

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021879Orig1s000

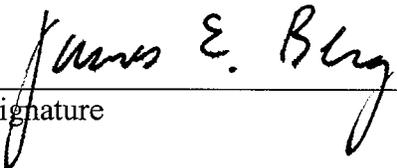
**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3.5.2 PATENT CERTIFICATIONS

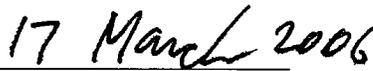
CERTIFICATION OF NO RELEVANT PATENTS

Pursuant to 21 U.S.C. § 355(b)(2)(A) and 21 C.F.R. § 314.50(i)(1)(ii), in the opinion and to the best knowledge of Avanir Pharmaceuticals, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

James E. Berg
Vice President, Clinical & Regulatory Affairs
Avanir Pharmaceuticals, Inc.



Signature



Date

EXCLUSIVITY SUMMARY

NDA # 021879

SUPPL #

HFD # 120

Trade Name Nuedexta

Generic Name dextromethorphan hydrobromide and quinidine sulfate

Applicant Name Avanir Pharmaceuticals

Approval Date, If Known 10/29/10

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 NO

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

505(b)(2)

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 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:

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES

NO

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

The approved indication is not a DESI upgrade. Nuedexta is a new combination product containing dextromethorphan hydrobromide and quinidine sulfate. Quinidine sulfate is a DESI upgrade product for cardiac indications at higher doses. Nuedexta is approved to treat pseudobulbar affect. The active ingredient is dextromethorphan. The purpose of the quinidine is to inhibit the metabolism of dextromethorphan by CYP2D6, increasing plasma concentrations of dextromethorphan in order to get the desired pharmacologic effect.

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.

N/A

YES

NO

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

NDA#

NDA#

NDA#

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

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

Please see attached tables

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:

Study 99-AVR-102 was a multicenter, randomized, double-blind, controlled, parallel-group study in 140 ALS patients with PBA.

Study 02-AVR-106 was a multicenter, randomized, double-blind, placebo-controlled study in 150 MS patients with PBA.

Study 07-AVR-123 was a multicenter, randomized, double-blind, placebo-controlled, study consisting of a double-blind phase and a nonrandomized open-label phase in MS and ALS patients with PBA.

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.")

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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"):

Study 99-AVR-102 was a multicenter, randomized, double-blind, controlled, parallel-group study in 140 ALS patients with PBA.

Study 02-AVR-106 was a multicenter, randomized, double-blind, placebo-controlled study in 150 MS patients with PBA.

Study 07-AVR-123 was a multicenter, randomized, double-blind, placebo-controlled, study consisting of a double-blind phase and a nonrandomized open-label phase in MS and ALS patients with PBA.

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 # 56,954	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND # 56,954	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>

! Explain:

Investigation #3
!
!
IND # 56,954 YES ! NO

(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
!
!
YES ! NO
Explain: ! Explain:

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 RPM completing form: Susan Daugherty
Date: 11/4/10

Name of Division Director signing form: Russell Katz, M.D.

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

SUSAN B DAUGHERTY
11/05/2010

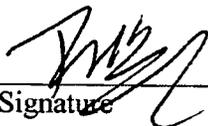
RUSSELL G KATZ
11/08/2010

1.3.3 Debarment Certification

1.3.3. Debarment Certification

Avanir Pharmaceuticals hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Randall E. Kaye, M.D.
Senior Vice President Clinical Research and Medical Affairs, Chief Medical Officer
Avanir Pharmaceuticals, Inc



Signature

3/25/2010

Date

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:
CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Division of Neurology Products
Susan Daugherty X6-0878

REQUEST DATE
10-25-10

IND NO.

NDA/BLA NO.
021879

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG
Nuedexta (dextromethorphan/quinidine)
Capsules

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

Steroid

DESIRED COMPLETION DATE
10-29-10

NAME OF FIRM:
Avanir Pharmaceuticals

PDUFA Date: 10-30-10

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE (IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission:

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Please review and comment.

SIGNATURE OF REQUESTER
Susan Daugherty 6-0878

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

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/s/

SUSAN B DAUGHERTY
10/25/2010



NDA 021879

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Avanir Pharmaceuticals, Inc.
101 Enterprise, Suite 300
Aliso Viejo, California 92656

ATTENTION: Randall E. Kaye, M.D.
Chief Medical Officer
Senior Vice President Clinical and Medical Affairs

Dear Dr. Kaye:

Please refer to your New Drug Application (NDA) resubmission dated April 30, 2010, received April 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Hydrobromide and Quinidine Sulfate Capsules, 20 mg/10 mg (b) (4)

We also refer to your July 19, 2010, correspondence, received July 19, 2010, requesting review of your proposed proprietary name, Nuedexta. We have completed our review of the proposed proprietary name, Nuedexta and have concluded that it is acceptable.

The proposed proprietary name, Nuedexta, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 19, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Susan Daugherty at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Denise Toyer, PharmD
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DENISE P TOYER
10/15/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

NDA 021879

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Avanir Pharmaceuticals, Inc.
101 Enterprise, Suite 300
Aliso Viejo, California 92656

ATTENTION: Randall E. Kaye, MD
Chief Medical Officer
Senior Vice President, Clinical and Medical Affairs

Dear Dr. Kaye:

Please refer to your New Drug Application (NDA) resubmission dated April 30, 2010, received April 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Hydrobromide and Quinidine Sulfate Capsules, 20 mg/10 mg (b) (4)

We also refer to your April 30, 2010, correspondence, received May 5, 2010, requesting review of your proposed proprietary name, Zenvia. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable (b) (4)

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of A Complete Submission for the Evaluation of Proprietary Names*, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012.”)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Susan Daugherty at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21879	ORIG-1	AVANIR PHARMACEUTICA LS INC	NEURODEX(DEXTROMETHOR PHAN PLUS QUINIDINE

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/s/

LAURIE A KELLEY
07/02/2010

CAROL A HOLQUIST
07/06/2010



NDA 21-879

INFORMATION REQUEST

Avanir Pharmaceuticals
Attention: Randall Kaye, MD Senior Vice President, Chief Medic
101 Enterprise
Suite 300
Aliso Viejo, CA 92656

Dear Dr. Kaye:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zenvia (dextromethorphan hydrobromide and quinidine sulfate) Capsules.

We are reviewing the Chemistry, Manufacturing, and Controls section 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. Provide in-process control limits for capsule weight and capsule length as you have proposed these as in-process controls.
2. Include a microbial test with limits in the drug product specification.
3. Provide container closure [REDACTED] ^{(b) (4)} HDPE bottles.
4. The provided stability data do not support the proposed ^{(b) (4)} months expiry dating period. Provide all available stability data for the primary stability batches for the assessment of expiry period for the product.
5. Revise the post approval stability commitment to include the first three commercial batches of each strength packaged into the proposed container closure system at the 40°C and 75% RH storage conditions and test initially and at 3 and 6 months time points.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief

Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21879	ORIG-1	AVANIR PHARMACEUTICA LS INC	NEURODEX(DEXTROMETHOR PHAN PLUS QUINIDINE

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/s/

RAMESH K SOOD
07/02/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **QTIRT**

FROM (Name, Office/Division, and Phone Number of Requestor):

**Division of Neurology Products
Susan Daugherty 6-0878**

DATE
June 10, 2010

IND NO.

NDA NO.
021879

TYPE OF DOCUMENT
**Complete Response to
approvable**

DATE OF DOCUMENT
April 23, 2010

NAME OF DRUG
**Zenvia
(dextromethorphan/quinidine)**

PRIORITY CONSIDERATION
high

CLASSIFICATION OF DRUG
ALS

DESIRED COMPLETION DATE
August 10, 2010

NAME OF FIRM: **Avanir**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Avanir Pharmaceuticals, Inc., the applicant for NDA21879, submitted a Complete Response on 4/30/10. This NDA is seeking the approval of Zenvia – a combination product containing dextromethorphan 20 ^{(b)(4)} quinidine 10 mg, administered twice a day for the treatment of pseudobulbar affect. During the first cycle review of this NDA, the Division of Cardio-Renal Products provided a consultative review (Reviewer: Dr. Shari Targum; dated 6/4/06).

The definitive clinical trials in original NDA submission (1/30/06) were conducted using a higher dose of quinidine, i.e., dextromethorphan 30 mg and quinidine 30 mg administered twice a day. As outlined in the Approvable Letter (10/30/06), the Division expressed concerns regarding the drug's association with an increase in the QT interval (thorough QT study 119) at the proposed daily dose and at supratherapeutic dose (only twice that of the recommended dose), in the context of the known proarrhythmic risk of quinidine. In response, the applicant conducted additional studies including a phase 3 clinical study (07-AVR-123) and a thorough QT study (08-AVR-126) assessing a new formulation using lower quinidine dose (10 mg). Outlier analysis and incidence of arrhythmia were also conducted in these new studies and integrated with all previously conducted clinical studies. A group of

cardiologists was convened to identify events of sudden death where arrhythmia might have been involved. The applicant presents these analyses in the “Analysis of Cardiac Safety for Zenvia” (Module 5.3.5.3 Cardiac Safety Report), and concludes that that while Zenvia has the potential to prolong the QT interval, the risk of Torsades de Points and other arrhythmias appears to be low, and that there was no significant incidence of arrhythmias in the accrued clinical experience. Please provide an expert assessment of whether the cardiovascular risk associated with Zenvia has been adequately assessed and appropriately characterized. Do you agree with the applicant’s conclusions regarding the overall cardiac safety profile of Zenvia?

