated that it is looking for a consistent, simple narrative that is easy to navigate and in which it is possible to find the information that is needed. The narratives that are not due to adverse events can be extremely succinct, as little as one or two sentences if that is all the information available. The narratives for deaths, discontinuations and other serious cases should contain all of the information stated in the example included with the preliminary meeting notes, but the information does not have to be in the exact order of the sample as long as it is consistent.

Acorda asked for clarification about how the narratives are currently written (by patient rather than by SAE term) and FDA expressed a preference to keep each event as an individual narrative, but that if there were multiple event terms at one time they could stay together. If, as an example, there were two different SAEs that occurred 6 months apart it would make more sense if they were written up as two separate narratives.

*****

Please submit CRFs and narratives for each subject listed as discontinued for

- “lost to follow-up.”
- “Other.”
- “Physician Decision.”
- “Patient Decision.”
Please provide narratives of all SAEs in all trials. We especially want details for all:

- Deaths
- SAEs
- Discontinuations due to Adverse Events (occasionally called “adverse dropouts.”)

For the narratives, we would like a common template for each report that is useful and easy to review. This useful common narrative template should sequentially and clearly report:

- Patient age and gender
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent (not extraneous) medical history
- Concomitant medications with start dates relative to the adverse events.
- Pertinent physical exam findings
- Pertinent test results (e.g. lab data, ECG data, biopsy data)
- Discussion of the diagnosis as supported by the available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information.

Please define “Premature Termination,” “Dropouts,” and “Discontinuation,” in the context of your NDA if these terms are used.
For the components of incidence calculations, please describe what is being counted (# of patients who have an event, # of events?) to calculate the numerator. Note that risk measures events per person, and rate should include a time component.

**********

Table Shells

Please be sure ALL AEs are presented, not just those deemed “drug-related.”

We want straight-forward, simple, easy-to-read shells with the pertinent information readily apparent.

For a quick overview reference, we would like a simple single table displaying the overall counts of the source and number of participants who received study medication and PBO for your combined trials.
Sample Overall Count Summary Table Shell:

| Overview of Source and Number of Participants (Participants Who Received Study Medications) |
|----------------------------------|---------------------------------|---------------------------------|----------------------------------|
| Clinical Phase 2/3 Integrated Safety Database | PBO | Fampridine | Other Comparators if Used |
| # Subjects Controlled Studies | | | |
| Diagnosis (Type of MS) | | | |
| # Subjects Controlled and Uncontrolled Studies | | | |
| Diagnosis (Type of MS) | | | |

Please provide a display of the total clinical experience with fampridine by dose, time, and formulation as far as known.

Please provide a simple summary table displaying all trial deaths, SAEs and TEAEs for the 3 core studies and the TQTc study.

To easily grasp drug exposure experience please provide the following variety of displays containing the following data:
Overall Number of Participants

Overall Duration

- Measures of central tendency (mean, median) by
  - Study
  - Study Pool
  - By RCT vs. OL
  - By important demographics

Distribution of Dose

- If dose ranges were used, please include modal dose

Duration by dose (or modal dose)

- Overall
  - For important subgroups

Sample Shells:

Any Exposure by Dose –

<table>
<thead>
<tr>
<th>Fampridine Dose</th>
<th>All</th>
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</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>N</td>
<td>%</td>
</tr>
</tbody>
</table>
Any Exposure by Duration

Table 2: All subjects ever exposed to fampridine: Distribution of Subjects by cumulative treatment duration

<table>
<thead>
<tr>
<th>All Subjects Ever Exposed to fampridine</th>
<th>Fampridine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Ever Exposed</td>
<td></td>
</tr>
<tr>
<td>≥ 3 months</td>
<td></td>
</tr>
<tr>
<td>≥ 6 months</td>
<td></td>
</tr>
<tr>
<td>≥ 12 months</td>
<td></td>
</tr>
<tr>
<td>Etc</td>
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Exposure by Dose AND Duration

Table 3: Dose/Duration Table Shell

Number (Percent) of Patients Receiving Fampridine According to Daily Dose and Duration of Therapy

<table>
<thead>
<tr>
<th>Duration (Weeks)</th>
<th>Dose (mg)</th>
<th></th>
<th></th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>Aaa mg</td>
<td>Bbb mgs</td>
<td>Total</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>XXX weeks</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>YYYY weeks</td>
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<td>(Any Duration)</td>
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<tr>
<td>%</td>
<td></td>
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</table>
7) Based upon a teleconference (February 5, 2008) between the Division and Acorda, we have developed a plan to summarize the potential risk of seizures associated with the use of Fampridine-SR in MS patients.

   a. Does the Division agree that the proposed plan is adequate? If this proposal is not adequate, what other information/analyses does the Division think should be included in the NDA? [See Section 7.5 Seizure Proposal]

   **FDA preliminary response:**
   
The plan is adequate, pending review. Please provide a display for the total seizure experience by time, by dose and by formulation for fampridine in all clinical trials (not just MS trials).

   **Meeting Discussion:**
   
   No additional comments.

   b. Acorda plans to develop a REMS for the NDA around the major contraindications expected in the future PI for Fampridine-SR. Although it is early in the process, does the Division have any comments on the approach Acorda has for handling the potential risk of seizure and severely renal impaired MS patients using Fampridine-SR tablets. [See Section 7.6 Risk Minimization Action Plan (RiskMAP)]

   **FDA preliminary response:**
   
   No. This will be addressed during the NDA review. It may be that the division concludes that a REMS is unnecessary.

   **Meeting Discussion:**
   
   No additional comments.

8) The integrated safety information provided in the original NDA with a cutoff of December 31, 2007 and will include information from the MS-F204 and TQT study. Additional safety information provided by the ongoing open-labeled extension studies (MS-F202EXT, MS-F203EXT and MS-F204EXT) will be provided as a separate safety update within the original application.

   a. Does the Division agree in the proposed format and content of updated safety data to be provided by the extension studies? [See Section 7.4.1 Overview of Sources of Information]
FDA preliminary response:
Data cutoff date should be at a maximum 6 months before the date of NDA submission.

Meeting Discussion:
Acorda plans to have a fully integrated data cut off of July 31, 2008. In addition, Acorda will provide narratives for any serious adverse events that occur in the ongoing open label studies through the end of October. FDA agreed that this would be acceptable.

b. The safety update after submission of the original NDA will provide for integrated safety data from all studies. Does the Division agree with the post submission update proposal? [See Section 7.4.1 Overview of Sources of Information]

FDA preliminary response:
The safety update must be submitted at a maximum 4 months after the submission of the NDA.

Meeting Discussion:
The safety update will include all updated information from the ongoing open label studies as well as the fasted study. This data will be integrated into the ISS and tables with an additional column for the safety update will be provided. FDA found this acceptable.

9) Does the Division have any additional requests or recommendations with regard to clinical safety?

FDA preliminary response:
Be sure your update shows differences from the initial submission and the updated safety information. Again, this information should be displayed in a simple, straight-forward fashion to improve review efficiency.

Meeting Discussion:
No additional comments.

Electronic Submissions
Acorda has engaged the services of (b)(4) to facilitate the electronic submission of this NDA in the cCTD format. The cCTD application and the SDTM datasets will
be compiled according to all current FDA specifications, along with the appropriate supporting documentation.

10) Does the Division have any comment on the information to be provided in the content plan for the NDA? [See Section 7.8 Electronic Submission Plan]

**FDA preliminary response:**

We would like to invite your participation in a pilot review project the Division and sponsors are finding quite useful. If you agree, we can send you the new Reviewer's Template, which is the actual document the Medical Officer will use for the fampridine review. Then your staff can hyperlink the template to your submission and return to us.

