DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021879

NDA APPROVAL

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) dated January 27, 2006, received January 30, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) Capsules.

We acknowledge receipt of your amendments dated April 30, May 5, June 29, July 16, 19, and 21, August 6 and 23, September 1, 16, and 21, and October 6, 27, and 28, 2010.

The April 30, 2010, submission constituted a complete response to our October 30, 2006, action letter.

This new drug application provides for the use of Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) Capsules for the treatment of pseudobulbar affect (PBA).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of

Labeling Technical Qs and As" at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels, dated October 27, 2010, revised as agreed upon in an October 28, 2010 electronic mail message from Art Rosenthal of Avanir, as soon as they are available, but no more than 30 days after they are printed. The revisions that were agreed upon include:

A. All Container Labels and Carton Labeling

1. As currently presented, the font type and weight used for the established name and dosage form make them appear less than ½ the size of the proprietary name. Ensure the established name is printed in letters that are at least ½ as large as the letters comprising the proprietary name. Additionally, the established name should have a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)]. Ensure the dosage form statement is the same size, type, font, etc. as the established name.

2. In the established name, the two active ingredients are separated by a forward slash (/). Replace the forward slash with the word "and" (i.e., dextromethorphan HBr and quinidine sulfate).

3. In the "Each capsule contains" statement, connect the two active ingredients with the word "and" (i.e., 20 mg of dextromethorphan hydrobromide and 10 mg of quinidine sulfate).

4. As currently presented, the bolded, green net quantity statement is as prominent as the proprietary name. Decrease the prominence of the net quantity statement by revising the color (e.g., white font) and debolding.

B. Container Label (Trade)

1. Relocate the strength to appear immediately below the proprietary and established names (as presented on the carton labeling). You may have to delete the blue/green graphic, which is as prominent as the strength, in order to accomplish this. The proprietary name, established name and strength should be the most prominent information on the principal display panel.

2. Relocate the 'Each capsule…' statement to the side panel, which is the usual customary location for this statement.

C. Container Label (Professional Sample)

Relocate the strength to appear immediately below the proprietary and established names (as presented on the carton labeling). You may have to delete the blue/green graphic, which is as prominent as the strength, in order to accomplish this. The proprietary name, established name and strength should be the most prominent information on the principal display panel.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 021879**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

EXPIRATION DATING

A 24 month expiration dating period is granted for Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) Capsules, dextromethorphan 20mg and quinidine 10 mg.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for birth to two years of age years because necessary studies are impossible or highly impracticable. This is because PBA involves exaggerated or contradictory episodes of laughing or crying given the patient's actual emotional state. In children age 2 and younger, verbal and non-verbal communication is not adequately developed to allow for accurate appraisal of the patient's actual emotional state, such that the condition cannot be diagnosed.

We are deferring submission of your pediatric studies for ages 2 to 16 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must

be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1702-1 Conduct a pharmacokinetic dose-ranging and safety study in patients 2 to 16 years of age with PBA.

Final Protocol Submission:	10/2011
Study/Trial Completion:	04/2013
Final Report Submission:	10/2013

1702-2 Conduct a Phase 3, 12-week, multiple center, double-blind, placebo-controlled efficacy and safety study in pediatric patients 2 to 16 years of age with PBA.

Final Protocol Submission:	10/2013
Study/Trial Completion:	04/2015
Final Report Submission:	10/2015

1702-3 Conduct a Phase 3 open-label extension safety study in pediatric patients 2 to 16 years of age with PBA.

Final Protocol Submission:	10/2013
Study/Trial Completion:	04/2015
Final Report Submission:	10/2015

Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessments**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of neuronal degeneration, prenatal developmental, reproductive and neurobehavioral toxicity, and adverse effects of dextromethorphan/quinidine on postnatal growth and development. In addition, an analysis of spontaneous postmarketing adverse events will not be sufficient to identify unexpected serious risks related to the potential for quinidine to act at the $5HT_{2B}$ receptor that could result in the serious risk of cardiac valvulopathy.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1702-4 - A juvenile neurotoxicity study in neonatal rats intended to assess the potential for Nuedexta to induce apoptotic neuronal degeneration in the human fetus. Dextromethorphan/quinidine should be administered during the postnatal period demonstrated to be the most vulnerable to this lesion.

The timetable you submitted on 10/25/2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2011
Study Completion:	06/2012
Final Report Submission:	09/2012

1702-5 - A pre- and post-natal development (including maternal function) study in rats, testing doses up to a high dose of 50 mg/kg/day dextromethorphan in combination with 100 mg/kg/day quinidine.

The timetable you submitted on 10/25/2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2011
Study Completion:	01/2012
Final Report Submission:	04/2012

1702-6 - An embryo-fetal development study in rabbits, testing doses up to a high dose of 50 mg/kg/day dextromethorphan in combination with 100 mg/kg/day quinidine.

The timetable you submitted on 10/25/2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2011
Study Completion:	07/2011
Final Report Submission:	10/2011

1702-7 - A juvenile rat toxicology study is required to identify the unexpected, serious risk of adverse effects of dextromethorphan/quinidine on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects of dextromethorphan/quinidine on growth, reproductive development, and neurological and neurobehavioral development.

The timetable you submitted on 10/25/2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2011
Study Completion:	07/2012
Final Report Submission:	12/2012

1702-8 - Studies to assess the *in vitro* binding affinity and functional activity of quinidine at the $5HT_{2B}$ receptor.

The timetable you submitted on 10/29/10 states that you will conduct these studies according to the following schedule:

Final Protocol Submission:	02/28/11
Study Completion:	08/31/11
Final Report Submission:	11/30/11

1702-9 - If quinidine is confirmed to be a $5HT_{2B}$ agonist, then an investigative study to assess the potential for quinidine to induce cardiac valvulopathy will be needed.

The timetable you submitted on 10/29/10 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/30/12
Study Completion:	03/30/13
Final Report Submission:	06/30/13

Submit all protocols to your IND 056954, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also

include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your voluntary submission dated April 30, 2010, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

ENCLOSURES:
Content of Labeling

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

/s/

RUSSELL G KATZ
10/29/2010