CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021879Orig1s000

SUMMARY REVIEW

MEMORANDUM

DATE: October 28, 2010

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

TO: File, NDA 21-879

SUBJECT: Action Memo for NDA 21-879, for the use of Nuedexta (dextromethorphan/quinidine) Capsules in the treatment of Pseudobulbar Affect (PBA)

NDA 21-879, for the use of Nuedexta (dextromethorphan/quinidine) Capsules in the treatment of Pseudobulbar Affect (PBA), was submitted by Avanir Pharmaceuticals on 1/27/06. PBA is characterized by uncontrollable episodes of laughing and/or crying, unrelated to the patient's emotional status, and occurs in the setting of numerous CNS lesions. The product is a fixed combination of dextromethorphan (DM) and quinidine (Q). The active anti-PBA moiety is considered to be DM, but DM is rapidly converted by CYP2D6 to dextrorphan (DX), a metabolite considered to not be active in this regard. Q is added to the combination to inhibit CYP2D6, with the intention of blocking the metabolism DM to DX.

The initial application contained the results of two randomized controlled trials, one in patients with amyotrophic lateral sclerosis (ALS) and one in patients with multiple sclerosis (MS) that examined a dose of DM 30 mg/Q 30 mg given twice a day; taken together, these studies were designed to document the effectiveness of the combination against PBA, as well as the contribution of each component (only the study in patients with ALS was designed to address this latter point).

The division issued an Approvable (AE) letter on 10/30/06, citing numerous issues that the sponsor needed to address, including both effectiveness and safety concerns.

Regarding effectiveness, the division noted that the study yielded statistically significant treatment differences on its primary outcome, the CNS-LS, a rating scale for PBA, but that the results were less than robust on a secondary outcome, the number of PBA episodes, the outcome that the division had strongly recommended that the sponsor use as the primary outcome measure.

Regarding safety, we noted that Q has been associated with "…serious ventricular arrhythmias, including torsades de pointes.", and that a thorough QT study revealed a mean maximum increase of about 10 msec, with an upper

bound of the 95% Confidence Interval (CI) of about 15 msec at the 30/30 dose, and a mean maximum increase in the QT of about 18 msec (95% upper bound of about 25 msec) at a DM 60/Q 60 dose.

We also expressed concern about the possibility that Q's ability to inhibit CYP2D6 could increase the levels of medications that are 2D6 substrates, giving rise to potentially serious interactions in the relatively sick populations with PBA.

In addition, we noted a previously described risk of significant arrhythmias in patients with atrial fibrillation/flutter.

We also noted 48 deaths in the open-label studies; we asked the sponsor to discuss this incidence, vis-à-vis what would be expected in a similar population.

We also noted what appeared to be a significant risk of falls/dizziness, and a single patient with elevated liver function tests (LFTs) with an elevated bilirubin, raising the question of whether or not DM/Q is a significant hepatotoxin.

Finally, we noted that it appeared that a 10 mg dose of Q was likely to result in a similar degree of 2D6 inhibition as the 30 mg dose of Q that had been studied.

The division and sponsor had numerous interactions after the AE letter was issued. Ultimately, the sponsor agreed to perform an additional study evaluating a fixed combination of DM 30 mg/Q 10 mg.

The AP letter also contained several pharmacology comments; specifically, we asked the sponsor to: perform a juvenile neurotoxicity study, perform dose finding studies in rat and rabbit in order to support appropriate doses for definitive reproductive toxicity studies, submit the results of the rat carcinogenicity study as soon as possible, and evaluate toxicity in a chronic non-rodent species.

In addition, the AP letter included several clinical pharmacology comments (we asked the sponsor to evaluate the inhibiting and inducing potential of Q and DM). There were several minor CMC and abuse liability comments as well.

The sponsor submitted a complete response on 4/30/10. This submission contained the results of a new controlled trial comparing DM30/Q10, DM 20/Q10, and placebo as well as updated safety, CMC, and clinical pharmacology data.

