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APPLICATION NUMBER:

21-911

SUMMARY REVIEW

MEMORANDUM

DATE: November 6, 2008

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-911

SUBJECT: Recommendation for action on NDA 21-911, for the use of rufinamide tablets as adjunctive treatment for adults with partial seizures and as adjunctive treatment for adults and pediatric patients with Lennox-Gastaut Syndrome (LGS)

NDA 21-911, for the use of rufinamide tablets as adjunctive treatment for adults with partial seizures and as adjunctive treatment for adults and pediatric patients with Lennox-Gastaut Syndrome (LGS), was submitted by Eisai Medical Research, Inc., on 11/17/05. The application contained the results of 8 controlled trials. An Approvable letter was issued on 9/15/06. That letter described numerous deficiencies as described below:

Effectiveness

Most of the trials examined the effects of rufinamide in patients with partial seizures; a single trial studied patients with LGS. The submitted effectiveness data in partial seizures gave inconsistent results, left the appropriate dose unclear, and demonstrated very small treatment effects.

Study ET1 compared 4 doses of rufinamide (200, 400, 800, and 1600 mg/day) to placebo. The protocol-specified linear trend test was positive, although the results were not linear, with the 800 mg/d dose demonstrating the largest effect. Beyond this, the treatment effect appeared quite small (about 1.5 seizure decrease/month compared to placebo). In addition, the results were not robust; in a standard ANCOVA that included country as a covariate, only the 800 mg-placebo contrast yielded nominal statistical significance.

Another study, in patients with generalized tonic-clonic seizures, did not demonstrate a statistically significant difference between 800 mg/day and placebo.

Study 21A, which compared 3200 mg/day to placebo, reached statistical significance on the protocol-specified Wilcoxon test, but failed to reach significance ($p=0.09$) on a more traditional ANCOVA with baseline seizure frequency and country as covariates. Again, the difference in seizure reduction between drug and placebo was about one seizure/month in this study.

Non-clinical

We noted that the rat carcinogenicity study was inadequate, due to excessive weight loss in the mid and high dose female rats. Because this weight loss was possibly due to unpalatability of the feed, we asked the sponsor to address the possibility of doing a carcinogenicity study with gavage dosing (there was preliminary evidence that higher doses could be achieved with gavage dosing).

The in vivo micronucleus assay in rat, the rat fertility study, and the rabbit embryofetal study were considered inadequate for various reasons. We asked that these studies be repeated.

We noted decreased whole and regional brain weights in juvenile rats, and asked the sponsor to further investigate this finding with additional histopathology and morphometry.

We noted that the developmental age range studied in the juvenile dog study was inadequate, and asked the sponsor to perform an adequate study.

Tradename

We found the sponsor's proposed tradename [redacted] to be unacceptable. In addition, we had several comments about the carton and container labels. **b(4)**

The sponsor responded to the Approvable letter in a submission dated 2/29/08. This response has been reviewed by Dr. Steven Dinsmore, medical officer, Dr. Jinhee Lee, Division of Medication Error Prevention and Analysis, Dr. Lisa Jones, safety reviewer, Dr. Ohidul Siddiqui, statistician, Drs. Ed Fisher, Lois Freed, and Paul Brown, pharmacology, Dr. Atul Bhattaram, Office of Clinical Pharmacology, Dr. David Claffey, chemist, and Dr. Norman Hershkowitz, Neurology Team Leader. In this memo, I will very briefly review the pertinent aspects of the sponsor's re-submission, and offer the rationale for the division's recommendation for action on the NDA.

Effectiveness

The sponsor has not submitted new studies. Rather, they have presented arguments to support their view that substantial evidence of effectiveness exists for rufinamide [redacted] **b(4)**

Briefly, with regard to Study ET1, the sponsor presented analyses of several secondary endpoints in order to establish the minimally effective dose (they noted that due to lack of normality in the seizure frequency data, a linear model could not adequately establish a minimally effective dose). A Wilcoxon rank-sum

test of the Seizure Frequency ratio (the number of seizures during double-blind/the number of seizures during baseline) revealed statistical significance for the 400, 800, and 1600 mg/day doses (although without any difference in effect among these doses). A requested Poisson regression analysis also revealed nominal significance for these doses, also without clear dose-response. Further, an ANCOVA on Ranks of Percent Change in Total Seizure Frequency yielded nominal significance of these 3 doses, with no clear dose response among them.