This will allow the review staff to drill down to pertinent areas of the submission quickly with as much detail as needed. We will be happy to work with you in this regard, including an extra meeting if needed to formulate a plan.

**Meeting Discussion:**

*FDA would provide Acorda with a template that would be populated with direct links into the NDA. The FDA medical officer is willing to have multiple meetings with Acorda representatives, as needed, to clarify issues that may arise along the way. This tool is not required to be completed prior to submission of the NDA. Acorda agreed to participate in this program.*

**Regulatory / Miscellaneous**

11) Would the Division please comment on the probability of a FDA Advisory Committee Meeting in support of the Fampridine NDA Review? If an advisory committee is expected, what would be the anticipated topics?

**FDA preliminary response:**

This remains a possibility pending review. Potential topics would similarly be selected pending the review.

**Meeting Discussion:**

*No additional comments.*

12) Acorda plans to conduct a Food-Effect Study in healthy subjects, using the proposed commercial 10 mg debossed tablets. Acorda believes that this study would supplement the existing food effect study completed with the clinical 12.5 mg
Fampridine-SR tablets (study 0494-006) and 25 mg Fampridine-SR tablets (study FeFa25F-SR-112003). The report would be included in the 120-day safety update after submission of the original NDA. Does the Division agree that this proposal is adequate and would not result in additional time added to the review clock? [See Section 6.2.3 Food Effect Study- FeFa10F-SR2008]

FDA preliminary response:

No. This study is not needed.

Meeting Discussion:

No additional comments.

ADDITIONAL COMMENT

Please provide the summary section as a review aid for CPB reviewer. Outline of the summary section of the HPBIO section is provided. At the time of NDA submission you can use this template to write the summary of the Clinical Pharmacology and Biopharmaceutics section of the NDA or provide it to the agency as a review aid. This summary section should be submitted electronically with appropriate hyperlinks to the relevant supporting data (Document is provided separately).

POST-MEETING ADDITIONAL COMMENTS

Clinical Pharmacology

Since Fampridine SR is an extended-release drug product, the sponsor should investigate the potential dose-dumping effect in the presence of alcohol in vitro using dissolution media containing various alcohol concentrations (e.g., increments of 5, 20, and 40%). Depending on the in vitro results, additional in-vivo study may be necessary.

Biostatistics

Efficacy Data Request for Statistical Review

The statistical reviewer would appreciate the sponsor to submit the data in the following format:

1. Efficacy Data – One efficacy data set for each study

   • We are primarily interested in efficacy analyses that are prospectively specified in the protocol or statistical analysis plan. Please submit the data corresponding to the primary
analysis in a single data set. Variables used in post-hoc analyses should be included in a separate efficacy data set for the study.

- Please include all efficacy variables, including derived variables, in one data set. You may separate primary and secondary efficacy data sets if the data set is too large to contain all efficacy variables due to many secondary efficacy variables. Each patient may have multiple records, with one record representing each visit or each recorded measurement, up to the visit (week) when the subject discontinued or completed the trial. For repeated measurements within one visit, data can be recorded using different variables such as score1, score2, ....

- Patients who prematurely discontinued should be indicated by a flag variable.

- Patients who have missing values due to premature discontinuation or other reasons should NOT have their values carried from previous visit. Missing values should be entered as " ".

- Imputed values (such as LOCF) and derived variable (such as difference from baseline) may be recorded as a separate variable.

- Baseline disease characteristics can be either included in the efficacy data if it will be used in efficacy analysis, or be included in demographic data if it will not be used in efficacy analysis.

- Please label all variables and provide a word or pdf document for more detailed explanation of the variables.

2. Demographic Data – One demographic data set for each study

- Please include demographic characteristics in one data set. Each patient should have one and only one line.

- Please label all variables and provide a word or pdf document for more detailed explanation of the variables.

3. Additional Data

All other variables that are not used in the efficacy analysis and that are not demographic characteristics used in the report should NOT be included in the two data sets described above. These variables can be included in an additional data set.

4. Please provide SAS source code for the protocol specified primary analysis of each study.

Statistical reviewer Dr. Sharon Yan can be reached at (301) 796-1165
CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW AID

This is only an example of the requested review aid. This can also replace the summary section of Clinical Pharmacology and Biopharmaceutics:

- Please fill the headings as it applies to your drug
- Additional specific headings can be included to suit the development of your drug/dosage form (for e.g. For extended release products, headings like comparability of the ER to IR product, for transdermal products section on effect of application site on the PK and adhesiveness of the product etc should be included)
- All statements in this summary section should be annotated with links similar to your “annotated label” that would allow the reader to locate all relevant data supporting the statement. Additional links should be provided, whenever possible, for the study report and any raw data located in a SAS transport file or other format that supports the QBR statement.
- Within the summary section text, relevant Tables and Figures to understand the data should be included and should not be referred to some Appendix.
- Results from various studies, pop pk analyses should be pooled to provide information under each heading, so that consistencies across studies can be determined. If results from two similar studies are different, plausible explanations of these differences should be included.
- If different formulations were used during the development, the section should mention what formulation was used (to-be marketed vs. clinical service formulation)
1.0 GENERAL ATTRIBUTES OF THE DRUG

This section contains background information about the drug and drug product to provide a context for assessing the results of the clinical pharmacology and biopharmaceutics studies.

1.1 Drug/Drug Product Information:

Dosage Form/Strengths:
Pharmacologic Class:
Chemical Name:
Physical Characteristics:

Formulation: Quantitative formula for all the dose strengths

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Wt (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation #/Capsule Strength</td>
<td></td>
</tr>
</tbody>
</table>

| | |
| | |
| | |
| | |
| | |

Total Size

1.2 Proposed mechanism(s) of action and indication(s)

1.3 Proposed dosage(s) and route(s) of administration?

2.0 GENERAL CLINICAL PHARMACOLOGY

2.1 Design features of the clinical pharmacology and clinical studies used to support dosing or claims:

Here describe the type of pivotal clinical studies in brief for each indication.

For treatment of A: For e.g.

The efficacy of Drug X in patients was established in X Phase 3 randomized, double-blind, parallel, placebo-controlled multi-center trials of Y weeks duration conducted as Z treatment of patients. Of these Z studies only Y studies used the proposed dosing regimen. The X mg/day dose was not replicated in any study. Should use key studies and supportive studies that are used for labeling the product.

Short tabular descriptions may be useful here, for example:
Should repeat this information for each indication if multiple indications are proposed.

2.2. **Clinical endpoints** (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies

*For treatment of A: For e.g.,*

The primary criterion to establish the efficacy of Drug X was the.....

The primary efficacy parameter was:

The secondary efficacy parameters were:

2.3 **Exposure-response relationships**

2.3.1 **Characteristics of exposure/effectiveness relationship**

*For Efficacy in patients with X:*

An exposure (dose)-response analysis was conducted in X patients pooled from X studies (Study numbers). Provide exposure or dose/response analyses data. This section should include information on all proposed doses and should also include relevant Tables and Figures of dose-response or exposure-response either from the PK-PD study conducted or from pivotal clinical trials that were used to label the drug product.

This section should also include information on any differences of exposure/dose –response for covariates such as dose, regimen, gender, age, race etc.

2.3.2 **Characteristics of the exposure-response relationships for safety (dose-response, concentration-response)**

If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

This section should include relevant safety information on all proposed doses and should also include relevant Tables and Figures.

This section should also include information on any differences of exposure/dose –response relationship for safety in covariates such as dose, regimen, gender, age, race etc.
e.g. Dizziness and somnolence were the most prevalent adverse events associated with treatment.

