

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021879Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: October 27, 2010

To: Russell Katz, MD, Director  
Division of Neurology Products (DNP)

Thru: Claudia Karwoski, Pharm.D., Director  
Division of Risk Management (DRISK)

From: **Nuedexta DRISK Review Team**  
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Subject: Review of proposed Risk Evaluation and Mitigation  
Strategy (REMS) for Nuedexta submitted April 23, 2010

Drug Name(s): Nuedexta (dextromethorphan hydrobromide and  
quinidine sulfate)

Application Type/Number: NDA 21-879

Applicant/sponsor: Avanir Pharmaceuticals Inc.

OSE RCM #: 2010-1362

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## **EXECUTIVE SUMMARY**

This review follows a request from the Division of Neurology Products (DNP) for the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) to review Avanir Pharmaceuticals Inc.'s April 23, 2010 submission for Nuedexta [dextromethorphan hydrobromide (DM) and quinidine sulfate (Q)] containing a proposed Risk Evaluation and Mitigation Strategy (REMS).

Avanir Pharmaceuticals Inc. submitted a voluntary proposed REMS and REMS supporting document for Nuedexta, in which the sponsor identified appropriate patient selection, the potential for serious drug-drug interactions, and the potential for diversion or abuse of Zenvia as the key safety concerns. The proposed REMS included a Medication Guide, communication plan consisting of a Dear Healthcare Provider letter, and surveillance of internet, medical literature, and drug abuse databases. The proposed timetable for assessment of the REMS was 18 months, 3 years, and 7 years from the date of approval.

Based on a review of the currently available data, DRISK believes that a REMS for Nuedexta is not needed at this time. The safety profile for Nuedexta is consistent with the known safety profile for the individual components in the drug combination and can be managed through labeling. There were no new or unique safety concerns unique for Nuedexta identified in the pivotal trials.

## 1 INTRODUCTION

This review follows a request from the Division of Neurology Products (DNP) for the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) to review Avanir Pharmaceuticals Inc.'s April 23, 2010 submission for Nuedexta [dextromethorphan hydrobromide (DM) and quinidine sulfate (Q)] containing a proposed Risk Evaluation and Mitigation Strategy (REMS).

## 2 BACKGROUND

### 2.1 REGULATORY HISTORY

On December 15, 2004, Avanir Pharmaceuticals Inc. submitted a new drug application (NDA 021-879) that received a priority review status for Neurodex capsules (DM 30mg and Q 30mg) indicated for pseudobulbar affect (PBA) in patients with neurological disorders associated with amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Alzheimer's disease, traumatic brain injury, and stroke.<sup>1</sup>

A proposed risk management plan (RiskMAP) was submitted on June 5, 2006. The proposed RiskMAP sought to prevent abuse by recreational drug users and misuse by patients using (1) education and outreach to physicians and patients; (2) monitoring potential recreational abuse, tampering, and/or diversion; (3) and monitoring untoward outcomes of potential abuse. OSE completed a review of the proposed RiskMAP November 1, 2006. OSE concluded at that time that education about abuse potential and monitoring for abuse were not useful ways to manage the risk given that dextromethorphan is readily available over-the-counter (OTC) for persons seeking to use it recreationally. Additionally, QT prolongation and resultant cardiac arrhythmias for recreational users and therapeutic use were the primary safety concerns for this product; and ultimately these issues were related to approvability of the risk benefit balance.

On October 30, 2006, the Agency issued an Approvable letter to the sponsor that cited issues regarding the efficacy and safety of the product, including:

- Study design concerns, including selection of the primary endpoint for Study 99-AVR-102, statistical analyses performed, inclusion of adequate patient populations for proposed indication, and confirmation of the synergistic effect of the drug combination over single ingredient DM
- Effects of Q on atrio-ventricular conduction, including QT prolongation/torsades de pointes, serious ventricular arrhythmias and use in patients with pre-existing atrial flutter/fibrillation
- Potential for clinically significant drug interactions with the administration of CYP3A4 inhibitors and/or other CYP2D6 substrates
- Effects of high levels of DM contributing to respiratory depression and failure in ALS patients
- Increased risk of dizziness and falls in controlled trials

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<sup>1</sup> The sponsor submitted the 505(b)(2) NDA application as a rolling review procedure. The completed application was submitted on January 27, 2006 and received January 30, 2006.