The applicant proposes the following Contraindication: “Patients with complete atrioventricular (AV) block without implanted pacemakers, or patients who are at high risk of complete AV block”, and following Warnings and Precautions: (b) (4)

The applicant also proposes a Medication Guide. Please provide an expert opinion whether the cardiovascular risk with Zenvia can be adequately mitigated with these proposed mitigation strategies (label restrictions and REMS). If not, what are your recommendations?

The application may be accessed at: \\CDSESUB1\EVSPROD\NDA021879\021879.enx
The PDUFA goal date is October 30, 2010

SIGNATURE OF REQUESTOR Susan Daugherty	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21879	ORIG-1	AVANIR PHARMACEUTICA LS INC	NEURODEX(DEXTROMETHOR PHAN PLUS QUINIDINE

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/s/

SUSAN B DAUGHERTY
06/10/2010



NDA 021879

ACKNOWLEDGE CLASS 2 RESPONSE

Avanir Pharmaceuticals
Attention: Randall Kaye, M.D.
Vice President, Clinical and Medical Affairs
101 Enterprise, Suite 300
Aliso Viejo, CA 92656

Dear Dr. Kaye:

We acknowledge receipt on April 30, 2010, of your April 30, 2010, resubmission to your new drug application for Zenvia (dextromethorphan hydrobromide and quinidine sulfate) Capsules.

We consider this a complete, class 2 response to our October 30, 2006 action letter. Therefore, the user fee goal date is October 30, 2010.

If you have any questions, call me at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Health Project manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21879	ORIG-1	AVANIR PHARMACEUTICA LS INC	NEURODEX(DEXTROMETHOR PHAN PLUS QUINIDINE

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/s/

SUSAN B DAUGHERTY
05/14/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21879	ORIG-1	AVANIR PHARMACEUTICA LS INC	NEURODEX(DEXTROMETHOR PHAN PLUS QUINIDINE

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/s/

SUSAN B DAUGHERTY
05/05/2010

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Meeting Cancellation Form

(Use this form to cancel a meeting that was granted and scheduled after which time the sponsor or FDA has subsequently cancelled.)

Please remember to update the Meeting Status field in IMTS for this cancellation.

Complete the information below and check form into DFS.

Application Type	NDA
Application Number	21-879
DATE Meeting Cancelled (per communication with requester)	11/12/09
Scheduled Meeting Date	11/18/09
Reason for Cancellation	Preliminary responses sufficient
Project Manager	Susan Daugherty

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21879	GI-1	AVANIR PHARMACEUTICA LS	NEURODEX(DEXTROMETHOR PHAN PLUS QUINIDINE

Meeting ID	Regulatory Program	Meeting Type	Meeting Code	Meeting Status
27656	None	C	Other	Canceled

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SUSAN B DAUGHERTY
11/13/2009

Meeting Date: November 18, 2009

Time: 1:00 – 2:00 PM EST

Sponsor: Avanir Pharmaceuticals

Product: Zenvia (dextromethorphan and quinidine) Capsules

Type C: pre-resubmission

Introductory Comment: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 18, 2009, from 1-2 PM EST between Avanir Pharmaceuticals and the Division of Neurology Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to [your development plan/the purpose of the meeting/to the questions] (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

1.1 Clinical Questions

Question 1: Does the agency confirm that study 07-AVR-123 combined with previously submitted data, is acceptable as the basis for approval as discussed and agreed at the approvable letter response face-to-face meetings and in the subsequent SPA correspondences?

Preliminary FDA Response:

Positive findings on review of study 07-AVR-123, combined with previously submitted data, would be adequate to support the efficacy of the new formulation of Zenvia with 10 mg quinidine.

Question 2: Does the FDA agree that the number of human subjects exposed and the duration of exposure will be adequate for the evaluation of the safety and efficacy of Zenvia?

Preliminary FDA Response:

The number of human subjects exposed and the duration of exposure is potentially adequate, but the division reiterates that the simple absence of an adverse event in

the exposed population is not necessarily adequate to address the adverse events of special interest identified in previous communications. For example, we noted that, absent other arguments, findings in study 07-AVR-123 were unlikely to be persuasive of cardiac safety of Zenvia in atrial fibrillation/flutter (10/4/2007 letter to IND 56,954).

Question 3: Does the Agency agree that no additional clinical pharmacology studies will be required for approval of Zenvia?

**Preliminary FDA Response:
Yes.**

1.2 Integrated Summary of Safety

Question 4: Does the Agency agree with the proposed ISS population pools to support the overall analysis of safety of Zenvia?

**Preliminary FDA Response:
The proposed population pools are acceptable.**

Question 5: Does the Agency agree that Avanir has provided an appropriate plan for summarizing the safety of the new formulations DM 30mg/Q 10mg and DM 20/Q 10 mg and the previous dose (DM 30 mg/Q 30 mg) formulation as described in ISS SAP?

**Preliminary FDA Response:
The large summary ISS table that you propose is acceptable. Tables of appropriate subsets of the data are also important to include, for example a table of the new formulations versus placebo, and a table of the old formulation versus placebo and individual constituent drugs.**

Question 6: Does the Agency agree that the proposed analyses adequately evaluate the AEs of special interest by the Agency?

**Preliminary FDA Response:
The acceptability of your arguments is a matter for review. On face, it is not clear that the Integrated Analysis of Cardiac Safety addresses a broad enough range of possible adverse cardiac effects of low dose quinidine, beyond QT prolongation.**

Question 7: Does the Agency confirm that the previously submitted RiskMAP (Attachment 8) adequately and appropriately addresses the abuse potential of Zenvia?

Preliminary FDA Response:

The proposed evaluations described in the RiskMAP document are appropriate for determining whether Zenvia produces an epidemiological signal indicative of abuse potential. Similarly, the educational plans are appropriate for promoting safe use of Zenvia. We acknowledge your commitment to conduct these evaluations and educational campaigns.

(b) (4)

1.3 Nonclinical Questions

Question 8: Does the Agency agree that the existing nonclinical studies for Zenvia provide adequate support for approval and any additional studies if needed, would be completed after approval as a Phase 4 commitment?

Preliminary FDA Response:

The adequacy of the existing nonclinical studies will be a matter of review, and cannot be further addressed at this time. However, if additional nonclinical studies are needed, they may be submitted post-approval.

Question 9: Does the Agency agree that it will not be necessary to incorporate a teratology evaluation into the pre- and post-natal study?

Preliminary FDA Response:

Yes.

Question 10: (a) Does the Agency agree that the proposed high doses are too high? (b) Does the Agency agree that it is not necessary to repeat the embryo-fetal developmental toxicity study? (c) If the Agency requires that the rabbit embryo-fetal developmental toxicity study to be repeated, can this be done as a Phase 4 commitment? (d) If the Agency requires an additional rabbit embryo-fetal developmental toxicity study, what doses are recommend?

Preliminary FDA Response:

As you have concluded, the results of the dose-range finding study in rabbit (submitted in Serial #0093) indicate that the 50 mg/kg DM/100 mg/kg Q dose “was well tolerated...and was considered to be a suitable upper dose level for an embryo-fetal toxicity study in rabbit” (#DMQ-121). Therefore, the embryo-fetal development study in rabbit will need to be repeated, testing doses up to a high dose of 50 mg/kg DM/100mg/kg Q. The repeat study may be conducted post-approval.

1.4 Chemistry, Manufacturing and Control (CMC) Information

Question 11: Does the Agency consider a proposed shelf life of (b) (4) months acceptable for both dosage forms?

Preliminary FDA Response:

The expiration dating period for the product will be assigned during the review of the application based on the quality and extent of the stability data provided.

Question 12: Does the Agency agree that the proposed bracketing designs are adequate for the stability evaluation of validation batches and for the post approval stability program?

Preliminary FDA Response:

The adequacy or the proposed bracketing design will be evaluated during the review of the application. On face, however, the proposal does not appear adequate. A bracketing design is intended to test the extremes of design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design. Each combination of extremes should be tested using at least three batches. The testing scheme outlined in Table 6 for validation batches provides for a maximum of two batches tested per strength/fill count combination. In order to support a bracketing approach you will first need to determine which capsule count configurations represent the extremes with respect to characteristics such as container wall thickness, closure geometry, surface area to volume ratio, headspace to volume ratio, water vapor permeation rate or oxygen permeation rate per dosage unit. Refer to ICH guidance "*Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*" for additional guidance.

