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RESEARCH**

*APPLICATION NUMBER:*

**021879Orig1s000**

**OTHER ACTION LETTERS**



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

We acknowledge receipt of your submissions dated:

|                   |               |                 |                   |
|-------------------|---------------|-----------------|-------------------|
| February 3, 2006  | May 30, 2006  | June 28, 2006   | September 6, 2006 |
| February 28, 2006 | June 5, 2006  | July 14, 2006   | October 9, 2006   |
| March 23, 2006    | June 6, 2006  | July 28, 2006   |                   |
| April 26, 2006    | June 13, 2006 | August 4, 2006  |                   |
| May 4, 2006       | June 26, 2006 | August 16, 2006 |                   |

We have completed our review of this application, as amended, and it is approvable. Before this application can be approved, however, you must address the issues described below.

#### Clinical Comments

Although we consider this application approvable, we have fundamental questions about both the effectiveness and safety of the product.

#### EFFECTIVENESS

We acknowledge that you have submitted the results of two randomized controlled trials that purport to establish substantial evidence of effectiveness of Zenvia in patients with Pseudobulbar Affect (PBA). We agree that Study 106, in patients with Multiple Sclerosis (MS), clearly can be considered one "positive" study contributing to such a finding. However, as you know, this study was not capable by design of establishing the contribution of the individual components of the product, as required by 21CFR300.50 (Fixed-combination prescription drugs for humans).

Study 102, in patients with Amyotrophic Lateral Sclerosis (ALS), was designed to establish the contribution of each component. We also acknowledge that the contrasts between the combination and the individual components reached statistical significance on the protocol specified primary outcome measure, the CNS-LS. However, as you also know, we had repeatedly expressed to you a preference for the designation of laughing and crying episodes as the primary outcome variable. We note that your protocol specified that you would analyze these episodes using Poisson regression.

However, as you acknowledge, the distribution of the episode data did not support the use of the Poisson regression model. Although your protocol did not specify an alternative analysis in this case, you have chosen to analyze the episode data using the NB1 negative binomial model (variance proportional to the mean).

Given the lack of a prespecified alternative to the Poisson model and the fact that there is no single well-established parametric alternative, we performed a Cochran-Mantel-Haenszel (CMH) test with modified ridit scores on the combination-DM comparison; regardless of whether the data for the one outlier patient 08-016 (see below) are included ( $p=0.13$ ) or excluded ( $p=0.19$ ), the results do not achieve significance.

We also investigated the NB2 negative binomial model (variance depends on the square of the mean). We believe that the NB2 negative binomial model also provides a reasonable alternative to the Poisson model. This model is less sensitive than the NB1 model in terms of measures of overall model fit to the inclusion of the one outlier in the Dextromethorphan (DM) group (patient 08-016, who had a total of 3010 laughing episodes during the study). In addition, with the NB1 model, the difference between the combination and the DM group increases when this patient's data are excluded, which is counterintuitive. In contrast, with the NB2 model, the difference between these groups decreases when this patient's data are excluded, as is expected. Therefore, we have analyzed the episode data using this latter model.

In this case, the combination-DM comparison is nominally significant ( $p=0.017$ ) when this patient's data are included, but not if these data are excluded ( $p=0.34$ ), or if the next worst episode count in the database (398) is imputed ( $p=0.13$ ). We recognize that this outcome measure is a secondary measure, but, again, we remind you that, on numerous occasions, we strongly suggested that it be deemed the primary outcome. The results we have obtained suggest that the combination may not provide an additional benefit beyond that provided by the DM component itself. You will need to adequately address this concern before we can conclude that the combination policy has been met. It is also worth noting that this finding raises the possibility that a much lower exposure to DM than is achieved with this product might be effective in controlling laughing or crying episodes in these patients (see below).

## SAFETY

Numerous findings in the safety database raise serious concerns about the safety in use of this product.

First, we note that quinidine is well known to be associated with serious ventricular arrhythmias, including torsades de pointes. These arrhythmias can occur at low quinidine doses in susceptible patients (e.g., those with congenital prolonged QT syndrome), but higher quinidine doses can also be associated with serious cardiac events, presumably in a dose related fashion.

In this regard, we note the results of Study 119, your thorough QT study. This study demonstrated that at the daily dose of the combination that you propose, the drug is associated with a maximum mean paired placebo and baseline subtracted QTcF of about 10 msec, with a 95% upper bound one-sided confidence interval of about 15 msec (we presume this increase is directly a result of the quinidine component), and that the prolongation persists throughout the dosing interval. You suggest that this is of little consequence because Agency guidance states that this degree of increase is "inconclusive" regarding its clinical significance. However, we disagree with your conclusion. In our view, quinidine

poses a known proarrhythmic risk, and as such this degree of QT interval increase raises serious concerns. In this regard, we also note that, in this study, over 4% of the EKGs in patients who received the recommended dose had QTc intervals that were increased between 30-60 msec above baseline, compared to 0.9% of those EKGs in the placebo arm.