- Modifications to the proposed RiskMAP regarding the addition of educating patients on proper storage of medication and providing information on:
  - how the sponsor plans to collect, analyze, and evaluate the information collected by monitoring various databases for abuse and misuse
  - the frequency of reporting to the FDA on the outcomes of the proposed RiskMAP
  - propose interventions if abuse or misuse of the product is determined

The sponsor resubmitted the application under the tradename Zenvia on April 23, 2010. The resubmission incorporated various updates based on the agency recommendations in the Approvable letter. Among the updates, the resubmission included a Phase 3 study 07-AVR-123<sup>2</sup>, which assessed the safety and efficacy of two lower dose formulations (DM 30mg/Q 10mg and DM 20mg/Q 10mg).

Additionally, Avanir Pharmaceuticals Inc. submitted a voluntary proposed REMS and REMS supporting document for Zenvia, in which the sponsor identified appropriate patient selection, the potential for serious drug-drug interactions, and the potential for diversion or abuse of Zenvia as the key safety concerns. The proposed REMS includes a Medication Guide, communication plan consisting of a Dear Healthcare Provider letter, and surveillance of internet, medical literature, and drug abuse databases. The proposed timetable for assessment of the REMS is 18 months, 3 years, and 7 years from the date of approval.

The Division of Medication Error Prevention and Analysis (DMEPA) did not approve the tradename Zenvia, but approved the alternate tradename Nuedexta for DM/Q on October 14, 2010; DM/Q will be referred to as Nuedexta henceforth in this review.

## 2.2 DISEASE AND DRUG BACKGROUND

PBA is an affective disinhibition syndrome characterized by spontaneous, involuntary episodes of crying and/or laughing that are independent of the patient's underlying mood; therefore, impacting the quality of life and emotional well being of an individual. It is a neurologic condition associated with disorders such as MS, ALS, Alzheimer's disease, traumatic brain injury, and stroke. The prevalence of PBA in each of these conditions is 7-52%, 2-49%, 10-74%, 5%, and 11-52%, respectively.<sup>3</sup> Currently, there are no FDA approved treatments for PBA. Off-label use of tricyclic antidepressants and selective serotonin reuptake inhibitors has been investigated for individual patients by healthcare professionals with limited success.

Nuedexta is a combination product comprised of DM and Q. DM is commonly used as an OTC cough suppressant; Q is a class IA antiarrhythmic drug. The postulated mechanism of action for Nuedexta is based on the activity of DM. DM is a

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<sup>2</sup> Study title: A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy and to Determine the Pharmacokinetics of Two Doses of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect (PBA) in Patients with Amyotrophic Lateral Sclerosis and Multiple Sclerosis.

<sup>3</sup> Strowd RE, Cartwright MS, Okun MS, et al. Pseudobulbar affect: prevalence and quality of life impact in movement disorders. *J Neurol* 08 April 2010; 257: 1382-1387.

sigma-1 receptor agonist, a low-affinity, uncompetitive antagonist of N-methyl-D-aspartate (NMDA) sensitive ionotropic glutamate receptors, and a weak serotonin reuptake inhibitor. Therefore, DM suppresses the release of excitatory neurotransmitters, including glutamate, and reduces the level of excitatory activity in the central nervous system. Q is a cytochrome p450 2D6 inhibitor; DM is extensively metabolized via cytochrome p450 2D6. When administered concomitantly, Q increases the systemic bioavailability of DM.

Nuedexta is available as capsules that contain DM 20mg/Q 10mg (b) (4) respectively. The recommended dose of Nuedexta is one capsule once daily for the first seven days and on the eighth day (and thereafter) the dose is increased to one capsule approximately every 12 hours.

### **3 MATERIALS REVIEWED**

The following document(s) were reviewed:

- Avanir Pharmaceuticals Inc. proposed REMS submission submitted April 23, 2010
- Avanir Pharmaceuticals Inc. proposed REMS supporting document submitted on April 23, 2010
- Avanir Pharmaceuticals Inc. proposed Prescribing Information (PI) for Zenvia<sup>®</sup> (dextromethorphan hydrobromide and quinidine sulfate) for injection, October 30, 2009
- Neurodex (dextromethorphan hydrobromide and quinidine sulfate) capsules, OSE RiskMAP review, dated November 1, 2006.
- Avanir Pharmaceuticals Inc. proposed Risk Minimization Action Plan (RiskMAP) submitted on June 5, 2006.

### **5 PROPOSED REMS**

#### **5.1 GOALS**

The proposed goals of the REMS are:

To educate healthcare professionals:

- About identification of patients with PBA for Nuedexta treatment.
- About the potential for serious drug interactions with Nuedexta, including those with MAOIs, drugs that prolong the QT interval, are strong CYP3A4 inhibitors, or undergo extensive CYP2D6 metabolism.
- About the potential for diversion or abuse and educating patients on proper storage.