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/s/

SUSAN B DAUGHERTY
11/09/2009

Application
Type/Number

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/s/

SUSAN B DAUGHERTY

09/16/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-879

MEETING GRANTED

Avanir Pharmaceuticals
ATTENTION: Randall Kaye, M.D.
Chief Medical Officer
101 Enterprise, Suite 300
Aliso Viejo, CA 92656

Dear Dr. Kaye:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zenvia (dextromethorphan and quinidine) Capsules.

We also refer to your September 9, 2009, correspondence requesting a meeting to discuss the Avanir planned response to the October 30, 2006 NDA Approvable Letter. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: November 18, 2009
Time: 1:00-2:00 PM
Location: White Oak CDER Building #22
Conference Room 1309
10903 New Hampshire Avenue
Silver Spring, MD 20993

Tentative CDER participants:

Robert Temple, M.D., Office Director
Russell Katz, M.D., Division Director
Alice Hughes, M.D., Division Safety Director
Ronald Farkas, M.D., Ph.D., Acting Medical Team Leader
Devanand Jillapalli, M.D., Medical Reviewer
Lois Freed, Ph.D., Supervisory Pharmacologist
C. Donald Thompson, Ph.D., Pharmacology Reviewer
Angela Men, Ph.D., Clinical Pharmacology Team Leader
Martha Heimann, Ph.D., Pharmaceutical Assessment Lead
Kun Jin, Ph.D., Biometrics Team Leader
Tristan Massie, Ph.D., Biometrics Reviewer

Susan Daugherty, Regulatory Project Manager
Corinne Moody, Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please e-mail me any updates to your attendees at susan.daugherty@fda.hhs.gov so that our security staff has sufficient advance time to prepare temporary visitor badges. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Susan Daugherty (301) 796-0878.

Provide the background information for the meeting (three copies to the application and 15 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by October 18, 2009, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21879

GI-1

AVANIR
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/s/

SUSAN B DAUGHERTY

09/16/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-879

Avanir Pharmaceuticals
Attention: Randall Kaye, M.D.
Vice President, Clinical and Medical Affairs
101 Enterprise, Suite 300
Aliso Viejo, CA 92656

Dear Dr. Kaye:

Please refer to your New Drug Application (NDA) submitted under section 505(i)/505(b) of the Federal Food, Drug, and Cosmetic Act for Zenvia™ (dextromethorphan/quinidine) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on February 26, 2007. The purpose of the meeting was to discuss the October 30, 2006 approvable letter for this application.

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 Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Minutes



FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: February 26, 2007
Meeting Type: Type C
Meeting Category: Post Action
Meeting Location: White Oak Bldg #22, Room 1419
Application Number: NDA 21-879
Product Name: Zenvia (dextromethorphan/quinidine)
Received Briefing Package February 26, 2007
Sponsor Name: Avanir.
Meeting Requestor: Jeanine Kuzcik
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Susan Daugherty
Meeting Attendees:

FDA Attendees

Division of Neurology Products (DNP)

Russell Katz, M.D., Director
Elizabeth McNeil, M.D., Acting Medical Team Leader
Ronald Farkas, M.D., Ph.D., Medical Reviewer
Kathleen Young, Ph.D., Pharmacology Reviewer
Susan Daugherty, Regulatory Project Manager
Kara Jastemski, Pharmacy Student Intern

Office of Translational Sciences

Robert Powell, Ph.D., Pharmacometrics Director

Division of Clinical Pharmacology I

Mehul Mehta, Ph.D., Director
Ramana Uppoor, Ph.D., Deputy Director
Sally Yasuda, Pharm.D., Reviewer

QT Interdisciplinary Review Team

Christine Garnett, Pharm.D., Pharmacometrics Reviewer

Division of Biometrics II

Kun Jin, Ph.D., Biometrics Team Leader
Tristan Massie, Ph.D., Biometrics Reviewer

External AttendeesAvanir Pharmaceuticals

Eric Brandt, President and CEO

Randall Kaye, M.D., Vice President, Clinical and Medical Affairs

Laura Pope, Ph.D., Senior Director, Clinical and Regulatory Affairs

Adrian Hepner, M.D., Senior Director, Medical Affairs

Teresa Brandt, Ph.D., Project Director, Clinical and Regulatory Affairs

Consultants to Avanir

Craig Pratt, M.D., Professor of Medicine, Weill Medical College of Cornell University

Ronald Thisted, Ph.D., Professor and Chairman, Department of Health Studies, University of Chicago

(b) (4)

Howard Lee, M.D., Ph.D., Associate Adjunct Professor, Department of Biopharmaceutical Sciences School of Pharmacy, University of California, San Francisco

1.0 BACKGROUND

On January 27, 2006, Avanir Pharmaceuticals submitted NDA 21-879 for Zenvia (dextromethorphan and quinidine) to reduce or eliminate Involuntary Emotional Expression Disorder (IEED) or pseudobulbar effect PBA. On October 30, 2006, an approvable letter was issued for NDA 21-879.

A post-action meeting was requested by Avanir in a letter dated November 21, 2006, received November 24, 2006, to discuss the approvable letter.

Responses to the questions posed by Avanir in the background package were electronically mailed to the sponsor on February 23, 2006.

Questions from the sponsor are not bolded or italicized. Responses from the FDA are in bold after questions 1-15 and then following each question. The meeting discussion is bolded and italicized and follows the sponsor's comments. Slides that Avanir presented at the meeting are attached.

2.0 DISCUSSION***Clinical Efficacy***

1. The CNS-LS is an acceptable primary outcome measure for Studies 99-AVR-102 and 02-AVR-106. Does FDA agree?
2. While there are limitations associated with relying on episode counts as a primary outcome measure in clinical studies, Avanir recognizes the importance of understanding episode count

effects for clinical relevance. The NB1 model analysis of episode counts, prespecified for Study 02-AVR-106 and accepted by FDA, achieved statistical significance for the comparison of DM/Q to DM when applied to Study 99-AVR-102. This finding supports the clinically effectiveness of DM/Q compared to DM in the prespecified secondary endpoint of episode counts. Does FDA agree?

3. In summary, the NB1 model is valid and provides an acceptable fit for the data and valid basis for statistical inference. The other methods do not represent the data, and thus do not enable valid statistical inference. Therefore, the statistical methods used by the Sponsor are appropriate for analyzing the impact of Zenvia on the reduction of laughing and/or crying episode counts. Using these methods, Zenvia produced positive results for the secondary outcome measure of episode count reduction in Studies 99-AVR-102 and 02-AVR-106. Does FDA agree?
4. The effectiveness of Zenvia in the treatment of IEED has been demonstrated in two adequate and well-controlled clinical trials, Studies 99-AVR-102 and 02-AVR-106. The clinical assessment of IEED using the CNS-LS and the results of the statistical analyses of laughing and crying events are acceptable to support the effectiveness of Zenvia in patients with IEED. Furthermore, based on Study 99-AVR-102, it has been conclusively established that Zenvia is more effective than either component. Does FDA agree?
5. A reformulation of Zenvia containing a reduced amount of quinidine (10 mg) would be expected to reduce the proarrhythmic risk of quinidine. PK/PD modeling alone is valid for predicting changes in QTc interval. Does FDA agree?
6. A reformulation of Zenvia containing a reduced amount of quinidine (10 mg) would be expected to produce DM levels that are substantially higher than DM alone. PK/PD modeling alone may be used to predict clinical efficacy. Does FDA agree?

Clinical Safety

7. A reduction in the dose of Q from 30 mg to 10 mg in the combination product would result in reduced plasma concentrations of Q, consequently resulting in a lower C_{max} even in the presence of a CYP3A4 inhibitor. Does FDA agree?
8. Although close evaluation of these cases indicates a lack of relationship of concomitant drug administration to the serious adverse events in question, reducing the dose of Q to 10 mg in Zenvia would further reduce the risk of adverse consequences in this vulnerable population. Does FDA agree?
9. Although close monitoring of susceptible patients with cardiac history may be required, reducing the dose of Q to 10 mg in Zenvia would further reduce the risk of cardiac arrhythmias in susceptible patients. Does FDA agree?
10. The death rate for ALS patients in the open label experience study of Zenvia is comparable to the published and expected death rate for patients with ALS; therefore, the deaths reported do not constitute a safety signal with respect to the use of this product. Does FDA agree?

11. Although close evaluation of these cases indicates a lack of relationship of respiratory failure to Zenvia, reducing the dose of Q to 10 mg in Zenvia would reduce both Q and DM exposure and provide an even higher margin of safety in this vulnerable population. Does FDA agree?
12. We acknowledge that the incidence rates for nausea, vomiting, and somnolence are higher in Zenvia than with the individual components or placebo. We have investigated the incidence of episodes of aspiration and find them to be an infrequent occurrence that may be related to the patient's underlying neurological condition. Nevertheless, reducing the dose of Q to 10 mg in Zenvia should provide an improved safety profile. Does FDA agree?
13. A thorough evaluation of these cases indicates a lack of relationship of falls to Q administration. However, reducing the dose of Q to 10 mg in Zenvia should result in reduced DM levels as well as Q levels. The lower levels of DM would likely result in decreased CNS AEs, and thus, reduce the risk of adverse consequences such as falls in this vulnerable population. Does FDA agree?
14. The investigator, in review of all the documents along with input from a gastroenterologist, felt that retrospectively, based on the clinical presentation and outcome, patient 136-9004 had a gall bladder stone that spontaneously passed. Detailed review of this case indicates that study drug was not involved, and the underlying explanation of passage of a gall bladder stone is logical and sound. Does FDA agree?
15. We agree that additional safety and efficacy studies in other populations will provide critical information regarding the use of Zenvia. These studies would be appropriate to continue post approval (e.g., in stroke or Alzheimer's disease). Does FDA agree?