The probability for a subject to experience dizziness (AE1) increased with the dose. At the X mg/day, the incidence of AE1 averaged to be approximately 30% (range: from >20% to <50%). Female patients apparently reported higher incidence of dizziness. It is clear that the variability was high among various trials as shown in the following figure (a). The ED₅₀ for incidence of dizziness was estimated to be X ± Z mg/day. ED₅₀ for severity of somnolence was estimated to be Y ± Z mg/day. 

The incidence and severity of AE1 can also be depicted by the following figures that differentiate the incidence of adverse events for the BID and TID regimens.

2.3.3 Effect on QT or QTc interval

Should include relevant Tables and figure showing Concentration-QTc relationship.

2.3.4 Justification of dose and dosing regimen based on known relationship between dose-concentration-response (In some cases, it may be possible to combine this with 2.3.2 and 2.3.3.)

The following are the proposed dosage regimen for patients:

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Age Group</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
<th>Increments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age Group:

This section should include what information is available for justifying the dose in a particular age group.

Regimen:

From a pharmacokinetic perspective:

Based on a half-life of x hours, .....appears to be suitable for the Y regimen. However, the sponsor has conducted pharmacokinetic studies to show that X mg q8h vs. Y mg q12h showed similar pharmacokinetic profiles.

Include figure where possible.

Figure: Pharmacokinetics over one dosing interval

Differences in steady state plasma concentration versus time profiles for q8h and q12h dosing regimens can also be evaluated by comparing the differences in Cmax and Cmin for these two dosing regimens. As the dosing interval is increased from q8h to q12h, the fluctuation between Cmax and Cmin would be expected to increase, while Cavg would be expected to remain constant. The following figure illustrates that the differences between regimens are small when individual and mean steady-state Cmax, Cmin, and Cavg values are compared following a dose of Y mg/day administered q8h and q12h in healthy subjects.
Include figures and Tables as necessary

From a pharmacodynamic perspective:

Include figures and Tables justifying the dose and regimen from a efficacy standpoint. Should include information on other regimens studied, but not selected for dosing recommendations and reasons why. This information can be obtained from efficacy studies, PK-PD analysis if conducted or simulation performed.

Conclusions from such analyses must be included. For e.g

These figures show that doses Y mg and above may perform better than the lowest recommended dose in patients based on the EC50 values. However, titrating with a lower dose is desirable for tolerability reasons.

These also show that both X/day and Y/day doses may be acceptable, however, for practical administration reasons X/day may be the preferred choice.

Summary efficacy Tables such as the following should be included.

<table>
<thead>
<tr>
<th>Study - Summary of RRatio analysis (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant based on Hochberg's procedure (p 0.049).
** Based on treatment means for the raw RRatio
*** Hochberg procedure applied to the ranked RRatio

<table>
<thead>
<tr>
<th>Summary of secondary endpoints (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*statistical significance for difference between X dose and placebo (and/or 95% CI exclude zero for Median change figures)
**subject numbers for ITT population are constant across secondary parameters in this table

From a safety perspective:

The two main adverse events of dizziness and somnolence was evaluated in terms of various doses given X/day and Y/day conditioned on severity of the adverse event. The following plots show that Y/day regimen had higher percent of observation for both dizziness and somnolence. This could be due to sustained concentration of Drug X with Y dosing.

Titration Scheme:
If a titration scheme is recommended information relevant to its selection should be included.

2.4 PK characteristics of the drug and its major metabolite?

2.4.1 Single dose and multiple dose PK pharmacokinetics?

Here provide tables and figures on mean pharmacokinetic parameters and refer to them in the subsequent sections.

Also include in this section whether the pharmacokinetics of the drug change with chronic dose, and information on whether the multiple dose PK is predicted from single dose PK, accumulation ratio, time to reach steady state etc.

2.4.2 General ADME characteristics of the drug

Absorption: may include information on transporter as well

Distribution: include information on protein binding etc

Metabolism:

Elimination:

2.4.3 Fate of drug as seen in mass balance studies

Include tables and figures from the mass balance study, also state whether these studies suggest renal or hepatic as the major route of elimination.

2.4.4 Comparison on PK between healthy subjects and patients

This section should also include information obtained from population analysis if conducted along with any definitive PK study conducted. Table and figures showing the differences in the two population should be included.

2.4.5 Degree of linearity or nonlinearity in the dose-concentration relationship

The non-linearity can be due to multiple dosing or due to increase of doses. Both should be described in this section.

This section must include tables showing dose proportionality with statistical evaluation of the data using power model analysis.

This section should also include figures of drug normalized PK parameters versus dose for all relevant PK parameters.

An example Table given below:

Multiple dosing Day 1 vs Day 10 – X-Y mg/day.

<table>
<thead>
<tr>
<th>Table</th>
<th>Study - Summary Results of the Assessment of Dose Proportionality Using the Power Model Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK Parameter</td>
<td>Day</td>
</tr>
<tr>
<td>PK Parameter</td>
<td></td>
</tr>
</tbody>
</table>
The results of the analysis demonstrate dose proportionality in AUC.

2.4.5 Inter-subject variability in PK parameter

Include Tables to show variability, information from different studies should be included. This section should also mention the possible causes of this variability.

3.0 INTRINSIC FACTORS

In the introductory paragraph of this section highlight the key intrinsic factors that influence exposure and response and what is the impact of such differences in efficacy and safety.

The following intrinsic factors should be discussed:

3.1 Effect of Renal Impairment:

This section should include information on the type of data available, can be presented in Tables such as...

<table>
<thead>
<tr>
<th>Group Creatinine Clearance*</th>
<th>Renal function</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &gt; 80 mL/min</td>
<td>Normal</td>
<td>8</td>
</tr>
<tr>
<td>2.50-80 mL/min</td>
<td>Mildly</td>
<td>8</td>
</tr>
<tr>
<td>3 30-49 mL/min</td>
<td>Moderately impaired</td>
<td>8</td>
</tr>
</tbody>
</table>

* according to Cockcroft and Gault

Include relevant figures and Tables showing the renal clearance with change of creatinine clearance. Include 90% CI in the Tables.

Dosage Adjustment: State if needed or not. If yes then what

Dosing recommendations should be provided in Tabulate format
### Sponsor's Proposal for Dosage Adjustment Based on Renal Function

<table>
<thead>
<tr>
<th>Creatinine Clearance (CLcr) (mL/min)</th>
<th>Total X Daily Dose(^a)</th>
<th>Starting dose (mg/day)</th>
<th>Maximum dose (mg/day)</th>
<th>Dose Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

\(^b\) Supplementary dose is a single additional dose.

### 3.2 Effect of Hepatic Impairment:

Information same as above should be included

### 3.3 Effect of Age:

**Elderly:**

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

**Pediatrics:**

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

### 3.4 Effect of Gender:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

### 3.5 Effect of Race:
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Page 25

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, if yes then what

3.6 Effect of pregnancy or lactation:

Similar information as above, if no information available state so.

4.0 EXTRINSIC FACTORS

In the introductory paragraph of this section highlight the key extrinsic factors (such as herbal, diet, smoking, alcohol) that influence exposure and response and what is the impact of such differences in efficacy and safety.

Also indicate in brief whether there are any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered.

4.1 In vitro basis of drug interactions

Include information on the following, this section should not be descriptive only but should include relevant Tables to show the results and indicate which of these can lead to possible in vivo drug interactions under each of these subheadings:

- Drug as substrate of CYP 450
- Drug as inhibitor of CYP 450
- Drug as inducer of CYP 450
- Drug interaction based on protein binding
- Drug as substrate of p-glycoprotein
- Drug as inhibitor of p-glycoprotein
- Any other transporter involved

This section can also include information from mass balance studies that suggest possible interaction, for e.g. if totally renally eliminated then there is a possibility of an interaction with drugs that are also renally eliminated.