To educate patients with PBA being treated with Nuedexta about:

- The potential for drug interactions and steps to take to mitigate risk.
- The potential for diversion or abuse and the importance of proper storage.

#### **5.2 REMS ELEMENTS**

The proposed REMS includes a Medication Guide, communication plan consisting of a Dear Healthcare Provider letter, and surveillance of internet, medical literature and drug abuse databases and not include any elements to assure safe use. The timetable for

assessment of the REMS is 18 months, 3 years, and 7 years from approval. Each element of the REMS is described below.

#### *5.2.1 Medication Guide*

The sponsor proposes a Medication Guide to be packaged and dispensed with each Nuedexta prescription and sample package. The Nuedexta packaging will contain a prominent notice to the pharmacist to include a Medication Guide with each prescription. Additionally, the Medication Guide will be available through Avanir Pharmaceuticals Inc.'s sales representatives, the product website, and by request via a toll-free support line.

#### *5.2.2 Communication Plan*

Avanir Pharmaceuticals Inc. proposed to implement a communication plan to health care providers to support the proposed Nuedexta REMS. The communication plan comprises a Dear Healthcare Provider (DHCP) letter that will be sent to neurologists, psychiatrists, office staff, and retail pharmacists. The DHCP letter will be distributed via direct mail during the month of product launch and yearly for 2 years thereafter. The DHCP letter will include the full prescribing information and the Medication Guide. Copies of all materials will be available through Avanir Pharmaceuticals Inc.'s sales representatives, the product website, and by request via a toll-free support line.

#### *5.2.3 Elements to Assure Safe Use*

The proposed REMS does not include any elements to assure safe use.

#### *5.2.4 Implementation system*

The sponsor did not propose elements to assure safe use; hence, an implementation system is not included as a component of the proposed REMS.

#### *5.2.5 Assessment of the REMS*

Avanir Pharmaceuticals Inc. proposes to submit REMS assessments to the FDA at 18 months, 3 years, and 7 years from the date of approval. The assessments will be based on adverse event surveillance, comprehension surveys, assessment of medication guide distribution and dispensing, and surveillance of internet, medical literature, and abuse and diversion databases.

## **6 DISCUSSION**

### **6.1 SPONSOR IDENTIFIED SAFETY CONCERNS INCLUDED IN THE REMS**

#### *6.1.1 Appropriate patient selection*

The sponsor states that appropriate patient selection is a goal of the REMS because clinicians must carefully balance the risks of Nuedexta with its benefits. They also state that the benefit of Nuedexta for individual PBA patients is a decrease in episodes of inappropriate daily laughing and crying episodes, as these involuntary emotional displays can be socially debilitating. Although the sponsor lists appropriate patient selection as a goal in the proposed REMS and an important message to communicate to prescribers, there is no information regarding patient selection in the proposed label.

### 6.1.2 *Drug-Drug interactions*

The key drug-drug interactions for Nuedexta are:

- Monoamine oxidase inhibitors (MAOIs) when used in combination with Nuedexta
- Strong CYP3A4 Inhibitors when used in combination with Nuedexta may result in increased levels of quinidine and/or dextromethorphan
- Inhibitors or substrates of CYP2D6 should be used with caution with Nuedexta, as they may have the potential to inhibit components of Nuedexta elimination and cause increased blood levels of dextromethorphan
- Drugs undergoing extensive CYP2D6 metabolism, when used concomitantly with Nuedexta may result in altered drug effects; dose modification of the concomitant medication should be considered
- Nuedexta should be used with caution in patients on drugs that prolong the QT interval

There is an additional concern that the risk for QT prolongation will be elevated among patients who intentionally abuse the drug for the euphoric effects of DM, in patients who are concomitantly administered drugs that also cause QT prolongation, and/or in patients who are concomitantly administered CYP3A4 inhibitors. The integrated summary of safety (ISS) for DM/Q did include an evaluation of the relationship between safety parameters and concomitant medications of special interest including CYP3A4 inhibitors and QT prolonging drugs. Additionally, these drug interactions, and others, for Q are well documented and well established. The DNP believes the risk for concomitant administration of other QT prolonging drugs and/or CYP3A4 inhibitors can be adequately addressed by the prescribing information. Furthermore, the risk for these potential interactions is reduced for the DM/Q combination using 10 mg Q as compared to FDA approved therapeutic doses.