Further, and equally, if not more, disturbing, the maximum mean paired placebo and baseline subtracted QTcF was about 18 msec (upper bound of the 95% CI was 25 msec) at the suprathreshold dose of the combination, which was only twice that of the recommended dose (at this dose, 7.2% of the EKGs were associated with an increase in QTc of 30-60 msec). Given that quinidine is metabolized by CYP3A4, and given the availability and use of numerous 3A4 inhibitors, we expect that, in practice, many patients may be exposed to levels of quinidine that were achieved with the suprathreshold dose used in this study (or higher), and that these levels will be associated with serious cardiovascular consequences. In addition, we have performed PK/PD modeling of quinidine's effect on the QT interval; we have determined that 5% of the population who receives the recommended dose of Zenvia would be expected to experience a prolongation of the QTc interval of about 19 msec.

In addition, quinidine's potent inhibition of CYP2D6 poses additional risks, especially in this vulnerable population. For example, we are aware of a death in the database that appeared likely related to elevated plasma levels of oxycodone, a substrate for both 3A4 and 2D6. The patient was also receiving, in addition to Zenvia, a potent 3A4 inhibitor (clarithromycin). The combination of 3A4 and 2D6 inhibition was likely responsible for the dangerously elevated oxycodone levels in this patient. We also note that at least one other patient in the data base was receiving oxycodone, Zenvia and another potent 3A4 inhibitor (erythromycin). These cases highlight the dangers that are potentially associated with the use of Zenvia, especially when it is used in association with other metabolic inhibitors and CYP2D6 substrates, as would be expected in the relatively sick populations in whom PBA may occur. We are very concerned that labeling statements warning against such use would not be entirely successful in preventing such concomitant drug use.

Finally, quinidine is known to be particularly dangerous in patients who are moving in and out of atrial flutter/fibrillation, due to the risk both of torsades de pointes, and of supraventricular tachycardia from quinidine effects on atrio-ventricular conduction. In this regard, we note at least one case in the database of a patient who entered the trial with a history of atrial flutter who became symptomatic (i.e., experienced palpitations) on treatment. The population in whom PBA is common may include many such patients, and we are concerned that these patients will be particularly vulnerable to serious ventricular arrhythmias if treated with Zenvia.

We note the occurrence of 48 deaths in the open-label experience, many in ALS patients, presumably due to respiratory failure. However, you have not provided evidence that this number of deaths, from this cause, would be expected in this time period in this population. We are concerned that the very high levels of DM produced by Zenvia in this vulnerable population may have contributed to respiratory depression in these patients. We also note the occurrence of a relatively large number of respiratory depression and failure events, categorized as serious adverse events. You will need to address our concern that this product may be associated with respiratory depression and failure in this vulnerable population (we include in this vulnerable population other populations in whom PBA may occur, including patients with stroke and Alzheimer's Disease, groups in whom you have obtained very little clinical experience).

We also note a 6% incidence of vomiting in the patients treated with Zenvia in Study 102 compared to no vomiting in the other treatment groups. We further note a 33% incidence of nausea in the Zenvia treated patients in this study, compared to 6-8% in the other treatment groups. These findings are particularly worrisome in vulnerable populations because of the risk of aspiration, especially in those patients with difficulty swallowing, in whom the risk of aspiration is even greater. Further, we believe the risk for aspiration may be especially great in these patients, given the 13% incidence of somnolence in the Zenvia treated patients compared to 3% in the DM patients and 0 in the quinidine-treated patients in Study 102 (we also note a 5% incidence of somnolence compared to 1% in the placebo group in Study 106).

We are also greatly concerned about the risk of falls in these patients. We have re-calculated the incidence of falls in both controlled trials, including those patients whose adverse event was categorized as an injury, but who clearly sustained their injuries as a result of falls. In Study 102, the incidence of falls was 13% in the Zenvia group, 12% in the DM group, and 0 in the quinidine group. A similar re-calculation of the incidence of falls in Study 106 yielded a 5% incidence of falls in the Zenvia group compared to a 3% incidence in the placebo group. The number of falls in Study 106 was too small to serve as a reliable indicator of risk in the MS population; however, Study 102 suggests that Zenvia increases the risk of fall in the ALS population.