Also indicate whether the in vitro studies are conducted at relevant therapeutic concentrations (in the same units as for the plasma data (e.g. ng/ml as opposed to μM or μmole/liter)).

4.2 In vivo drug interactions

Give a tabular listing of all drugs and indicate whether a dosage adjustment is necessary. This section can be subdivided into pharmacokinetic and pharmacodynamic interactions.

**Pharmacokinetic Interactions:**

For e.g. Influence of Drug X on the pharmacokinetics of concomitant drugs and the influence of these drugs on the pharmacokinetics of Drug X is summarized in the following Table:

<table>
<thead>
<tr>
<th>Concomitant Medication</th>
<th>doses evaluated</th>
<th>Drug X on Co-Med</th>
<th>Co-Med on Drug X</th>
<th>Evaluation Method</th>
<th>Dosage Adjustment</th>
</tr>
</thead>
</table>
5.0 GENERAL
BIOPHARMACEUTICS

5.1 BCS Classification of the drug

This section should include information on solubility, permeability and dissolution of the drug product, which are the basis of classifying the drug and formulation. All relevant tables and figures should be included.

5.2 Relative Bioavailability of the to-be-marketed formulation to those used in the clinical studies

This section should include tables showing the test and reference comparisons, geometric mean of PK parameters, geometric mean ratios and 90% CI.

If the formulations are not bioequivalent this section should also indicate what safety and efficacy issues may arise, if any. In case of failed BE studies, this section should provide other supporting data regarding the to-be-marketed formulation that would aid in the decision making for the approval of the product.

5.3 Absolute Bioavailability and Relative Bioavailability to other dosage forms/route of administrations

This section should include tables showing the test and reference comparisons, geometric mean of PK parameters, geometric mean ratios and 90% CI.

5.4 Food effect

Provide tables as well showing the ratios and 90% CI. Also indicate if type of meal (light, medium, high) has an effect, if necessary.
IND 17,627
Page 27

Also provide the dosing recommendations based on the results of the Food Effect study. Indication if clinical trials were done with or without regard to food. If different across studies tabular listing of clinical studies and their dosing administration in relation to meals. Include any population analysis data if available.

If a fed BE study was conducted, provide justification for doing so, that will help reviewers in decision making.

5.5 Dissolution and IVIVC if appropriate

This section should include dissolution method and specifications and justification for selecting the method (for example stirring speed, media etc).

5.6 Alcohol Effect (for ER products):

This is to rule out dose dumping. Should provide the data in tabular format based on in vitro dissolution in different concentrations of alcohol. If in vivo data are available, include in this section as well.

6.0 ANALYTICAL

This section should highlight the method used in analytical assays and provide its validation parameters. This can be done in a tabular format.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>parent</th>
<th>-metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>LC/MS/MS</td>
<td>LC/MS/MS</td>
</tr>
<tr>
<td>LLOQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QC samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-day accuracy and precision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-day accuracy and precision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freeze-thaw stability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benchtop Stability at RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term at 70°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
If several different analytical methods were used, the difference in method and the LLOQs should be given, for example in a Table:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Method</th>
<th>Assay Sensitivity ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>340</td>
<td>LC/MS</td>
<td>X</td>
</tr>
<tr>
<td>344</td>
<td>LC/MS</td>
<td>Y</td>
</tr>
</tbody>
</table>

Assay cross validation results should also be provided.

In this section in Tabular format also provide the assay performance from each study (QC data).
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/s/

RUSSELL G KATZ
12/31/2008
Date: February 6, 2008

IND: 17627 Telecon

Teleconference Date: February 6, 2008     Time: 4:00 pm

Meeting Sponsor: Acorda Therapeutics

Contact: Brian Walter, 914-347-4300, ext. 139

Product: Fampridine

From: James Reese

Telecon Minutes:

FDA asked for this telecon to discuss the frequency of seizures associated with fampridine use.

- The Agency is concerned about the frequency of seizures reported in recent submissions. Several cases have occurred at doses of 10mg BID. The Agency asked the sponsor to address this issue in the NDA submission. The rate and background should be addressed.
  - Acorda does not yet have a full analysis, but has sent an overview.

- Fampridine’s background rate should be compared to other products. Rates from placebo and drug arms of studies of other products should not be combined. The background rate from controlled trials is needed. The rate of seizures needs to be considered for this indication.

- There appears to be a dose relationship between the drug and seizures.
  - Acorda asked if they could separate out the 10mg group when they do the analysis?
  - The Agency responded that there are issues.
    - The rate at higher doses cannot be ignored.
    - What are the confidence intervals for the data.
    - The indication drives the concerns.
The Risk/benefit of the drug is always considered

FDA Attendees
Russell Katz
Eric Bastings
Rob Harris
James Reese
<table>
<thead>
<tr>
<th>Linked Applications</th>
<th>Sponsor Name</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND 17627</td>
<td>ACORDA THERAPEUTICS INC</td>
<td>4-AMINOPYRIDINE</td>
</tr>
</tbody>
</table>

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

/s/

JAMES H REESE
03/07/2008
From: Reese, James  
Sent: Friday, March 07, 2008 10:32 AM  
To: 'Brian Walter'  
Subject: 17627  

Brian,

We have the following request:

In reference to IND 17627, submission SN284, we recommend that you revise the protocol to add the analysis of walking speed and to compare the change from baseline to endpoint in the walking speed between the treatment groups. We also recommend that you add the analyses to compare Fampridine-SR responders with non-responders in the Multiple Sclerosis Walking Scale (MSWS-12) and CGI. These analyses will not be considered as part of the primary analyses as they are in MS-F203, but will help to confirm the findings in MS-F203 and to provide additional information which will allow us to evaluate the efficacy more accurately. The analysis methods for the Ashworth Assessment of Spasticity, MSWS-12, SGI, and CGI need to be added to the SAP.

Jim

James H. Reese, Ph.D., RAC  
Regulatory Project Manager  
DNPIODE1\CDER\FDA
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/s/

JAMES H REESE
03/07/2008
MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 31, 2007
TIME: 9 AM – 10 AM
LOCATION: White Oak, Building #22, Conference Room 1311
APPLICATION: IND 17, 627 Fampridine SR
TYPE OF MEETING: Pre-NDA Meeting
MEETING CHAIR: Dr. Russell Katz

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION
Russell Katz, M.D. - Division Director
Eric Basting, M.D. - Deputy Division Director
Jody Green, M.D. - Medical Reviewer
Martha Heimann, Ph. D - CMC Team Leader
John Duan, Ph.D. - Clinical Pharmacology Reviewer
Charles Thompson, Ph.D. - Pharmacology / Toxicology Reviewer
David Hawver, Ph.D. - Pharmacology / Toxicology Supervisor (Acting)
CDR Teresa Wheelous - Sr. Regulatory Management Officer

ACORDA Therapeutics Attendees and Titles
Andrew Blight, Ph.D. – CSO
Ron Cohen, M.D. – CEO
Bill Dollard, Ph.D. – Sr. Director, Manufacturing
Brian Walter, Ph.D., - Sr. Director, Regulatory Affairs
Susi Antoniuk – Assoc. Director, Regulatory Affairs
Sharon Hamm, Pharm. D. – Sr. V. P., Elan Pharm.

BACKGROUND:
MEETING OBJECTIVES:
DISCUSSION QUESTIONS

Chemistry, Manufacturing, and Controls
1. Is the current drug substance specification for fampridine acceptable for NDA submission? If not, please elaborate.

Pre- Meeting Comment:
The proposed test parameters appear appropriate for drug substance quality control. The adequacy of the analytical procedures and acceptance criteria will be evaluated during the NDA review.