The application has been reviewed by Dr. Loretta Holmes and Tselaine Jones Smith, Division of Medication Error Prevention and Analysis (DMEPA), James Hunter and Dr. Lori Love, Controlled Substance Staff (CSS), Antoine El-Hage, Division of Scientific Investigations (DSI), Interdisciplinary Review Team for QT Studies, Dr. Devanand Jillapalli, medical officer, Dr. Lydia Gilbert-McCLain, Division of Pulmonary and Allergy Products, Dr. Suchitra Balakrishnan, Division of Cardiovascular and Renal Products, Dr. Tristan Massie, statistician, Dr. Ju-

Ping Lai, Joo-Yeon Lee, and Dr. Li Zhang, Clinical Pharmacology, Dr. D. Charles Thompson, pharmacologist, Dr. Lois Freed, pharmacology team leader, Dr. Thomas Wong, Chemist, and Dr. Ronald Farkas, neurology team leader.

As noted above, the sponsor submitted the results of a single controlled trial (Study 123), in which patients with either ALS or MS were randomized to receive DM30/Q10, DM20/Q10, or placebo, each given twice a day, for 12 weeks. The primary outcome was the change from baseline in laughing/crying episode rate. Secondary outcomes included the change in CNS-LS (Center for Neurologic Study-Lability Score), and other measures.

As described by Drs. Massie, Jillapalli, and Farkas, the comparisons of both dose groups to placebo reached statistical significance on the primary outcome ($p<0.0001$); numerically, the low dose combination was somewhat superior to the high dose combination. On other outcomes, some analyses favored the high dose compared to the low dose, and some favored the low dose compared to the high dose. In general, there were no consistent differences between the dose groups when comparing medians (in many cases, more appropriate than analyzing means). The analyses were complicated to some extent by differences at baseline in some potentially important variables (e.g., time from diagnosis to enrollment). Although in some analyses there seemed to be more of an effect in the ALS compared to the MS populations, this was inconsistent and the study was not powered to detect differences in response between diagnoses.

Regarding safety, the sponsor performed another thorough QT study of the DM30/Q10 combination, and found a mean maximum increase in QT interval of about 10 msec (95% CI upper bound of about 12.6 msec).

In general, there were no specific safety issues of concern that occurred at an importantly different rate on drug compared to placebo, including any significant episodes of QT prolongation or cardiac arrhythmias, and falls. In addition, closer examination of the previously identified patient with elevated LFTs and bilirubin revealed that the patient resumed treatment with Nuedexta without recurrence; this case can reasonably be attributed to mononucleosis, as the sponsor suggests.

However, there was an increased incidence of death in the drug groups, compared to that in the placebo group. Specifically, 3 patients in each Nuedexta group died, compared to one in the placebo group. All deaths occurred in ALS patients, and two of the deaths in the 30/10 dose group and the one placebo death occurred about one month after discontinuation of treatment, and did not appear to have been the result of an adverse event that began during treatment.

Dr. Jillapalli has examined this issue in great detail. He agrees with the sponsor that the deaths appeared to be related to respiratory failure, and found that the incidence of non-fatal respiratory failure was no greater in either of the drug

groups than in the placebo group. Dr. Massie has also performed some statistical analyses of the data, and concluded that the probability of such an imbalance (or one larger) if there is no real difference between the treatment groups was 0.28. For these reasons, the review team has concluded that, although the possibility exists that Nuedexta increases mortality in this population, this is very unlikely, given the data in hand.

The sponsor has also attempted to compare the mortality described in the AP letter with background mortality rates in the general ALS population. According to this analysis, the mortality seen in the Nuedexta database is lower than the background rate in the ALS population. These sorts of comparisons are difficult to interpret, and we cannot conclude that Nuedexta decreases mortality in patients with ALS, but the analyses are to some degree reassuring.

The capacity for Q to cause torsades de pointes and other serious ventricular arrhythmias, at the recommended dose of 20 mg/day, has been extensively discussed with the review team, as well as with the director of the Office of Drug Evaluation I and members of the Division of Cardiovascular and Renal Products. Although all agree, of course, that much higher doses of Q can cause serious ventricular arrhythmias, including torsades de pointes, there is general agreement that the risk of torsades de pointes is likely to be extremely low at 20 mg/day, and, as a result, would be difficult to detect in any reasonably sized study.