Further, we calculated the incidence of an increased risk of falls in both studies, by adding the incidences of events that could reasonably be considered to predispose to falls. In this analysis, we combined various event terms, including disoriented, dizzy, lightheaded, shaky, unstable, etc. (we acknowledge that these calculations presuppose that each event reported occurred in separate individuals; this, of course, may not be true). When these events were combined, the incidence of events in Study 102 that could be considered to predispose to falls was 43% in the Zenvia group, 27% in the DM group, and 5% in the quinidine group. In Study 106, the incidence of these predisposing events was 41% in the Zenvia group, and 23% in the placebo group. Although the specific terms to include in these calculations could be a matter for discussion, we believe grouping appropriate terms is clinically meaningful (an examination of dizziness alone shows a 20% incidence in the Zenvia group, a 15% incidence in the DM group, and a 3% incidence in the quinidine group in Study 102 and a 26% incidence in the Zenvia group and a 9% incidence in the placebo group in Study 106). These numbers are disturbing, given the potential serious consequences of falls in these populations. Please address these concerns.

Although we acknowledge that there do not seem to be important systematic laboratory changes induced by treatment with Zenvia, we are particularly concerned about the occurrence of significant hepatic injury in patient 136-9004 who became jaundiced after 2 ½ months of treatment with study drug. This patient had significant elevations in AST, ALT, and bilirubin, with a mild increase in alkaline phosphatase. No viral or chemical cause for these changes was found, and, although this patient was receiving treatment with numerous concomitant medications, none would have been expected to have caused this injury. The pattern of injury seen in this patient is very similar to that seen with other drugs known to result in hepatic failure. For these other drugs, the incidence of hepatic failure in general use is about 10% of the incidence of the finding of hepatic injury in clinical trials (e.g., in this case, the incidence of the finding of hepatic injury is about 1/1000 patients; the incidence of hepatic failure in general use, if this case is drug related, would be expected to be about 1/10,000). We recognize that, typically, such cases of drug-induced serious liver injury occur in the setting of a general, systematic increase in liver function tests, which did not occur here. Nonetheless, this case is troubling, and raises the concern that Zenvia is hepatotoxic. Please address this concern. We note

that, if this patient was receiving active drug, it will be critical to closely follow him, to determine if an alternative underlying explanation for these findings emerges (e.g., episodes of alcohol abuse, underlying malignancy, etc.).

These concerns, taken together, raise serious questions about the safety of Zenvia in the vulnerable populations for whom it is intended, and, as described above, these concerns will need to be addressed before the drug can be approved. Further, we note, again, that numerous vulnerable populations (e.g., patients with Alzheimer's Disease) have not been adequately studied, and we believe that they will need to be before the drug can be approved.

We also again note that lower doses of both the quinidine and DM components of the combination may result in a product that is equally effective, and potentially much safer, than the current proposed product (we remind you that the results of the analyses of the laughing/crying episodes at least suggest that [substantially] lower exposures of DM may control these events). We recognize that you have chosen your dose of quinidine based on a finding that this dose converted 8/8 extensive metabolizers of 2D6 (EMs) into poor metabolizers (PMs), as assessed by urinary metabolic ratio. We remind you, however, that a 10 mg dose of quinidine converted 6/7 EMs to PMs. It is clear that the lowest dose of quinidine that will give the desired effect is much to be preferred; this is similarly true for the dose of DM, and further dose finding to identify the lowest effective doses of each component should be undertaken.

Because of these fundamental questions about the safety and effectiveness of Zenvia, we do not believe we can draft product labeling at this time. Therefore, we have not included draft labeling with this letter.

### Clinical Pharmacology Comments

1. The following *in vitro* studies should be conducted preferably prior to approval to be included in labeling.
  - Evaluate quinidine as an inhibitor and as an inducer of P450s
  - Evaluate dextromethorphan (DM) as an inhibitor and as an inducer of P450s

Please refer to the Draft Guidance for Industry: Drug Interaction studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (<http://www.fda.gov/cder/guidance/6695dft.htm>). The results of these *in vitro* studies would indicate whether further *in vivo* drug interaction studies are needed.

2. The following proposed dissolution method and specifications are acceptable:

**Apparatus:** USP Apparatus 1 (Basket)

**Medium:** Simulated Gastric Fluid, without enzymes, pH 1.2

**Volume:** 900 ml

**Rotation Speed:** 100 rpm

**Specification:**

**Dextromethorphan:** 15 minutes: Q= (b) (4)

**Quinidine:** 15 minutes: Q= (b) (4)

Nonclinical Comments

1. You have not provided sufficient justification for the high doses used in the reproductive toxicology studies in rat (fertility and early embryonic development, embryofetal development, and pre- and post-natal development) and rabbit (embryofetal development). In none of the studies was dose-limiting toxicity observed, and the dose-range finding studies in rat and rabbit do not convincingly establish that higher doses could not have been tolerated.