Meeting Discussion: Not Discussed
2. Is the current drug product specification for Fampridine-SR Tablets acceptable for NDA submission? If not, please elaborate.

Pre-Meeting Comment:
The proposed test parameters appear appropriate for drug product quality control. The adequacy of the analytical procedures and acceptance criteria will be evaluated during the NDA review.

Meeting Discussion: Not Discussed

3. Is the plan to identify and qualify in the NDA an alternate drug product manufacturing site for Fampridine-SR Tablets acceptable for NDA submission? If not, please elaborate.

Pre-Meeting Comment:
In general, the proposal to qualify an alternate manufacturer appears reasonable; however, the equivalence of the products to be manufactured at the two sites will be a matter of review. You will need to provide initial stability data (3 months accelerated and long-term) for three tablet batches manufactured at the [redacted] facility. Please note that incorporation of manufacturing information relevant to either site by cross-reference to a Type 2 DMF may result in difficulties during review of the NDA. The primary reason for this is that due to DMF confidentiality requirements we are unable to incorporate information contained in a DMF into the review of the NDA, or into the review of a second DMF. Additionally, we would not be able to discuss any specific concerns related to the comparability of the two manufacturers with you, or with your suppliers. Thus, we encourage you to provide sufficient documentation for the Elan and [redacted] manufacturing processes within a single submission.

Meeting Discussion:
• The sponsor clarified that all CMC information for the drug product will be submitted in the NDA, not in DMFs.
• Possible approaches to address the requirement for stability data to support the [redacted] facility were discussed. The Agency noted that one alternative would be to submit certificates of analysis for process validation batches at least three months prior to the action date. The sponsor noted that, in addition to the stability studies summarized in the briefing package, extensive stability data are available for tablet batches manufactured at the [redacted] facility using drug substance sourced from [redacted]. The firm subsequently decided not to use [redacted] as a supplier for commercial batches. It was agreed that the Agency would consider a proposal to use the available data for the [redacted] batches. The sponsor will submit a Type C - CMC meeting request through the ONDQA PM, Scott Goldie.

4. Is the proposed NDA registration stability package for the drug product acceptable to support NDA submission and to support a 36-month expiration dating period? If not, please elaborate.

Pre-Meeting Comment:
Although the stability package described may be deemed acceptable for filing of the NDA, assignment of the expiration dating period will be a matter for review. Our decision will be based on the extent and quality of the data for the primary stability
batches. The designation of drug product batches as primary stability batches should be consistent with the number of batches and batch selection criteria discussed in the ICH guidance Q1A(R2) Stability Testing of New Drug Substances and Products. We note that the stability data provided in Appendix D, Attachment 2, was generated using formulation development batches, not the primary registration stability batches. As noted in the briefing package, a number of the batches presented as primary stability batches are not fully representative of the proposed commercial product. These batches (Elan lots PS1112, 0000022747, and 0000022748) differ with respect to film-coat color, debossing, packaging and bottle fill count. We acknowledge that the Division previously agreed the debossing and the difference in fill count would not impact on designation of these lots as primary stability batches. You should; however, therefore, provide appropriate data, e.g., batch analysis data including comparative dissolution profiles, to demonstrate that the properties of the primary stability batches are comparable to the to-be-marketed tablets. Additionally, you will need to provide information to support the equivalency of the packaging used for primary stability batches to the proposed commercial bottles. Additional stability data may be submitted during the NDA review. Additional data received within the first 5 months after submission of the NDA will be reviewed as part of the original application; however data received later may not be reviewed during the same review cycle.

Meeting Discussion:
- The sponsor confirmed that dissolution profile data are available.
- The sponsor will provide appropriate data (e.g., head space analysis, USP tests, and comparative stability data) to support equivalence of stability and commercial bottles.

5. Acorda plans to submit in the NDA one executed batch record from each of the two drug product manufacturers. Is the plan acceptable? If not, please elaborate.

Pre-Meeting Comment:
Yes

Meeting Discussion: Not Discussed

6. Given that Orphan Drug Designation has been granted for Fampridine-SR Tablets in this indication, please confirm that it is acceptable to request a Categorical Exclusion from an Environmental Assessment.

Pre-Meeting Comment:
Orphan Drug Designation is not directly relevant to whether the NDA will qualify for categorical exclusion. Based on the indication and proposed dosage regimen, however, it appears likely that the application would qualify for categorical exclusion under 21 CFR § 25.31(b) if the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). You will need to evaluate whether your product will qualify for a categorical exclusion on this basis, or meets one of the other criteria described in 21 CFR § 25.31. A formal claim of categorical exclusion should be provided in the NDA submission. Refer to Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications.

Meeting Discussion: Not Discussed
ADDITIONAL CMC COMMENTS:
DMF (b)(4) is referenced for information on fampridine drug substance manufactured by
(b)(4) is referenced for information on Fampridine Extended
Release Tablets manufactured by Elan. Although you may reference both of these DMF
in the NDA; the following information should be included in the NDA submission itself:

- A list of all facilities involved in manufacturing, testing, or packaging of the bulk
drug substance or drug product. This list should include complete addresses,
registration numbers and contact information for each facility. All functions (e.g.,
drug substance testing, tablet manufacture, stability testing, etc.) that will be
performed by each facility should be identified.
- The acceptance specification for the bulk drug substance (including analytical
procedures and supporting methods validation data), batch analysis data for all
drug substance batches used in nonclinical studies, and justification for the
proposed specification.
- The drug product specification (including analytical procedures and supporting
methods validation data) and justification for the proposed specification.

Meeting Discussion:
The sponsor will address all of the additional CMC points, but noted that since some of
the nonclinical studies are extremely old, detailed information for the drug substance
batches used may not be available. Information is available for the batches used in the
pivotal nonclinical studies.

ADDITIONAL CMC DISCUSSION:
At the end of the meeting the sponsor whether the Agency would consider a proposal for
a reduced testing stability protocol to support a (b)(4) sample packaged in a 30 cc bottle.
It was agreed that this proposal could be included in the CMC meeting request for the
Pathogen site stability proposal.

Nonclinical Pharmacology and Toxicology
7. Acorda seeks confirmation that no additional studies are required for impurity
qualification.
Pre-Meeting Comment:
The study reports submitted in support of qualification of the (b)(4) impurity
appear, on face, to be adequate. A final determination of the adequacy of the data will be
a matter of review and cannot be further addressed at this time. Based on the information
provided, we agree that nonclinical studies are not needed to qualify impurity 2HBA.
Meeting Discussion: Not Discussed

8. Specifically with respect to carcinogenicity studies, lifetime studies have been
performed in mice and rats. These study reports were originally submitted to IND 51,333
in April 1999 (Serial Nos. 029 and 030) and later resubmitted on 16 August 2002 (Serial
No. 090) with a request that the reports be submitted to the Carcinogenicity Assessment
Committee for review. As electronic datasets were subsequently requested, Acorda
assumes the reports have been reviewed. We seek confirmation that the studies are
adequate.

Pre-Meeting Comment:
Based on the available information, it would appear that the carcinogenicity studies in mouse and rat are adequate, with the following exception:

- Due to an excessive body weight effect in high dose male rats, a full battery of tissues should be examined microscopically in the lower dose groups. However, a final determination of the adequacy of the studies will be based on additional review of the data and cannot be further addressed at this time.

Meeting Discussion:

- The sponsor asked for clarification regarding the recommendation that tissues from the lower dose groups be examined microscopically. The Division noted that an excessive decrease in body weight (relative to controls), as demonstrated in high-dose male rats, may reduce the sensitivity to detect tumors; therefore, it is important to adequately evaluate potential tumorigenic responses in the lower dose groups in which body weight was not similarly affected.
- When the histopathology data are available for the lower dose groups, a new statistical analysis will need to be conducted.