Responses to Clinical Questions 1-15:

The text below addresses the clinical issues raised in your meeting questions (questions 1-15), in a format designed to best communicate both the unresolved issues in the Zenvia NDA, along with possible remedies for these issues. Numbers of your specific meetings questions are referred to above areas of corresponding text.

In the Approvable Letter for Zenvia, we raised issues of concern regarding both the safety and the efficacy of Zenvia. In your current submission, you propose to address several of the key safety issues through a reformulation of Zenvia containing 10 mg quinidine instead of 30 mg quinidine. We agree that a different formulation of Zenvia might have fewer safety risks while being efficacious. You have not outlined in this meeting package arguments or proposals for collecting additional data that are likely to lead to a finding of safety for the 30 mg Q formulation of Zenvia. Given data in the NDA that we find raises serious questions about the safety of the current formulation, we believe that establishing safety of the current formulation may be impossible. We believe, therefore, that the current discussion for this meeting should focus mainly on the additional data that would be

necessary for you to demonstrate the safety and efficacy of a new formulation of Zenvia.

Efficacy

[questions 1, 2, 3, 4]

We will accept that Zenvia (30 mg Q formulation) has been shown to be more effective than either component.

Safety

The major safety issues raised in the Approvable letter are as follows: (a) cardiac effects of quinidine, (b) drug interactions involving CYP 2D6 and CYP 3A4, (c) possible respiratory depression from Zenvia as a contributing factor in the deaths of ALS patients, (d) nausea and vomiting in populations at risk for aspiration, and increased falls in populations already at risk from falls (e) lack of adequate clinical experience in stroke, Alzheimer's disease, and other diseases in which Zenvia is intended for use, and (f) possible case of severe drug-induced liver injury.

(a) cardiac effects of quinidine

[questions 5, 7, 9]

We agree that for a reformulation of Zenvia containing 10 mg quinidine, modeling alone can be used to predict changes in QTc interval. However, 10 mg quinidine may have cardiac adverse effects not adequately described by QTc interval alone. For example, we are still concerned about potential adverse effects of 10 mg quinidine in patients with atrial fibrillation/flutter. You must still present evidence that 10 mg quinidine is acceptably safe in the intended patient population. You should incorporate in your response effects on quinidine levels of concomitant CYP 3A4 inhibitors. You should also specifically present a risk/benefit assessment of 10 mg quinidine in patients that are genetic CYP 2D6 poor metabolizers, in whom quinidine would have no benefit, but would presumably retain those risks not directly related to CYP inhibition. Given the availability of tests to determine CYP 2D6 metabolizer status, you should either incorporate such testing in labeling, or present a compelling argument why this apparent risk-reduction method should not be used.

Following are detailed comments regarding PK/PD modeling of QTc interval change [question 10]:

We agree that PK/PD modeling can be used for predicting changes in QTc interval. However, we still recommend periodic monitoring of ECGs and electrolytes in your clinical trials.

A PKPD model for quinidine using the data from your TQT study was developed by the agency. Our assumption was QT prolongation observed for Zenvia is due to only to quinidine and its metabolites. Both direct- and delayed-effect linear models were used to describe the relationship between quinidine concentrations and the change in the QTcI interval.

A model-based predicted mean and 90% confidence interval for various quinidine doses is summarized in the following table. The mean and 90% confidence interval for the prediction was computed by multiplying the mean Cmax by the mean and 90% confidence interval of the slope.

Quinidine Dose (Mean Cmax)	Mean (90% Confidence Interval)		
	FDA's Direct Effect Model1	FDA's Delayed Effect Model2	E14 Metric
30 mg (179 ng/ml)	8 (5, 10)	10 (7, 13)	10 (5, 15)3
60 mg (356 ng/ml)	15 (10, 20)	20 (14, 26)	18 (13, 25)4
10 mg (60 ng/ml)5	3 (2, 3)	3 (2, 3)	Not applicable
1. Slope (90% CI): 42.8 (29.1, 56.4) ms per 1000 ng/ml			
2. Slope (90% CI): 55.6 (38.8, 72.4) ms per 1000 ng/ml			
3. Max mean change occurred at 6 h post dose			
4. Max mean change occurred at 5 h post dose			
5. Predicted Cmax value assuming linear pharmacokinetics			

(b) drug interactions involving CYP 2D6 and CYP 3A4

[questions 7, 8]

Your pharmacokinetic studies examining quinidine inhibition of CYP 2D6 suggest that most patients taking 10 mg quinidine would be converted to phenotypic poor metabolizers. Therefore, the risk of adverse drug interactions involving CYP 2D6 metabolized drugs may be little changed for most patients by a reformulation of Zenvia containing 10 mg quinidine.

Following are detailed comments regarding Q and CYP 3A4 inhibitors:

We believe that the pharmacokinetics of quinidine are linear, and the mean Cmax for a 10 mg dose is expected to be approximately 60 ng/ml. We note that the mean Cmax of 40 ng/ml reported in Table 2 (page 24) of your briefing document may not be accurate as this concentration is below the limit of quantitation for the analytical assay (LLQ = 50 ng/ml). With a potent inhibitor such as ketoconazole, a 40% increase in Q is seen (according to the labeling of Q).

[question 11]

Concomitant use of Zenvia with oxycodone and CYP 3A4 inhibitors occurred relatively frequently in your NDA studies (for example, subject 107-03-002, who died of oxycodone overdose). Higher than intended levels of oxycodone from drug interactions might also occur with a reformulation of Zenvia since most patients are

converted to CYP 2D6 poor metabolizers from 10 mg quinidine. While CYP 2D6 inhibition is not, of itself, an unacceptable safety risk for many patient populations, you must address how this risk can be acceptably mitigated in the target population of Zenvia, composed in large part of neurologically compromised patients taking multiple medications including oxycodone and CYP 3A4 inhibitors.

(c) possible respiratory depression from Zenvia as a contributing factor in the deaths of ALS patients

[question 10]

We remain concerned that Zenvia might cause respiratory depression, even a modest degree of which might be a meaningful risk in a population such as ALS with compromised respiratory function. Additionally, adverse drug interactions between Zenvia and other medications used by this population (such as oxycodone) might further increase the risk of respiratory depression.

Part of your argument that Zenvia (with 30 mg quinidine) does not cause respiratory depression is based on respiratory rate measurements submitted in your NDA. However, these respiratory rate measurements appear to be distributed in a biologically implausible pattern, with a large percentage recorded as 16- or 20 breaths/minute. The value of this type of data in assessing respiratory effects of Zenvia is therefore doubtful. Collecting more objective respiratory data with the reformulated Zenvia would help to clarify this issue.

The expected rate of death from respiratory failure in ALS is very high, such that to confidently exclude even a clearly meaningful increase in death rate (from any cause) would require a large, long term placebo-controlled study. Because of the high ‘background’ rate of death, comparison of death rates across different open-label ALS studies appears to us incapable of persuasively excluding even a clinically meaningful affect on death rate. Specific deaths in Zenvia development appear plausibly related to adverse effects of Zenvia. If the adverse effects of Zenvia (such as falls and vomiting) can be adequately minimized through a reformulation, we would consider such a decrease as evidence against an unacceptable rate of death from Zenvia.

(d) nausea and vomiting in populations at risk for aspiration, and increased falls in populations already at risk from falls

[questions 2,3,4,6,12,15]

The proposed reformulation of Zenvia with 10 mg quinidine might be associated with less nausea, vomiting, and fall than the current formulation, but this can only be adequately determined through a controlled clinical trial. If the incidence of these adverse events were not meaningfully decreased in a new formulation of Zenvia, safety risks might still outweigh benefits, despite the decreased exposure to Q.

We strongly encourage you to explore several exposure levels for

dextromethorphan, including lower exposures (lower beyond the decrease expected from 10 mg instead of 30 mg quinidine).

PK/PD modeling of effectiveness and safety (dose-limiting toxicities) may be useful for selecting doses for the next clinical trial. You have performed exposure-effectiveness modeling which suggests a rather flat relationship, implying lower exposure/doses might also provide effectiveness. However, we reiterate that modeling efficacy of a reformulated Zenvia from current data is not of itself adequate evidence of efficacy

The efficacy data submitted to date for the 30 mg quinidine formulation of Zenvia, in combination with a single adequate positive study, would support the efficacy of the new formulation. As is our general policy, controlled trials for a chronic indication for Zenvia should be at least 3 months duration.