Regarding the rat studies, the highest combination dose tested in the fertility and early embryonic development and embryofetal development studies (50 mg/kg dextromethorphan/100 mg/kg quinidine) was associated only with salivation and a small decrease (5%) in body weight gain (embryofetal development study only). In the dose-range finding study, the high dose (100 mg/kg dextromethorphan/100 mg/kg quinidine) was only administered for three days, apparently due to clinical signs (reduced activity, ataxia, piloerection) on Day 3, although these findings were not documented in the individual line listings. The highest combination dose tested in the pre- and post-natal study (30 mg/kg dextromethorphan/100 mg/kg quinidine) resulted in no maternal toxicity. There were several instances of total litter loss at the high dose; however, it is not clear that they were drug-related or dose-limiting.

Interpretation of the results of the embryofetal development study in rabbit was complicated by the lowering of doses at different periods during gestation and the addition of animals that received the lower doses for the full dosing period. (The latter was apparently necessary due to technical problems, i.e., the loss of fetuses during processing.) The doses were lowered from the initial high dose (50 mg/kg dextromethorphan/100 mg/kg quinidine) in response to body weight effects that we do not consider sufficient to warrant such action. In the dose-range finding study in rabbits, the highest combination dose administered (100 mg/kg dextromethorphan/100 mg/kg quinidine) was not adequately evaluated (being given for only 6 days), and was associated only with a sporadic increase in respiration rate and a decrease in food consumption that was not accompanied by an effect on body weight.

The adequacy of the embryofetal studies are of particular concern considering the increase in total malformations (all skeletal) in the rabbit study and the skeletal effects observed in the rat study.

We recommend that you conduct appropriate dose-range finding studies in rat and rabbit in order to select adequate doses for the definitive studies; the high doses need to produce some degree of maternal or fetal (or offspring) toxicity. If the results of these dose-range finding studies establish that a higher dose could not have been tolerated, then repeat studies would not be needed. In the rat, you should consider exploring combination doses between 50/100 and 100/100 mg/kg (dextromethorphan/quinidine).

2. The chronic toxicity of the combination of dextromethorphan and quinidine was assessed only in rat. We agreed to the assessment of chronic toxicity in a single animal species; however, this was based, at least in part, on the fact that chronic toxicity would be assessed in rodent in the 2-year rat carcinogenicity study. Therefore, ideally the single chronic toxicity study would have been conducted in non-rodent. In fact, you originally proposed to conduct a chronic toxicity study in dog.

Dextromethorphan is currently approved for short-term use (e.g., temporary relief of cough due to colds), whereas Zenvia is intended for chronic administration. In addition, plasma levels of dextromethorphan are increased up to 40-fold following administration of Zenvia compared to dextromethorphan alone. Since the maximum recommended dose of dextromethorphan in OTC products (120 mg/day) is only two times the recommended daily dose of Zenvia, it is clear that systemic exposure to dextromethorphan will substantially exceed the exposure for which there is previous human experience, at least in patients who are CYP2D6 extensive metabolizers (EMs).

We note your commitment to perform a chronic toxicology study in non-rodent under IND 62,567 (End of Phase 2 meeting minutes, 11/12/03). If this study is ongoing or has been completed, a final study report should be submitted for review. If not, you will need to conduct a chronic study in non-rodent. You have concluded that the dog is an inappropriate animal model; however, you have not provided sufficient data to establish this. If the dog is documented to be an inappropriate species, you should consider another non-rodent species, such as monkey or minipig. Whether or not the chronic non-rodent study will be needed prior to approval will depend on availability of an appropriate non-rodent animal model and an overall evaluation of the nonclinical and clinical data.

3. You need to conduct a juvenile neurotoxicology study in an appropriate animal species to assess the potential for Zenvia to induce apoptotic neurodegeneration during development. In the animal species selected, the timing of dosing during development should cover the vulnerable period in humans (i.e. last trimester through postnatal ages 2-3). This study may be conducted post-approval. Please propose a time line for conduct of the study and submission of the final study report.
4. The 2-year carcinogenicity study in rat was not required for the NDA. However, since the study was initiated in mid-2003, it should be completed. The final study report should be submitted as soon as possible.

#### Abuse Liability Comments

In addition to the proposed educational plan under your proposed Risk Minimization Plan (RiskMAP), you should educate patients on the safe storage of Zenvia in the home, away from children, adolescents and from anyone for whom the product has not been prescribed.

You should provide information on how you plan to collect, analyze and evaluate the information collected by monitoring various databases for abuse and misuse of the product; provide information on the frequency of reporting to the FDA on the outcomes of the proposed RiskMAP; and propose interventions if abuse or misuse of the product is determined.

#### Chemistry, Manufacturing and Controls Comments

Please update stability data with all available data at the time of resubmission.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not

follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Russell Katz  
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