Further, there also seems to be general agreement that, at a dose of 20 mg/day of Q, the only pharmacologic effect expected is blockade of the IKr channel, and that Q's well-known other pharmacological effects would not be expected to occur (nor have they been seen in the data). Therefore, arrhythmias not related to increased QT interval would not be expected. This would include our originally expressed concern about Q's effects in patients moving in and out of atrial fibrillation/flutter. Indeed, the sponsor makes the case that there is no adequate data that unequivocally establishes that the risk of serious ventricular arrhythmias known to occur with Q is increased in patients with atrial fibrillation/flutter, and that the apparent association is due to the fact that Q has mostly been used in these patients.

As noted above, Nuedexta does prolong the QT interval at the recommended dose. Again, after discussions with our colleagues, it appears that there is also a consensus that the degree of QT prolongation is not of great concern in and of itself, but that there may be patients in whom there is a real risk of torsades de pointes (for example, those taking other QT prolonging drugs).

COMMENTS

We had previously concluded that Nuedexta (then called Zenvia) had been shown to be effective in the treatment of PBA in patients with ALS and MS, but

issued an AP letter primarily due to numerous safety concerns. As a result, we asked the sponsor to examine the safety and effectiveness of a combination consisting of lower doses of both DM and Q.

The sponsor has performed such a study, and this study has established the effectiveness of two new combinations, DM30/Q10, and DM20/Q10. The study did not examine the contribution of each component, but this had been established in previous studies. In my view, there are several questions related to effectiveness that must be considered.

The first concerns which dose to approve (assuming that safety has been adequately evaluated; more on this below).

Both dose combinations have been shown to be effective, and, in general, there seems to be no important differences between the two doses. There are, however, some analyses that suggest some superiority of the higher dose combination. In other similar cases, we would ordinarily approve the lower dose, and state in product labeling that the higher dose seemed not to confer any additional benefit. (b) (4)

In this case, however, if we approve the 20/10 combination but do not approve the 30/10 combination, the higher dose combination will not be able to be achieved by practitioners (higher doses than 20/10 BID could, of course, be achieved by giving some combination of the 20/10 strength other than one capsule BID, but this will result in higher Q (and DM) doses than would be necessary if we approved the 30/10 combination).

Consideration of which strength(s) to approve also raises another question.

There is only one study at the 20/10 dose, the only dose we are contemplating approving. Although we do not ordinarily require replication of the effectiveness of each dose of a treatment that we approve, if that lower dose is the **only** dose that will be available, we might ask the question of whether or not a single trial at that dose is adequate.

In this regard, I would make two points.

First, the results at the 20/10 strength were robust, with a p-value for the contrast on the primary outcome measure of $p<0.0001$.

Second, we know that the degree of CYP2D6 inhibition achieved with 10 mg Q is essentially the same as that achieved with the 30 mg dose of Q. Therefore, it is reasonable to conclude that the effectiveness of 30/30 would be about the same

as the effectiveness of 30/10 (because the plasma levels of DM are about the same in both cases). Further, from Study 123, we know that the effectiveness of 20/10 is essentially the same as at 30/10, which we have just concluded is about the same as at 30/30, a dose we know to be effective from other studies. Therefore, we would expect that 20/10 would be about as effective as 30/30, providing a significant degree of replication (albeit based on cross-study comparisons).

Given the desire to limit the exposure to DM levels and these other factors, then, I believe it is appropriate to approve only the 20/10 combination (assuming adequate safety).

The next question related to effectiveness concerns the specific claim to be granted. Specifically, should we approve Nuedexta for the PBA associated with ALS and MS, or for a more global claim; that is, for the PBA associated with all other neurologic conditions in which it occurs?

Both Drs. Jillapalli and Farkas recommend that Nuedexta be indicated for the treatment of PBA associated with ALS and MS. Dr. Jillapalli primarily bases his recommendation on what he believes is a lack of adequate safety data in other populations, namely patients with stroke, who are elderly and have underlying cardiac and pulmonary disease. Dr. Farkas is also concerned about safety in other populations, but he also concludes that effectiveness cannot easily be generalized to conditions not studied in controlled trials. He recommends that at least one other setting in which PBA occurs (e.g., stroke) be studied before a "general" claim could be considered.