### 6.1.3 *Potential for abuse/misuse due to dextromethorphan*

The sponsor states that some teenagers and young adults intentionally abuse large amounts of medicines containing DM to induce an altered state of consciousness due to the euphoric effects experienced by the active metabolite of DM, dextrophan. They concluded that DM abuse occurs primarily in adolescents and that the attraction in this group is that DM is readily available over-the-counter as a single ingredient and is relatively low in cost. A review of the abuse potential by the Controlled Substance Staff concluded that the prescription status of this product and narrow indication for use would result in less as compared to the abuse potential of over-the-counter DM. Additionally, the concomitant administration of Q with DM will inhibit the metabolism to dextrophan via CYP2D6 inhibition. Therefore, individuals abusing this combination product are more likely to experience somnolence and other negative effects of DM rather than the euphoric effects of dextrophan.

## 6.2 ADDITIONAL SAFETY CONCERNS

### 6.2.1 *QT prolongation/Torsades de points, cardiac dysrhythmia, and proarrhythmic events due to quinidine*

The primary safety concern for this product is the risk of QT prolongation due to Q. The potential for Q to prolong the QT interval is a dose-dependent effect that increases in severity with increasing doses. Due to this risk, the sponsor reduced the amount of quinidine in each capsule from 30 mg to 10 mg in the resubmission based on the agency's concerns and recommendation. Additionally, 2 QT studies were completed by Avanir Pharmaceuticals Inc. (05-AVR-119 and 08-AVR-126) to investigate the effects of Q on cardiac repolarization. The sponsor stated that the study investigating the proposed combination DM/Q using 10 mg Q did not show evidence of an effect on heart rate, AV conduction, or cardiac depolarization. The studies were reviewed by the Division of Cardiovascular and Renal Products (DCRP) and the Interdisciplinary Review Team for QT Studies (IRT-QT); a slight risk for QT prolongation was noted as compared to placebo and moxifloxacin. They noted that although Q prolongs the QTc interval, the effect appears finite and predictable. No clinically relevant effects on the PR and QRS intervals were noted by DCRP or IRT-QT, which is consistent with the assessment of non-clinical data regarding channel potencies.

Furthermore, the dose of Q in the DM/Q combination is subtherapeutic (normal dosage for immediate release Q is 200 to 400mg every 4-6 hours for atrial fibrillation and flutter or life threatening ventricular arrhythmias); therefore, the risk for QT prolongation is reduced as compared to the FDA approved therapeutic doses of Q. No reports of torsades de pointes or significant ventricular arrhythmias in the clinical studies were observed for DM/Q; however, the studies were of limited size, limited ECG sampling, and limited information.

### 6.2.2 *Respiratory depression due to dextromethorphan*

Respiratory depression is an adverse reaction associated with the administration of DM. Among patients in the controlled studies for PBA, 1.9% of patients receiving DM 20 mg/Q 10 mg experienced dyspnea, 3.6% of patients receiving DM 30 mg/Q 10 mg experienced dyspnea, and 2.7% of patients receiving placebo experienced dyspnea.

Review of the cases with a fatal outcome due to respiratory depression identified a disproportionate number of deaths among patients with ALS receiving DM/Q as compared to MS patients receiving DM/Q and the placebo group. Study 07-AVR-123 reported 10 deaths, all of which occurred in ALS patients. Of these 10 deaths, 7 occurred during the double-blind phase (3 each in the DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg groups and 1 in the placebo group) and 3 occurred during the open-label phase. Per the sponsor, all 10 deaths occurred as a result of respiratory depression secondary to disease progression. A similar effect was observed in the open-label safety study (02-AVR-107) that investigated the higher combination dose of DM 30 mg/Q 30 mg in which the majority of the deaths occurred in ALS patients (81% of deaths). Additionally, of the ALS patients that died, the cause of death was primarily disease progression, including respiratory failure and other similar respiratory associated events, per the manufacturer.

Patients with ALS typically experience a loss of muscle strength and coordination due to progression of the disease that may include breathing and swallowing difficulties. Additionally, an adverse reaction associated with the administration of DM is respiratory depression. Patients with ALS may be at an increased risk for respiratory failure due to the additive effect of respiratory depression associated with DM administration and loss of muscle functionality associated with the underlying disease. In a review of these cases with a fatal outcome due to respiratory failure, the Division of Pulmonary and Allergy Products (DPARP) concurred with the sponsor's assessment regarding the cause of death and its association with disease progression and did not identify a safety concern. DPARP also concluded that the information provided in the case narratives and baseline differences between treatment groups and placebo did not support a treatment-related effect between the cause of death and administration of Nuedexta. The DNP also concluded that respiratory-related deaths and adverse events are a very common occurrence in patients with ALS; therefore, a drug-related effect for these events is difficult to detect without an adequately designed study with sufficient power.