The bioavailability of the new dose/formulation will need to be established. This can be done by obtaining full PK profiles in a subset of the subjects (e.g. n=24) in the phase 3 clinical trial. We also recommend that sparse PK samples are collected in all subjects to allow for establishing an exposure response relationship, both for safety and efficacy. The PK should evaluate DM, dextromethorphan, and quinidine, and will require a more sensitive quinidine assay than was used for the original studies. Please submit your proposal for evaluation.

(e) lack of adequate clinical experience in stroke, Alzheimer's disease, and other diseases in which Zenvia is intended for use

[questions 1,15]

The clinical experience with Zenvia in stroke, Alzheimer's disease, and other populations in which it would be used is currently very limited. Although a matter of discussion, if you conduct a short-term controlled trial of a new formulation of Zenvia with enough patients from several patient groups including stroke, Alzheimer's Disease, and ALS, additional long-term experience with the new formulation might not have to be complete before approval.

For any additional Zenvia efficacy studies, we prefer counts of laughing and crying episodes as the primary outcome variable. We are willing to accept CNS-LS as the primary outcome variable, but will consider episode counts as a key secondary outcome. Episode count data is particularly valuable for describing efficacy of Zenvia given the lack of clarity in definition (and naming) of pseudobulbar affect/IEED. We suggest that any new study be designed to measure baseline episode rates.

(f) possible case of severe drug-induced liver injury

[question 14]

The case of possible drug-induced liver injury in the Zenvia NDA (patient 136-9004) remains of concern. Evidence for a gall stone etiology is not adequately compelling to discount drug-induced liver injury. Imaging studies were largely negative for a common duct stone, and the large elevation in AST and ALT in conjunction with

modest increase in alkaline phosphatase appears typical of non-cholestatic hepatocellular injury.

Meeting Discussion:

Efficacy

The sponsor proposed at the meeting, a 3-arm randomized withdrawal study using 30 mg DM with 10 mg Q, 15 mg DM with 5 mg Q, and placebo. The Division suggested that one arm use 15 mg DM with 10 mg Q, rather than the proposed 15/5 combination, because 5 mg of Q might not provide the necessary inhibition of CYP 2D6. The Division also raised the possibility that an arm with 30 mg Q, 30 mg DM could be useful to establish assay sensitivity. If such a multi-arm study showed efficacy in the 30 mg Q, 30 mg DM arm, but not in lower dose combinations, the Division would be willing to reconsider the approvability of the higher dose.

The sponsor proposed conducting the randomized withdrawal portion of the trial for 4 weeks. The Division indicated that 3 months of efficacy data was necessary. The proposed primary analysis of episode counts for this withdrawal study might be problematic because the withdrawal of patients will lead to missing data that is potentially informative (non-ignorable) and may cause the proposed analysis to be biased. Time-to-failure might be a more appropriate efficacy measurement for such a study.

The sponsor and Division agreed that the primary endpoint should be daily episode count and that CNS-LS would be the secondary endpoint.

Safety

The sponsor proposes a 2-week, 4-arm safety study in healthy volunteers. The Division indicated that use of a healthy volunteer population would likely not provide data useful for assessing safety in patients. The sponsor proposed monitoring somnolence, dizziness and sedation in healthy volunteers to assess the risk of falls in patients. The Division expressed doubt that fall risk in patients could be adequately characterized from such data.

The sponsor proposes to address the drug-drug interaction with CYP2D6 and 3A4 inhibitors issue with labeling. The Division is concerned that labeling, alone, might not be sufficient for safe use of the product by the intended patient populations.

The sponsor proposes the use of modeling studies to predict the adverse event profile. The Division pointed out that to have any potential meaning, modeling would have to be based on interpolation between tested doses, not on extrapolation to doses either higher or lower than those tested.

The sponsor may submit a Special Protocol Assessment (SPA) or request a meeting

with the Division for additional feedback from the Division about Phase 3 studies.

Nonclinical

16. Based on data from studies conducted with DM/Q to date and submitted in the NDA, and as discussed in this submission, incrementally higher doses would not have been tolerated in rats or rabbits. Importantly, selective and significant embryofetal toxicity was observed in the rat and rabbit embryofetal toxicity studies and in the rat pre- and post-natal development study. Final approved labeling will incorporate full information as provided above and as detailed in the study reports submitted in the NDA. Avanir considers there is no need for further reproductive toxicology or dose finding studies because no significant additional information would be gained by repeating the studies. Does FDA agree?

FDA Response:

No. You have provided no new data to justify the high doses used in the reproductive toxicology studies in rat and rabbit. Therefore, we continue to recommend that you conduct appropriate dose-range finding studies in these species in order to select adequate doses for definitive studies. The need for repeat definitive studies will depend on the results of the dose-range finding studies.

Meeting Discussion:

The Sponsor will conduct new dose-range finding studies in rat and rabbit. If the results of the dose-range finding studies indicate that the pivotal studies need to be repeated, the Sponsor proposes to submit them post approval. The Sponsor stated that it is not expected that the results of the repeat studies will require a change in the pregnancy category.

The Division noted that the clinical population will include patients of reproductive age and that there will likely be sufficient time to complete the reproductive toxicology studies concurrent with the new clinical studies. The Division agreed to further consider the timing of submission of the study reports.

Post-meeting Note: *After further internal discussion, the Division has determined that, based on the available nonclinical data, the final study reports for repeat reproductive toxicology studies do not need to be submitted prior to approval. However, dose-range finding studies should be initiated immediately. Pivotal studies that need to be repeated (if any) should be initiated as soon as possible following analysis of the dose-range finding data. For each study, the Sponsor needs to commit to a time line for completion and submission of a final study report.*

If new data (e.g., from the dose range finding studies) indicate a particular concern regarding reproductive toxicology, the issue of timing of submission of any or all pivotal studies (i.e., pre or post approval) would need to be reconsidered.

17. Based on an agreement with the Division that a single chronic toxicology species would be sufficient to support an NDA for IEED, Avanir proposed to initiate the studies in the second species after receiving approval of Zenvia for IEED. Therefore, Avanir plans to conduct a chronic toxicology in a non-rodent species and initial plans are to conduct the study in the Beagle dog in order to explore the apparent sensitivity in that species. Does FDA agree?

FDA Response:

We encourage you to initiate the chronic nonrodent study as soon as possible. We have no recommendations on which nonrodent species should be tested, except that justification should be provided for your selection. Whether or not the chronic study would be needed prior to NDA submission will depend, as stated in the Agency's Approvable letter, on an overall evaluation of the nonclinical and clinical data.

Meeting Discussion:

The Sponsor will initiate a chronic toxicology study in a non-rodent species within six months.

18. Avanir plans to initiate a juvenile neurotoxicology study in the rat within 18 months following Zenvia approval contingent on the clinical requirements for a pediatric study. Does FDA agree?

FDA Response:

No. The juvenile neurotoxicology study is needed to specifically address the potential for induction of apoptotic neurodegeneration during the developmental stage corresponding to the vulnerable period in humans that includes the last trimester through postnatal ages 2-3. This study is not to be a standard juvenile animal study, and thus is not intended solely to support use in the pediatric population. Therefore, the need for this study is not contingent on clinical requirements for a pediatric study. As stated in the Agency's Approvable letter, this study may be conducted Phase 4.

Meeting Discussion:

The Sponsor will initiate a juvenile neurotoxicology study during Phase 4.

19. Avanir plans to submit the carcinogenicity final study report when it is available; it is estimated that this will be early in the third quarter of 2007. Does FDA agree?

FDA Response:

Yes.

Meeting Discussion:

The Sponsor will submit the carcinogenicity final study report in the third quarter of 2007.

Abuse Liability

20. We propose to modify the RiskMAP in accordance with FDA suggestions.

FDA Response:

1. **CSS reviewed the Sponsor's proposed modifications to the RiskMAP and find the changes adequate.**
2. **The following should be noted: if a future submission applies to a reformulation of the Zenvia components, dextromethorphan and quinidine, CSS will need to reevaluate all data collected by the Sponsor in order to assess the potential for abuse of the new product.**

The response to this question was not discussed.

CMC

21. Avanir plans to submit stability information as it becomes available and all available updated stability data will be provided in the full response to the approvable letter.

Additional Clinical Pharmacology Comment:

The Sponsor has committed in section 4.2 of the submission to conduct *in vitro* drug metabolism studies (inhibition and induction) post approval. The Office of Clinical Pharmacology recommends that these *in vitro* studies should be conducted prior to approval to allow for labeling regarding the potential for interactions. Depending on the results of the *in vitro* studies, *in vivo* studies may be required.

Meeting Discussion:

The Sponsor stated that they will conduct these studies prior to approval as suggested.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time.

4.0 ACTION ITEMS

1. The Sponsor will initiate a chronic toxicology study in a non-rodent species within six months.
2. The Sponsor will initiate a juvenile neurotoxicology study during Phase 4.
3. The Sponsor will conduct new dose-range finding studies in rat and rabbit.
4. The Sponsor will submit the carcinogenicity final study report in the third quarter of 2007.