I have discussed these issues extensively with Drs. Jillapalli and Farkas since their reviews have been written.

Putting aside safety for the moment, my view is that effectiveness can reasonably be extrapolated to PBA that occurs in other neurologic conditions not studied in controlled trials. My view is primarily based on the observation that the two models studied, ALS and MS, are significantly and sufficiently different from each other in pathology and anatomic location of lesions to permit the conclusion that Nuedexta produces its effects on PBA via some (unknown) pathway common to them both, and given the clear distinctness of the primary pathology of the two conditions, it is reasonable to conclude that this "common pathway" is likely to be similar in other settings in which the underlying primary events are yet again different from one another. I certainly agree with Dr. Farkas's point that the underlying pathobiology of PBA is poorly understood. In my view, though, this can be considered to be consistent with the conclusion that, regardless of the primary underlying events, Nuedexta can be considered to be effective in all settings in which it occurs, given the clear effectiveness in the two (very) disparate settings in which it has been studied.

Dr. Farkas is rightly concerned that there are behavioral changes seen in patients with Alzheimer's Disease (AD) that may mimic PBA, and that it is unclear that PBA actually occurs in patients with AD, although the sponsor clearly believes it does, and we have reason to expect that the sponsor would wish to promote Nuedexta's use in patients with AD. I believe that labeling can be written that can make clear that PBA is a distinct syndrome, and that Nuedexta has not been shown to be safe and effective for any other behavioral abnormalities that might occur in the setting of other neurologic diseases.

The safety concerns have also been extensively discussed with the review team.

In my view, the concerns raised in the AP letter have been adequately addressed.

At the lower strength, no important cardiac or other adverse events have been seen. It is true that the number of patients exposed to the 30/10 and 20/10 doses in Study 123 was relatively low (about 200), but given the considerations discussed above (that is, the general agreement that at these doses of Q, the risks of significant cardiac events is very low), we have no obvious reason to be concerned about the occurrence of significant arrhythmias. Other safety issues highlighted in the AP letter (potential consequences of administering Nuedexta with other CYP2D6 substrates and inhibitors, CYP 3A4 inhibitors, and QT prolonging drugs) can reasonably be dealt with with adequate warnings in product labeling.

Potential respiratory failure seems not to be a significant risk, nor do falls or vomiting at these doses. There is no real evidence of significant hepatotoxicity in the data submitted.

The question of the safety of Nuedexta in the elderly population with underlying cardiac and/or pulmonary disease has also been discussed extensively with staff from this division as well as from the cardiology division. The consensus is that the cardiac and respiratory effects of Nuedexta are well known, and pose no risks that are unacceptable and that cannot be adequately described in product labeling. This includes the important issue of potential interactions between Nuedexta and other drugs (e.g., CYP2D6 substrates, CYP3A4 inhibitors, drugs that prolong the QT interval).

All issues discussed in the AP letter have been adequately addressed (or will be; see below), and there are no other issues precluding approval. We have determined that a Medication Guide is unnecessary, and consequently there is no need for a Risk Evaluation and Mitigation Strategy (REMS).

We will impose numerous PMRs for the following studies (see Dr. Freed's memo for further discussion of these studies):

1) Studies in pediatric patients (pharmacokinetic study, controlled trial, and open-label safety study, all in patients 2-16 years of age)
2) Neurotoxicity study in neonatal rats
3) Pre- and post-natal development study in rats
4) Embryofetal study in rabbits
5) Post-natal growth and development study in rats
6) Studies to assess the in vitro binding of Q at the $5HT_{2B}$ receptor (a recent literature report suggests that Q is an agonist at this receptor; these agonists are associated with cardiac valvulopathy in humans)
7) A study to investigate Q's potential to cause cardiac valvulopathy in animals, if it is shown to be a $5HT_{2B}$ agonist

For the reasons given above, then, I will issue the attached Approval letter, with agreed upon product labeling.

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/s/

RUSSELL G KATZ
10/29/2010