### *6.2.3 Falls due to dextromethorphan*

Among patients in the controlled studies for PBA, 13.1% of patients receiving DM 20 mg/Q 10 mg experienced falls, 20% of patients receiving DM 30 mg/Q 10 mg experienced falls, and 12% of patients receiving placebo experienced falls. Additionally, 10.3%, 17.3%, and 6.6% of patients, respectively, experienced dizziness with or without a reported event of fall.

## **8 CONCLUSION AND RECOMMENDATION(S)**

In summary, DM and Q have both been approved by the FDA as individual products and have been extensively used over many years. The safety profile for each drug has been well established. The dose of Q included in the drug combination is much lower than the recommended daily dose of Q when used for the treatment of atrial fibrillation/flutter or life threatening arrhythmias. The potential for abuse of this product is mitigated by the prescription status of the combination product as compared to OTC access of single ingredient DM for recreational use.

DRISK believes that a REMS for Nuedexta is not needed at this time. The safety profile for Nuedexta is consistent with the known safety profile for the individual components in the drug combination and can be managed through labeling. There were no new or unique safety concerns unique for Nuedexta identified in the pivotal trials.

Should DNP raise further concerns with the risks outlined above or identify additional risks associated with Nuedexta warranting more extensive risk mitigation or a formal risk evaluation and mitigation strategy (REMS), please send a consult to OSE DRISK.

This review serves to close the existing consult request for Nuedexta under NDA 21-879, dextromethorphan hydrobromide and quinidine sulfate. Please notify DRISK if you have any questions.

## APPENDIX: REFERENCES

- Proprietary Name Review for Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) capsules, DMEPA review, dated October 14, 2010.
- Zenvia (Dextromethorphan hydrobromide 30 mg / Quinidine Sulfate 30 mg, capsules), CSS review, dated October 7, 2010.
- Zenvia (dextromethorphan hydrobromide and quinidine sulfate) capsules, DPARP Review, dated October 7, 2010.
- Zenvia (dextromethorphan hydrobromide and quinidine sulfate) capsules, DCRP Review, dated October 4, 2010.
- Clinical Review for Zenvia (dextromethorphan hydrobromide and quinidine sulfate) capsules by DNP, dated September 25, 2010
- Neurodex (dextromethorphan hydrobromide and quinidine sulfate) capsules, Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review, dated September 17, 2010.
- DsARM Advisory Committee Meeting to discuss the DEA request for and abuse potential evaluation and scheduling recommendation for dextromethorphan, September 14, 2010.<sup>4</sup>
- Resubmission letter for Zenvia (dextromethorphan hydrobromide and quinidine sulfate) capsules by Avainr Pharmaceuticals Inc., Aliso Viewjo, CA, submitted April 23, 2010.
- Avainr Pharmaceuticals Clinical Overview for Zenvia, submitted on April 23, 2010
- Approvable letter for Zenvia (dextromethorphan hydrobromide and quinidine sulfate) capsules by Russell Katz, M.D., Director Office of Neurology Products, dated October 30, 2006.
- Neurodex (Dextromethorphan hydrobromide 30 mg / Quinidine Sulfate 30 mg, capsules). Abuse Liability, Product Labeling and Risk Minimization Action Plan (RiskMAP), CSS review, dated October 5, 2006.

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<sup>4</sup> Transcript available at:

[www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM228267.pdf](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM228267.pdf)

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/s/

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REEMA JAIN  
10/27/2010

CLAUDIA B KARWOSKI  
10/28/2010  
concur



**MEMORANDUM**

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

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**DATE:** November 1, 2006

**TO:** Russell Katz, M.D., Director  
Division of Neurology Products

**THROUGH:** Gerald Dal Pan, MD, MHS, Director  
Office of Surveillance and Epidemiology (OSE)

**FROM:** OSE Risk Management Team

**DRUG:** Neurodex Capsules (dextromethorphan hydrobromide 30mg/  
quinidine sulfate 30mg)

**NDA#:** 21-879

**SPONSOR:** Avanir Pharmaceuticals

**SUBJECT:** Review of Proposed Risk Management Plan (RMP) submitted  
June 5, 2006

**PID #:** D060640

**1 EXECUTIVE SUMMARY**

This consult follows a request from the Division of Neurology Products (DNP) for the Office of Surveillance and Epidemiology (OSE) to review the proposed Risk Minimization Action Plan (RiskMAP) for Neurodex tablets.

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/s/

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Mary Dempsey  
11/1/2006 08:49:55 AM  
DRUG SAFETY OFFICE REVIEWER

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