5.0 ATTACHMENTS AND HANDOUTS

The slides presented by the sponsor at this meeting are attached.

Zenvia™ (dextromethorphan/quinidine)

Food and Drug Administration
Avanir Pharmaceuticals
Presubmission Meeting

February 26, 2007

Responses to Nonclinical and Clin/Pharm Questions

- ❖ Question 17 (nonrodent chronic toxicology study)
 - Agree. Program will be initiated within 6 months
- ❖ Question 18 (juvenile neurotoxicology study)
 - Agree. Conduct study Phase IV
- ❖ Question 19 (carcinogenicity study report)
 - Agree. Submit final report Q3 2007
- ❖ Clinical pharmacology in vitro studies
 - Agree. Initiate and complete in vitro studies prior to approval

Responses to Nonclinical and Clin/Pharm Questions

- ❖ Question 16 (reproductive toxicology dose-finding studies)
 - Agree. Conduct new dose-finding studies in rat and rabbit
 - If a new full reproductive toxicology program is indicated, the results may not be available until after approval. Existing data indicate classification of pregnancy category C, which would not change with a new program.

Fundamental Clinical Question

- ❖ Additional clinical data necessary to confirm the safety and efficacy of a new formulation of Zenvia

How do we optimize the efficacy and safety of Zenvia?

- Effectiveness in terms of improvement in episode counts
- Safety risk with respect to cardiac effects, DDI, respiratory depression, N/V/Falls, underlying neurological conditions, and liver injury

Clinical Research Proposal

- ❖ Randomized Withdrawal – Efficacy
 - Enriched patient population (107 Open-Label Study)
 - DM/Q (Multiple lower doses) and Placebo
- ❖ Safety Trial Design
 - Healthy Subjects
 - Multiple dose and Intensive PK/PD
- ❖ Both learn and confirm trials will be analyzed together using a dose-exposure-response model-based approach to determine the optimal dose

Randomized Withdrawal Efficacy Study

- ❖ **Design:** multicenter, 4-week duration, double-blind randomized, three-arm parallel treatment comparing different doses of Zenvia and placebo, following withdrawal from open-label study 02-AVR-107 (DM30/Q30 bid)
- ❖ **Objective:** to confirm the dose-exposure-response relationship for the purpose of identifying an lowest efficacious dose in patients with IEED as a result of an underlying neurological condition or brain injury
- ❖ **Study Population:** eligible patients participating in on-going study 02-AVR-107 will be enrolled
- ❖ **Study Treatment:**
 - Treatment A: 30/10 bid
 - Treatment B: 15/5 bid
 - Treatment C: placebo

Randomized Withdrawal Efficacy Study

❖ Efficacy

- Primary endpoint:
 - Increases in daily laughing/crying episode count
- Secondary endpoints:
 - Increases in CNS-LS score
 - Time to relapse

❖ Safety

- Physical exam and Vital signs
- 12-lead ECG
- Clinical laboratory tests (including genotyping)
- Respiratory assessment
- Adverse event reporting

❖ Pharmacokinetics

- Random sampling PK data will be collected at certain study visits. Plasma concentrations of DM, DX, and Q* will be measured

*A more sensitive quinidine bioanalytical assay will be developed

Intensive Safety / PK Study

- ❖ **Design:** single center, 2-week duration, double-blind randomized, four-arm parallel treatment studying different doses of Zenvia and placebo
- ❖ **Objective:** to investigate dose-exposure-response relationships between DM/Q dose/concentrations and key safety biomarkers and clinical adverse reactions in subjects
- ❖ **Study Population:** Healthy volunteers
- ❖ **Study Treatment (approx. 24 subjects/treatment arm):**
 - Treatment A: 30/30 bid
 - Treatment B: 30/10 bid
 - Treatment C: 15/5 bid
 - Treatment D: placebo

Safety / PK Study

❖ Safety assessment

- Physical exam and Vital signs
- Clinical laboratory Tests (genotype)
- 12-lead ECG
- Assessment of Respiratory depression
- Adverse Event reporting

❖ Pharmacokinetics

- Plasma concentrations of DM, DX, and Q will be measured after single dose administration, and at steady state concentrations.

Dose-Exposure-Response Analysis

- ❖ Efficacy

- Mixed-effects analysis linking DM exposure to daily episodes (negative binomial model) and CNS-LS (inhibitory Emax or similar models)

- ❖ Safety

- Mixed-effects logistic regression analysis linking DM exposure to the occurrence of nausea, dizziness, and other key safety endpoints

- ❖ Deriving an optimal dose by combining predicted responses and predicted safety profiles

Cardiac Effects of Quinidine

- ❖ The Agency continues to express concerns regarding cardiac effects of quinidine.
- ❖ Avanir agrees with the FDA's comments that:
 - The proposed formulations (and confirmatory PK/PD modeling) with a reduced exposure to quinidine will reduce QTc prolongation
- ❖ Avanir also suggests:
 - The minimally effective dose of Q for converting atrial fibrillation to NSR is 325 mg t.i.d., therefore, the highest proposed dose of DM/Q is appx 1/50 of that dose and would not be expected to have an effect at that level
 - We will continue to carefully assess cardiac effects in future clinical studies and will propose appropriate labeling statements

Drug Interactions Involving CYP 2D6 and 3A4

- ❖ The Agency continues to have concerns regarding drug-drug interactions
- ❖ Avanir agrees with FDA comments:
 - With a potent inhibitor such as ketoconazole, a 40% increase in Q is seen.
- ❖ Avanir suggests that development of labeling statements are appropriate to mitigate the risks of co-administration of medications that are metabolized by 2D6 and 3A4 inhibitors

Drug-Induced Liver Injury

- ❖ The Agency continues to have concerns regarding liver injury
- ❖ Avanir agrees to:
 - Continue to follow liver function (and assess for potential hepatocellular injury) in all ongoing and future clinical trials
 - If no additional hepatic findings, include in labeling that there is one unexplained clinical report of hepatocellular injury

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/s/

Russell Katz
3/26/2007 01:48:24 PM

Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Friday, February 23, 2007 3:39 PM
To: 'Jeanine Kuczik'
Cc: Daugherty, Susan B (CSO)
Subject: responses for 2-26 meeting

Good Afternoon Jeanine,

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 26, 2007 from 1:00-2:30 between Avanir and the Division of Neurology Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to [your development plan/the purpose of the meeting/to the questions] (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

Please note that the FDA responses are in bold text following questions 1-15 and then following each question thereafter.

Best Regards,
Soozee

FDA Responses to questions regarding Zenvia

7 pages has been withheld immediately following this page. The information withheld is a duplicate copy of the "FDA Responses to questions regarding Zenvia" found in the February 26, 2007 Meeting Minutes located in this document review section.

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/s/

Susan B. Daugherty
2/23/2007 04:39:16 PM
CSO

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/s/

Susan B. Daugherty
2/9/2007 03:01:33 PM

REQUEST FOR CONSULTATION

TO (*Division/Office*): Division of Cardio-Renal Products/HFD-110 (QT Review team)

FROM: Division of Neurology Products, HFD-120

DATE:
January 8, 2007

IND NO.:

NDA NO.:
NDA 21-879

TYPE OF DOCUMENT :
Post Action Sponsor
Meeting Request (Briefing
Packages to be submitted 4
wks prior to the meeting)

DATE OF DOCUMENT:

NAME OF DRUG:
Zenvia
(quinidine/dextromethorphan)

PRIORITY CONSIDERATION:
Standard

CLASSIFICATION OF DRUG:
Txt of Psuedobulbar Affect

DESIRED COMPLETION DATE:
February 20, 2007

NAME OF FIRM: Avanir

COMMENTS/SPECIAL INSTRUCTIONS:

On October 30, 2006 DNP issued an AE letter for the above referenced NDA. The sponsor has requested a meeting to discuss the issues raised in this letter. Two reviews were conducted by Dr. Targum which can be located in DFS. The medical officer for this project is Dr. Ron Farkas (301-796-1931). Meeting notices have been sent and briefing packages will be submitted 4 weeks prior to the meeting.

SIGNATURE OF REQUESTER:

Melina Griffis (301-796-1078)

METHOD OF DELIVERY (Check one):

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/s/

Melina Griffis

1/8/2007 03:13:23 PM

Griffis, Melina

From: Griffis, Melina
Sent: Monday, November 27, 2006 2:51 PM
To: (b) (4)
Subject: RE: Zenvia(TM) NDA 21-879, SN 0029 - Request for Presubmission Meeting

Hi Jeanine,

Sorry for the typo, the meeting date is 2/8/07

From: Griffis, Melina
Sent: Monday, November 27, 2006 2:04 PM
To: (b) (4)
Subject: RE: Zenvia(TM) NDA 21-879, SN 0029 - Request for Presubmission Meeting

Hi Jeanine,

I have you confirmed for a meeting on 2/207 between 9:30 am- 11:00 am. Briefing documents are required 4 weeks prior to this date.