9. Please confirm that no additional nonclinical studies will be required to support the NDA, assuming no new safety issues arise during continued clinical development.

Pre-Meeting Comment:
Based on the summary provided in the briefing package, the following additional nonclinical data will be needed to support an NDA:

- Plasma exposure (Cmax, AUC) data in the animal species (and strains) tested in the pivotal toxicology (including general and reproductive toxicology and carcinogenicity) studies for parent compound and all major metabolites circulating in human. If these data were not collected in the pivotal (or other relevant) studies, then bridging studies will need to be conducted using similar doses and route(s) of administration. These data are needed in order to determine the relevance of the animal species to human and to document that the toxicity of parent compound and major human metabolites has been adequately tested in the nonclinical studies.

Also, see preliminary response to Nonclinical Question 8.

Meeting Discussion:
- At the meeting, the sponsor provided a list of proposed TK studies (reproduced below). The sponsor proposed conducting TK bridging studies for the reproductive toxicology studies in non-pregnant animals. The Division stated that this approach would appear reasonable, but that a more definitive response would be provided after further internal discussion.
• The Division confirmed that TK data would need to be provided in dog to confirm the adequacy of the chronic toxicity study in that species. The Division reminded the sponsor that TK analysis in animals needs to include quantitation of parent compound and major human metabolites. [Note added: based on further internal discussion, we have the following additional comments regarding your list of proposed TK studies:

• The TK bridging studies to support the embryo-fetal development and the preand post-natal development studies should be conducted in pregnant animals, unless you have data to document similar kinetics in pregnant and non-pregnant animals.

• The TK bridging studies need to be conducted at the same doses and with the same dosing regimen used in the definitive studies.

Clinical Pharmacology
10. Acorda seeks confirmation that no additional in vivo clinical pharmacology studies are required.
Pre-Meeting Comment:
Additional clinical pharmacology studies are required.

  o You should characterize whether there are gender, age, and race differences for the pharmacokinetics of fampridine in future clinical studies if such information is not available.
  o See Question 11.
  o Please clarify the differences of the formulation used between the Phase 3 clinical/to-be-marketed and the food effect study, renal impairment study and other pivotal clinical pharmacology studies.

Meeting Discussion:

  o The sponsor stated that the effects of gender, age and other covariates will be investigated using population approach.
  o The sponsor clarified that the previously conducted food effect studies used formulations of 25 mg (IR) and 12.5 mg (SR), which were different from the to be-marketed formulation of 10 mg (SR). The Agency emphasized that the food effects are formulation dependent and the sponsor should provide the detailed comparison among the formulation used. Another food effect study has to be conducted if there is not enough information to justify and apply the results from the existing food effect study to the final 10 mg SR formulation.

11. With respect to drug interaction studies, does FDA agree that no further in vivo studies appear warranted at this time?
Pre-Meeting Comment:
We do not agree. Additional studies are warranted at this time. In vitro studies have not provided sufficient evidence to exclude the in vivo studies.
- Studies for CYP2C19 and 2E1 were not conclusive.
- CYP2B6 and 2C8 have not been evaluated.
- Induction potential of fampridine has not been evaluated.
- Major transportors such as P-gp have not been evaluated.

You should conduct the in vitro studies listed above. If the studies show signal for potential drug interactions, in vivo studies should be performed.

**Meeting Discussion:**
The sponsor stated that the in vitro studies will be conducted. The CYP 2C19 study will be repeated.
Transporter studies will include P-gp studies only.

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**Linked Applications Sponsor Name Drug Name**

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<tr>
<th>IND 17627</th>
<th>ACORDA</th>
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<td>THERAPEUTICS INC</td>
<td>4-AMINOPYRIDINE</td>
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/s/

RUSSELL G KATZ
12/21/2007

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-1161
(fax) 301-796-9842
New email address: teresa.wheelous@fda.hhs.gov
IND 17,627

Acorda Therapeutics
ATTENTION: Brian A. Walter, Ph.D.
Senior Director Regulatory Affairs
And Quality Assurance
15 Skyline Drive
Hawthorne, NY 10532

Dear Dr. Walter:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Fampridine-SR Tablets.

We also refer to your December 22, 2006, request, serial number 230, for a special clinical protocol assessment, received December 26, 2006. The protocol is entitled MS-F204: “Double-Blind, Placebo-Controlled, 13-Week, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine-SR (10 mg b.i.d.) in Patients with Multiple Sclerosis”.

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

1. Pending the availability of clinical results, does the Division agree that the two studies (MS-F203 and MS-F204) would be adequate to support an NDA for Fampridine-SR?

   A. Tentatively, yes. However, please add the following secondary endpoints already evaluated in Study MS-F203: Ashworth Assessment of Spasticity, MSWS-12, SGI, and CGI. Statistical significance need not be demonstrated for these secondary endpoints in the new trial, but this information will be considered in the review of all of the evidence available on efficacy.

   B. FDA also would like to have data to evaluate whether the drug effect on gait is present throughout the dosing interval, or if there is an end-of-dose wearing off of efficacy. This could be accomplished by, at least at one of the visits, evaluating patients at various times during the dosing interval, or by evaluating patients at different times at the various visits, to cover the dosing interval.
C. Please also note that the labeled indication will be based on substantial evidence from clinical trials. It is premature to finalize the indication at this time, but it is not clear that you will have the evidence required to support the indication proposed in your cover letter. You will need to justify your proposed indication in the NDA.

2. Does the Division have any comments or suggestions regarding the design of the MS-F204 study (ATTACHMENT A), especially regarding the primary, secondary endpoints, duration of study, sample size, statistical analysis plan and concomitant therapy?

A. Please include your PK and/or PK-PD analysis plan in the protocol and justify your sampling scheme (one sample per visit, time unknown) based on prior knowledge of the pharmacokinetics of Fampridine-SR.

B. Please specify the criteria for determining whether the normal assumption is violated in the analysis of LEMMT.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our “Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products”). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cker/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call James H. Reese, Ph.D., Regulatory Project Manager, at 301-796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-- Russell Katz
2/8/2007 12:23:03 PM
IND 17,627

Acorda Therapeutics
ATTENTION: Brian A. Walter, Ph.D.
Senior Director Regulatory Affairs
And Quality Assurance
15 Skyline Drive
Hawthorne, NY 10532

Dear Dr. Walter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Fampridine.

We also refer to the meeting between representatives of your firm and the FDA on December 7, 2006. The purpose of the meeting was to discuss the proposed NDA for Fampridine for the treatment of patients with multiple sclerosis.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call James H. Reese, Ph.D., Regulatory Project Manager, at (301) 796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure
Meeting Date and Time: December 7, 2006
Meeting Type: C
Meeting Category: Pre-NDA
Meeting Location: White Oak, Bldg 22, Rm 1309
Application Number: IND 17,627
Product Name: Fampridine
Sponsor Name: Acorda Therapeutics
Meeting Chair: Russell Katz
Meeting Recorder: James Reese
Meeting Attendees:

FDA Attendees
Russell Katz
Eric Bastings
Kun Jin
James Reese

Acorda Attendees
Christine Redmond
Karin Kook
Lawrence Marinucci
Ron Cohen
Andrew Blight
Brian Walter

1.0 BACKGROUND

- This meeting was held to discuss the NDA for Fampridine for the treatment of patients with multiple sclerosis.
2.0 DISCUSSION

2.1 Clinical

Question 1a): Does the Division agree that the results of the MS-F203 study meet all requirements of the SPA?

FDA response: On face, yes. Review of the complete data (when an NDA is submitted) will be necessary to provide a definite answer.