Melina Griffis, R.Ph, CDR-USPHS
*Senior Regulatory Project Manager
Division of Neurology Products, CDER, FDA
10903 New Hampshire Avenue, Bldg. 22, Rm. 4355
Silver Spring, MD 20993-0002
Office: 301-796-1078
Fax: 301-796-9842
Email: melina.griffis@fda.hhs.gov*

From: (b) (4)
Sent: Tuesday, November 21, 2006 5:05 PM
To: Griffis, Melina
Cc: (b) (4)
Subject: Zenvia(TM) NDA 21-879, SN 0029 - Request for Presubmission Meeting

Dear Melina,

Attached is an Information Amendment to Zenvia NDA 21-879 presenting a request from Avanir Pharmaceuticals for a Presubmission Meeting to discuss the October 30, 2006 Approvable Letter. This request provides proposed meeting dates and background information on the meeting purpose, agenda and attendees. Please note that we are also submitting an electronic/paper copy of this meeting request formally to the NDA.

Would you please confirm receipt of this meeting request and provide us with confirmation of the scheduled meeting date as soon as possible. We will provide full supportive information along with a proposed agenda and list of Sponsor attendees approximately 4 weeks prior to the scheduled meeting date.

Please give me a call to discuss if you have any questions or comments and many thanks for your help in scheduling this meeting and for your continued support of Avanir and this NDA.

All the best,

(b) (4)

<< File: SN 0029.pdf >> << File: 21Nov06 FDA Form 356h.pdf >>

(b) (4)

This message is intended only for the use of the individual or entity to which it is addressed and may contain information that is privileged, confidential or exempt from disclosure under applicable federal or state law. You are hereby notified that any dissemination, distribution or copying of this communication, except in accordance with its intended purpose, is strictly prohibited.

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/s/

Melina Griffis

11/27/2006 03:10:16 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 20, 2006

TO: NDA 21-879

THROUGH: Ramesh Sood, Ph.D., Branch Chief, DPA-1, ONDQA

FROM: Martha R. Heimann, Ph.D., Pharmaceutical Assessment Lead

SUBJECT: **Completion of Methods Validation for NDA 21-879**
Zenvia (dextromethorphan and quinidine sulfate) Capsules

NDA 21-879 was received on January 27, 2006 and an 'Approvable' letter was issued on October 30, 2006. All CMC deficiencies were resolved during the review cycle and the reviewer, Dr. Gurpreet Gill-Sangha recommended approval of the application. The HPLC methods for determination of Dextromethorphan HBr (DM) and related substances in the DM drug substance (CTMLP-1245) and determination of DM and Quinidine Sulfate (Q) and related substances in the drug product (CTMLP-720) were referred to the Division of Pharmaceutical Analysis (DPA) for evaluation on June 26, 2006. Validation studies were completed on August 31, 2006. The methods were found suitable for control and regulatory purposes. The evaluating chemist, Dr. Mike Trehy, notes in his comments, however, that, although the (b) (4) impurity) standard was detected with a (b) (4), the sloping baseline caused by gradient elution does make trace analysis difficult.

I have examined the original datasheets and agree with Dr. Trehy that analysis of the (b) (4) impurity at trace levels may be difficult due to the sloping baseline. The limit of quantitation (LOQ) stated in the application for this impurity method is (b) (4) and the calculated (b) (4) ratio for the (b) (4). The methods can therefore be considered adequate for quantitation of this impurity at the (b) (4) specified in the application.

The methods have been verified by an FDA laboratory. These are now the regulatory methods.

Attachment (paper copy to archival NDA only):
DPA Validation Report

cc: NDA 21-879
HFD-120/MGriffis
ONDQA/DPA-1/RSood
ONDQA/DPA-1/MHeimann
ONDQA/DPA-1/SGoldie

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/s/

Martha Heimann
11/21/2006 01:45:11 PM
CHEMIST

Ramesh Sood
11/21/2006 02:51:28 PM
CHEMIST



METHODS VALIDATION MATERIALS RECEIVED

NDA 21-879

Mr. James E. Berg
VP Clinical and Regulatory Affairs
Avanir Pharmaceuticals
11388 Sorrento Valley Road
San Diego, CA 92121

Dear Mr. Berg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neurodex (Dextromethorphan Hydrobromide and Quinidine Sulfate) (b)(4) Capsules and to our July 12, 2006 letter requesting sample materials for methods validation testing.

We acknowledge receipt on July 27, 2006 of the sample materials, equipment and documentation that (b)(4) sent to the (b)(4)

If you have any questions, you may contact me by telephone (314-539-3866), FAX (314-539-2113), or email (duckhee.toler@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Duckhee Toler
Chemist
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

Duckhee Toler

7/27/2006 12:38:26 PM

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-420/Director, Division of Medication Errors and Technical Support

FROM: HFD-120/Division of Neurology Products

DATE:
July 25, 2006

IND NO.:

NDA NO.:
NDA 21-879

TYPE OF DOCUMENT:
Alternative Name Review Request

DATE OF DOCUMENT:

NAME OF DRUG:
Zenvia Tablets

PRIORITY CONSIDERATION:
Priority Review requested User fee due date is 10/30/06

CLASSIFICATION OF DRUG:
Psuedobulbar Affect in ALS Patients

DESIRED COMPLETION DATE:
September 4, 2006

NAME OF FIRM: Avanir Phamraceuticals

****** Note- Please refer to completed consult # 0501921. There is a pending OCC review of the policy regarding foreign trade names during this time the sponsor is also requesting review of an alternative name (see below). ******

COMMENTS/SPECIAL INSTRUCTIONS:

Proposed Proprietary Name: Zenvia

Trademark registration status/Countries registered(if known): Registered but country unknown

Company tradename: Avanir Pharmaceuticals

Other proprietary names by same firm for companion products: none

United States Adopted Name, dosage form, strength and dosing schedule:

Dextromethorphan hydrobromide plus quinidine sulfate, capsules, 30 mg/ 30 mg, given BID

Indication for use: For the treatment of pseudobulbar affect (PBA), also known as pathological laughing and crying/weeping, emotional lability, and emotional incontinence.

Carton & container labeling as well as the proposed PI and can also be located in the EDR

SIGNATURE OF REQUESTER:

Melina Griffis (301-796-1078)

METHOD OF DELIVERY (Check one):

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/s/

Melina Griffis

7/25/2006 04:11:46 PM

REQUEST FOR CONSULTATION

TO (Division/Office): ODS

FROM: HFD-120/Division of Neurology Products

DATE:
July 21, 2006

IND NO.:

NDA NO.:
NDA 21-879

TYPE OF DOCUMENT:
RiskMAP

DATE OF DOCUMENT:

NAME OF DRUG:
Neurodex Tablets
(quinidine/dextromethorphan)

PRIORITY CONSIDERATION:
User fee due date is
10/30/06

CLASSIFICATION OF DRUG:
Psuedobulbar Affect in
ALS Patients

DESIRED COMPLETION DATE:
September 8, 2006

NAME OF FIRM: Avanir Phamraceuticals

COMMENTS/SPECIAL INSTRUCTIONS:

Please review and provide comments to the RiskMAP submitted to pending N21-879. The submission can be located in the EDR under N21-879; amendment 0017 (dated 6/5/2006), Section 1.16; Risk Management Plans.

SIGNATURE OF REQUESTER:

Melina Griffis (301-796-1078)

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Melina Griffis

7/21/2006 03:45:47 PM



NDA 21-879

Avanir Pharmaceuticals
Attention: James Berg
11388 Sorrento Valley Road, Suite 200
San Diego, CA 92121

Dear Mr. Berg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neurodex (dextromethorphan hydrobromide and quinidine sulfate) Capsules.

On June 29, 2006, we received your June 26, 2006 submission of the final study report for a thorough QT study in healthy volunteers, which is considered a major amendment to this application. The receipt date is within 3 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 October 30, 2006.

If you have any questions, call Melina Griffis, R. Ph, Sr. Regulatory Project Manager, at (301) 796-1078.

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

7/17/2006 01:20:00 PM



REQUEST FOR METHODS VALIDATION MATERIALS

NDA 21-879

Mr. James E. Berg
Avanir Pharmaceuticals
11388 Sorrento Valley Road
San Diego, CA 92121

Dear Mr. Berg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neurodex (Dextromethorphan Hydrobromide and Quinidine Sulfate) Capsules, (b) (4).

We will be performing methods validation studies on Neurodex Capsules, (b) (4) as described in NDA 21-879.

In order to perform the necessary testing, we request the following sample materials and equipment:



- A copy of the latest test method, only if the methods submitted with the application to the Center have changed.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Duckhee Toler

NDA 21-879

Page 2

1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3866), FAX (314-539-2113), or email (duckhee.toler@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Duckhee Toler
Chemist
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

Duckhee Toler

7/12/2006 11:01:31 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-879

Avanir Pharmaceuticals
Attention: James Berg
11388 Sorrento Valley Road, Suite 200
San Diego, CA 92121

Dear Mr. Berg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neurodex (dextromethorphan hydrobromide and quinidine sulfate) Capsules.