Meeting Discussion:
• No Comment

Question 1 b): Does the Division agree that these data, supported by similar outcomes using an identical, but retrospective ITT analysis of the MS-F202 study, provide sufficient clinical evidence of safety and effectiveness of Fampridine-SR to support the initial NDA for this drug candidate?

FDA response: No. The Agency generally requires two adequate and well-controlled studies, each convincing on its own, to establish substantial evidence of effectiveness. In some instances, the Agency relies on one study plus confirmatory evidence. You are referred to the May 1998 Guidance document on “Providing Clinical Evidence of Effectiveness for Human Drug and Biological products”. The relevant section of that document states:

“reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.”

However, you are proposing a symptomatic treatment with no effect on morbidity or mortality. Therefore, the Agency can not rely on a single trial plus confirmatory evidence from a post-hoc analysis of a separate trial in this instance.

Meeting Discussion:
• Acorda discussed the difficulties involved in doing another trial. For example, it is difficult to recruit naïve patients without prior experience with Fampridine.

Question 1 c): If not, what additional information is required to support the NDA for Fampridine-SR?

FDA response: A second adequate & well-controlled trial that is prospective, and not retrospectively analyzed.

Meeting Discussion:
• Acorda began by asking what needed to be confirmed by another trial? They described why they believe they had presented adequate data.

• The Agency stated that nevertheless, the data that had been provided so far does not meet the standard of substantial evidence of effectiveness by 2 separate studies, each
convincing on its own. Changing the precedent was not warranted by the indication (symptomatic treatment).

- The Agency suggested a randomized withdrawal study design (RWSD). The clinical outcome would have to be stated prospectively.

- Acorda asked if the Agency was open to a non-withdrawal study with the primary outcome of timed walk responder analysis? The Agency said that they would have to see the study design, but that the approach appeared reasonable, and that the primary outcome did not have to include all of the elements of Study MS-F203. Also, the new study does not have to be as long as Study MS-F203, and a shorter duration (e.g., 4 weeks) is acceptable.

- Acorda asked if they decided to submit an RWSD study, could it be submitted as an SPA? The Agency agreed to an SPA.

Question 2: Is the current number of people exposed to Fampridine adequate for the safety review for the NDA?

FDA response: On face, yes. You state the SR formulation has been evaluated in 617 people with MS, including 305 for more than 6 months, 144 for > 1 year, and 129 for > 2 years, and that ongoing extension studies of both Study 202 and 203 have recruited an additional 445 patients, 374 of whom remain active. You state that the majority of these patients have received 10 mgs bid, but the exact numbers are not given. This appears to fulfill the requirement for at least 300 patients exposed at the proposed dose for 6 months and at least 100 for 12 months, but we would like to see a table showing the number of patients exposed at various doses (i.e., below the proposed dosing regimen, and at or above the proposed dosing regimen) for various durations (e.g., single dose, 2 weeks, 4 weeks, 3 months, 6 months, 9 months, and 12 months) to confirm our response.

Meeting Discussion:

- Acorda indicated that the figure of 617 included the 445 patients. They would clarify the numbers in the NDA. The total at this point is close to 1450 patients.

Question 3: The Fampridine-SR development plan provided for the collection of a large number of ECGs from people exposed to Fampridine over time on treatment. Based upon the available clinical QT data and the preclinical in vitro and in vivo studies, does the Division agree that additional ECG data are not needed for Fampridine-SR?

FDA response: No. The Serial QTc Study referenced in the submission (Serial 112) was conducted in 1999. It does not appear to fulfill the requirements of a thorough QT study. For example, if not precluded by considerations of safety or tolerability due to adverse effects, the drug is expected to be tested at substantial multiples of the anticipated maximum therapeutic exposure. Also, the study is to include a positive control.

While we are willing to consult the FDA QT review team to determine if the study you have completed can substitute for a thorough QT study, this on face appears unlikely, and our advice to you is to design and conduct a thorough QT study. We refer you to the October 2005
Guidance for Industry E14 “Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs”.

Meeting Discussion:

- QT should be characterized at exposures that some patients are likely to achieve (e.g., through drug-drug interaction or impaired renal or hepatic clearance).

- If 40 mg is still found to be the maximum tolerated dose, this should be justified in the NDA.

Additional Comment:
Meeting Discussion:

- Acorda stated that there is only minor metabolism of Fampridine. Ninety-five percent is excreted unchanged in the urine.

- Acorda asked if the proposed RWSD study could be the second of the two studies that are needed. FDA agreed.

- Acorda was told that they may ask for an end-of-phase 2 meeting to discuss the CMC and nonclinical issues.
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/s/
Russell Katz
1/10/2007 08:27:41 AM
DATE: May 2, 2005

To: Mitch Katz

Company: Acorda Therapeutics
Fax number: (914) 347-4560
Phone number: (914) 347-4300 x115

From: Teresa Wheelous
Division of Neuropharmacological Drug Products
Fax number: (301) 594-2859
Phone number: (301) 594-2850

Subject: IND 17,627 Fampidine SR for Multiple Sclerosis – April 8, 2005 Special Protocol
Telecon Minutes

Total no. of pages including cover: 4

Dr. Katz,

The following are telecon minutes of our April 8, 2005 meeting, in which we discussed the March 2, 2005 Special Protocol Assessment, Protocol MS-F203 (serial 177), for Walking Speed in Multiple Sclerosis.

Thank you,
Teresa Wheelous

Document to be mailed: ☐ YES ☑ NO
MEMORANDUM OF TELECON

DATE: April 8, 2005

APPLICATION NUMBER: 17,627 S-177

BETWEEN:
   Name:
   Ron Cohen,
   Andrew Blight
   Christine Redmond
   Lawrence Marinucci
   Asra Warsi
   Anita Islam.

Call In #1-888-955-5366 PC:120505
   Representing: Acorda

AND
   Name:
   Dr. Russell Katz
   Dr. Eric Bastings
   Dr. Janeth Rouzer-Kammeyer
   Dr. Sharon Yan
   Dr. Kim Jin
   CDR Teresa Wheelous

SUBJECT: Special Protocol Assessment, Protocol MS-F203 (serial 177), for Walking Speed in Multiple Sclerosis

BACKGROUND: Acorda sent on March 2, 2005 a revised protocol for Study MS-F203, following a teleconference with the Division on December 20, 2004, during which the Division expressed several concerns regarding the primary endpoint and analysis plan.

Acorda is now proposing a sequential analysis that will define the primary endpoint as follows:
1. First, Acorda will test if there are significantly more responders in the treatment group than in the placebo group. This test will be performed on data from all ITT subjects.

2. Second, Acorda will compare the responders and non-responders (ITT) for their improvement on the MSWS-12 score as a measure of the global impact of walking improvements on perceived disability. A statistically significant improvement in responders compared to non-responders in this measure will serve to validate the clinical meaningfulness of the responder criterion.

3. Third, Acorda will test for significant improvement in walking speed at the last visit on drug for the Fampridine-treated responders versus the placebo-treated group (responders plus non-responders).
Acorda requested a Special Protocol Assessment, and asked the following questions:

- Whether the Division considers Acorda’s new definition of the primary endpoint and the analysis plan adequate for the demonstration of efficacy
- If this trial is positive according to the proposed criteria, whether the Division agrees that it would be one of the adequate and well controlled studies that demonstrate efficacy
- Whether the division has any additional suggestions on the approach.