We also refer to your submission January 30, 2006 which we identified as the final submission to this application in order to begin the user fee clock.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on March 31, 2006 in accordance with 21 CFR 314.101(a).

We have the following information requests related to your submission:

1. We have not been able to locate more information on two references (#30, #34 below) cited in the "Expert Report: Abuse Liability Assessment of Neurodex" document. Both of these citations are abstracts of studies. We would like to review either a published article describing these studies in more detail or the actual data which formed the basis of the abstracts.

30. Zawertailo, LA, Busto, U., Tyndale, RF and Sellers, EM Dextromethorphan's active metabolite contributes to its abuse liability. *Clinical Pharmacology & Therapeutics* 63(2), 217. 1998

34. Zawertailo, LA, Buyso, U, Tyndale, RF, and Sellers, EM Effect of quinidine preadministration on the psychoactive effects of dextromethorphan. *J Clin Psychopharm* (submitted 2004)
2. Please document the use of naloxone as a specific antidote to dextromethorphan overdose.

The following items below have been previously requested via email.

3. Please identify the equipment used to manufacture and package Neurodex capsules based on SUPAC classification.
4. Drug substance batch DM0303024 shows the (b) (4) as per your information in the October 18, 2005 amendment. You have also stated that the impurity (b) (4) is an in-process impurity of dextromethorphan. However, the drug product batch GZ18M manufactured using the drug substance batch DM0303024 shows the level of (b) (4) at release to be (b) (4). Provide an explanation for the increase in the level of impurity (b) (4).
5. Provide release and stability data from any other drug product batches manufactured using the proposed commercial formulation for Neurodex capsules.
6. Provide rejection rate information due to any appearance (pin-holes or dents) or other issues for batch GZ18M and all other batches manufactured using the revised commercial formulation. How does this differ from the rejection rate seen in primary stability and clinical batches?
7. Confirm that for batch GZ18M the samples placed on stability do not involve only capsules that passed 100% visual inspection test. Also confirm that the practice of hand-selecting capsules based on visual appearance will not be used for future stability studies.
8. DM and Q in drug product specifications are identified by HPLC method CTMLP-720. As per ICH Q6(a), identity test solely by a single chromatographic retention time is not regarded as being specific. However, the use of two chromatographic procedures, where separation is based on different principles or a combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS or GC/MS is generally acceptable. Provide the updated drug product specifications to include relevant identity tests for DM and Q and the appropriate analytical test.
9. Provide an updated Certificate of Analysis (CoA) for the drug product reference standard to incorporate testing by analytical method CTMLP-720 for impurity (b) (4) since the USP methods used do not detect (b) (4).
10. Provide container closure (b) (4) data for bottles and seal integrity/leak test for unit dose packaging for Neurodex capsules as per USP<671>. Delineate if there are any in-process controls for the packaging process of Neurodex capsules.
11. Please submit a dataset for study 106 that contains the patients' responses for each of the 7 individual items of the CNS-LS at each visit. A dataset for study 106, in the standard .xpt format, similar to the CNSLS.xpt dataset submitted for study 102 would suffice.

12. Please provide the composition for the Lot DM9912074 used in the chronic rat, reproductive toxicity and neurotoxicity studies, with the level of ^(b)₍₄₎

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.

If you have any questions, call Melina Griffis, R.Ph., Regulatory Project Manager, at (301) 796-1078.

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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this page is the manifestation of the electronic signature.**

/s/

Russell Katz
3/31/2006 02:01:56 PM



NDA 21-879

Avanir Pharmaceuticals
Attention: James Berg
11388 Sorrento Valley Road, Suite 200
San Diego, CA 92121

Dear Mr. Berg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neurodex (dextromethorphan hydrobromide and quinidine sulfate) Capsules.

We also refer to your responses to the Controlled Substance Staff (CSS) comments contained in our letter dated August 25, 2005. The CSS has the following comments related to your submission:

1. The proposed abuse liability section still lacks information related to overdose/safety issues. CSS disagrees with the assertion regarding the lower abuse potential of Neurodex when compared to other DM products.
2. A plan to monitor for post-marketing abuse patterns must be submitted.
3. The CSS may have further comments and recommendations after the NDA has been filed.

If you have any questions, call Melina Griffis, R. Ph, Sr. Regulatory Project Manager, at (301) 796-1078.

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

1/18/2006 05:05:17 PM

REQUEST FOR CONSULTATION

TO (*Division/Office*): Controlled Substance Staff
HFD-009, (Attention: Corinne Moody)

FROM: Division of Neurology Products, HFD-120

DATE:
Oct 20, 2005

IND NO.:

NDA NO.:
NDA 21-879

TYPE OF DOCUMENT :
Response to FDA Request

DATE OF DOCUMENT:
Sept 26, 2005

NAME OF DRUG:
AVP-923 (Neurodex) Tablets

PRIORITY CONSIDERATION:
Standard

CLASSIFICATION OF DRUG:
Txt of Psuedobulbar Affect

DESIRED COMPLETION DATE:
Dec 1, 2005

NAME OF FIRM: Avanir

COMMENTS/SPECIAL INSTRUCTIONS:

Attached (desk copy) is a response from the sponsor to your comments of August 9, 2005 (signed off in DFS 8/11/05). Please review and provide any necessary feedback. This submission is also available electronically in the EDR.

SIGNATURE OF REQUESTER:

Melina Griffis (301-796-1078)

METHOD OF DELIVERY (Check one):

MAIL

G HAND

SIGNATURE OF RECEIVER:

SIGNATURE OF DELIVERER:

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/s/

Melina Griffis

10/20/2005 02:58:14 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-879

Avanir Pharmaceuticals
Attention: James Berg
11388 Sorrento Valley Road, Suite 200
San Diego, CA 92121

Dear Mr. Berg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neurodex (dextromethorphan hydrobromide and quinidine sulfate) Capsules.

We also refer to the August 9, 2005, submission received under a rolling review which we identified in our September 13, 2005 letter as the final submission to this application. Upon further review, we have determined that your submission of August 9, 2005 did not contain a comprehensive ISS and is therefore not considered the final submission to this application.

If you have any questions, call Melina Griffis, R. Ph, Senior Regulatory Project Manager, at (301) 796-1078.

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
10/19/2005 07:57:32 AM

October 21, 2005

This letter acknowledged the August 9, 2005 submission, submitted under a rolling review procedure, as the final submission to the application. Upon further review, the Division determined that the submission of August 9, 2005 did not contain a comprehensive ISS and was therefore not considered the final submission to this application. Refer to the advice letter dated October 19, 2005.



NDA 21-879

Avanir Pharmaceuticals
Attention: James E. Berg
Vice President, Clinical and Regulatory Affairs
11388 Sorrento Valley Road, Suite 200
San Diego, CA 92121

Dear Mr. Berg:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neurodex (dextromethophan hydrobromide and quinidine sulfate).

We also refer to the Division's letter of August 25, 2005 refusing to file this application under 21 CFR 314.101(d). Upon further review, we have determined that the primary reasons stated as the basis for our action, which were related to difficulties with the electronic aspects of the submission, may have been related not to deficiencies in your submission, but to difficulties experienced in accessing the data among Division staff. Therefore, we are rescinding our refusal to file action.

In addition, please note that we consider the final submission to this application, submitted under a rolling review procedure, to be the August 9, 2005 submission of animal carcinogenicity data. Therefore, the receipt date of the application will be considered August 10, 2005. We will notify you within 60 days from this date regarding the filing status of your application.

If you have any questions, call Courtney Calder, Pharm.D, Regulatory Project Manager, at 301-594-5528.

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
9/13/2005 02:26:08 PM

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/s/

Courtney Calder
9/12/2005 04:07:43 PM

REQUEST FOR CONSULTATION

TO (*Division/Office*): Deborah Liederman, M.D., Director
HFD-009/Controlled Substances Staff
Attention: Corinne Moody

FROM: Russell Katz, M.D., Director
HFD-120/Division of Neuropharmacological Drug
Products

DATE:
June 6, 2005

IND NO.:

NDA NO.:
21-879

TYPE OF DOCUMENT :
New NDA

Date of Submission:
June 29, 2005 (However, it
has been rolling in)

NAME OF DRUG:
AVP-923 (Neurodex)

PRIORITY CONSIDERATION:
Might get priority
review

CLASSIFICATION OF DRUG:
Pseudobulbar affect

DESIRED COMPLETION DATE:
Filing meeting is August 9
(1-2pm)
We will determine priority
then.

COMMENTS/SPECIAL INSTRUCTIONS:

This NDA is located in the EDR. Please review the submission and provide comments as necessary.

SIGNATURE OF REQUESTER:

Courtney Calder
301-594-5528

METHOD OF DELIVERY (Check one):

MAIL

G HAND

SIGNATURE OF RECEIVER:

SIGNATURE OF DELIVERER:

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/s/

Courtney Calder
7/6/05 01:45:57 PM

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/s/

Courtney Calder
7/6/05 05:28:46 PM