DISCUSSION:

- The Division agreed that the Sponsor has addressed some of the FDA concerns with regard to the responder criterion [by adding the second step of the primary analysis]; however, the Division had remaining concerns regarding the maintenance of the effect, which were discussed during the teleconference. In particular, the Division remained concerned that the proposed endpoint did still allow that the treatment may result in a negative response slope among responders, with no clinically significant drug effect at the last visit. The Division emphasized that the endpoint as defined allows that one could lose effect during the treatment period and still be positive on the analysis- that one could do very much worse on drug at the end of the treatment period than at the beginning yet still beat placebo.

- The Division also remarked that for the 3rd step of the analysis testing, the Fampridine responder group is a small selective group which is very likely to beat the placebo group regardless of the treatment effect. In fact, if the roles of comparison groups were reversed, it is likely that the responders in the placebo group would beat the Fampridine group (responders and non-responders) as well. Acorda agreed that this might be the case, but pointed out that the endpoint analysis is not meant to prove efficacy, but only to prove that some treatment effect is maintained at the final visit for the Fampridine responders. The Division accepted the argument.

- The Division asked how missing values are dealt with if a subject has less than three double-blind treatment assessments. Acorda responded that those subjects will be considered as non-responders. The Division pointed out that missing non-treatment assessment values will increase the chance for a patient to be a responder. Acorda agreed with the view, but argued that missing values in the pre-treatment phase should be balanced between the treatment groups because those assessments occur before randomization. To address the possible bias introduced by an imbalance in missing values between the treatment groups, the Division asked Acorda to conduct a sensitivity worst-case scenario analysis, in which subjects in the Fampridine group with missing post-treatment assessment are considered non-responders.

- It was concluded that the protocol with the minor changes discussed could be, if positive, one of the adequate and well controlled studies that demonstrate efficacy. As usual, the division will evaluate the risk and benefits of the treatment to determine approvability.
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/s/

Teresa Wheelous
4/25/05 04:33:24 PM
CSO

Russell Katz
4/29/05 04:34:18 PM
MEDICAL OFFICER
MINUTES OF TELEPHONE CONFERENCE CALL BETWEEN ACORDA AND DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS (DNDP)

20 December at 1:30 p.m.

FDA Attendees
Russell Katz, M.D. Director
Eric Bastings, M.D. Neurology Team Leader
Teresa Wheelous Sr. Regulatory Management Officer

Acorda Attendees
Andrew Blight, Ph.D. Chief Scientific Officer
Ron Cohen, M.D. President and CEO
Mitch Katz, Ph.D. Vice President, Clinical Programs
Lawrence Marinucci Associate Director, Biostatistics
Andrew Goodman, M.D. Associate Professor of Neurology, Univ. Rochester
Karin Kook, Ph.D. Regulatory Consultant
Chris Polman, M.D., Ph.D. Professor of Neurology, Free University Amsterdam
Mark Tuszynski, M.D., Ph.D. Professor of Neurosciences, Univ. California, San Diego

Dr. Russell Katz opened the telephone conference call by acknowledging the delay in responding to Acorda’s request for feedback on the draft protocol submitted. He then indicated that the Division had two significant concerns with the proposed protocol. First, they did not agree that the proposed response criterion has been validated as being clinically meaningful. Specifically, there is overlap between responders and non-responders in the 95% confidence intervals for SGI and the MSWS-12 measures. The second issue, a point already acknowledged by Acorda, is that one can potentially have a decrement in response over time and still be considered a responder. He added that the Division has other comments that relate to handling of data from subjects who drop out, how many non-treatment visits are included, and other details that are “somewhat problematic”. These were not further addressed. The discussion then turned to the two points raised.

Dr. Andrew Blight replied that Acorda also does not consider the response definition to be clinically validated by previous studies. The study proposed will collect the necessary information for that validation. If a temporal decrement in walking speed occurs, it will be evident in the data. Dr. R. Katz replied that his concern is that this aspect is not addressed in the proposal.

In response to Dr. Ron Cohen’s question of the Division’s position should the study turn out “positive”, with data similar to that in the new analysis of the last study, including maintenance of effect and a positive effect on a subjective measure. Dr. R. Katz
responded that the Division will still worry about the other outcomes if they are not pre-specified. Everyone needs to know the rules up front. He wants to avoid any potential for argument after the fact. What the Division would like to see is a prospectively designated global measure and a measure of walking, and would expect a “win” on both. As an example, he cited the Division’s approach to drugs for the treatment of Alzheimer’s disease; it is not enough just to have the measures in the protocol.

He further clarified that the Division has no problem with Acorda performing the study. The real issue is that if it will be designated as one of the pivotal studies, then the Division must worry about the primary endpoint. The Division wants the definition of an outcome to be such that when it is positive, the meaning will be evident.

Dr. Polman asked whether the clinical validation could come from other studies. Dr. R. Katz responded that it depended on the nature of that evidence. If there is a robust experience that shows a strong correlation between this scale, i.e., the responder algorithm, and a global, it may be possible. He added that he thought such literature did not exist. In contrast, if the only available literature addressed untreated patients, that would be problematic as this would be akin to having an unvalidated surrogate endpoint.

Dr. Cohen then returned to the response definition and asked if one resolution might be to require that the final on-treatment measurement be one of those that is better than baseline. Dr. R. Katz replied that that seemed to help, but there could still be issues, such as a negative slope. It is difficult to pre-specify what the slope should be. Dr. Cohen agreed that it was useful to agree on what a “significant decrement” is, for example, if the decline is to below the level of the placebo group.

Dr. Cohen also asked for clarification with respect to inclusion of the global criterion, specifically, whether it needed to be applied to the entire cohort. Dr. R. Katz answered that it could be applied to responders only in determining whether or not there is a “win” on the primary endpoint; additional analyses should include all patients. To this, Dr. R. Katz stated that eventually the Division will also be concerned about long-term effects.

Dr. R. Katz concluded by saying that the Division is willing to consider a responder criterion for a pivotal trial based on walking speed, plus a global measure, used as a two-pronged definition. Some statistical significance criterion will need to be applied to the global. Dr. Cohen asked if there would be any requirement for a specific magnitude of change in the global measure. Dr. R. Katz replied that no specific magnitude of change would be required. only that the global measure be statistically significant in a positive direction. One approach could be to identify those patients who are responders, then look at the global measure in these patients. Ideally, his preference is defining a responder on the basis of both measures, but he acknowledged that this definition of response would be somewhat arbitrary. Drs. Blight and Cohen cited clinician expert concern regarding the variability associated with global measures in this particular patient population. Dr. R. Katz acknowledged this concern and said that perhaps the MSWS-12 is a better global
measure to use. He in turn asked whether there were other scales; the Division does not want to make an approval decision based on criteria that are not clinically appropriate.

Dr. Cohen asked about the possibility of using \[\text{[classifier]}\] as an additional endpoint, but Dr. Eric Bastings responded that \[\text{[classifier]}\] could not be considered as a global measure and is not indicative of function. Dr. R. Katz added that if globals are a concern, another approach would be a 50% increase in walking speed, which might be considered clinically significant in itself. Dr. Tuszyński said at this point that he understood the Division’s perspective in wanting to understand the benefit with respect to quality of life. Nonetheless, subjective scales are difficult in MS patients, in part because of the lability of the condition.

Mr. Lawrence Marinucci has whether a nested testing approach could be used. For example, maintenance of improved walking speed would be demonstrated first, followed by a test on the global measure. There would need to be a “win” at the first step in order to proceed to the second step. Dr. R. Katz answered that the Division has no problem with such an approach, however, it is usually done to see if additional information can be added to the label. He cited an example of where this approach still might not address the Division’s concerns: if there was a significant effect on the primary endpoint but the slope (which would be designated a secondary endpoint) were negative. FDA would not view this as a “win”.

The telephone call, scheduled for 30 minutes because of other commitments, concluded at approximately 2:10. Dr. R. Katz committed to provide the secondary issues in writing.