Dr. Siddiqui noted that the sponsor had included the placebo group in its dose response analyses. Further, he noted that the dose groups were coded inappropriately (non-proportional to the actual doses-see his review, page 6). When the doses were coded proportionally to the actual doses in his dose-response analysis, and placebo was excluded, the p-value for the dose-response slope was 0.086, implying that none of the doses (200-1600 mg/day) differed materially.

Dr. Siddiqui notes that in numerous of the secondary analyses performed by the sponsor (see his Tables 1 and 2, pages 4,5, and Table 5, page 7), adjustments for multiplicity were not performed, and that when they were, only the 1600 mg/day dose group achieved significance. I am not certain that adjustments for multiplicity need to be made in these cases. A typical analysis would test the high dose first, and, if significant at p=0.05, could continue to test subsequently lower doses in a similar way. However, regardless of the analyses performed, there appears to be no consistent dose response among 400, 800, and 1600 mg/day, an important conclusion essentially similar to that we had reached in our initial review.

As noted earlier, Study 21A was positive by the protocol-specified Wilcoxon rank-sum test of the percent change in partial 28 day seizure frequency. A secondary analysis performed by the sponsor on the log of the post-baseline seizure frequency that included the log-transformed baseline seizure frequency, country, sex, and age as covariates yielded a p value of 0.092. As Dr. Siddiqui notes, these analyses (Wilcoxon and ANCOVA) are typically performed on data for other AEDs, and for these other AEDs they typically yield consistent results.

In the re-submission, the sponsor attributed the lack of statistical significance in the ANCOVA to the lack of normality of the data, despite the log transformation. For this reason, the sponsor presented the results of an ANCOVA on ranks of percent change from baseline in seizure frequency including rank of baseline seizure frequency and country as covariates. This analysis yielded a p-value of 0.008.

Dr. Siddiqui performed an additional analysis of ranks (given the sponsor's claims that analyses of ranks on the non-normal [transformed and non-transformed] data are more appropriate). Dr. Siddiqui's analysis examined ranks of total 28 day seizure frequency during double blind with rank of seizure

frequency at baseline and age as covariates, and treatment, country, and gender as factors in the model. This analysis yielded a p-value of 0.118. These analyses suggest a lack of robustness of the data.

Finally, Dr. Siddiqui notes that, as noted in our original reviews and Approvable letter, in general the change in (mean, median) seizure frequency compared to placebo in these 2 studies is quite small (see his Table 8, page 10).

The sponsor and Dr. Bhattaram of our Office of Clinical Pharmacology have performed pharmacokinetic/pharmacodynamic (PK/PD) analyses. Although Dr. Bhattaram has raised some concerns about the sponsor's analyses (for example, they assumed a constant placebo response over time, an assumption he feels is not valid (see his Figure 4), he has found a positive dose response relationship in adults, but no such relationship in children and adolescents, the latter finding attributed perhaps to different placebo responses between adults and pediatric patients. He notes that plasma levels for a given dose of rufinamide are about the same in adults and pediatric patients. He also notes that the reduction in seizure frequency in adults at a dose of 45 mg/kg/day (a relatively high dose in adults) is about 11-13% (see his Table 3).

It should also be noted that Dr. Siddiqui observed a clear difference in the median number of baseline seizures between the rufinamide and placebo groups in the Lennox-Gastaut study (290 szs/month vs 205 szs/month, respectively). We had asked the sponsor to address this discrepancy. They have examined their data, and have concluded that there were no systematic abnormalities in the randomization process, and that similar baseline discrepancies existed in other studies of patients with LGS (e.g., felbamate) that supported approval. They note that, given the sometimes extraordinary number of seizures patients with LGS can have, such discrepancies are not necessarily unanticipated. They further cite the overwhelmingly positive results of the study as evidence of the robustness of the result.

Safety

The sponsor has adequately resolved the questions we asked in our Approvable letter. In particular, as Dr. Jones notes in her review of QT shortening, there was no difference in the proportion of patients with an episode of QT shortening of <350 msec (see her Table 1, page 6), but there were clearly more patients who experienced at least one decrease of QT of at least 20 msec on rufinamide compared to placebo (see her review, page 8). However, there seems to be no relation to dose, at least at the doses studied in the formal QT study, 2400 mg/day to 7200 mg/day.

Non-clinical

In order to address our concern that the rat carcinogenicity study was inadequate because of excessive weight loss that might have been due to unpalatability of the feed, the sponsor performed a 3 month study in which drug was given by gavage. As noted by Drs. Freed and Fisher, the weight loss could not be avoided by gavage feeding. Therefore, an additional study in which drug is given by gavage will not be required.

The sponsor has also performed an adequate in vivo micronucleus study that is negative.

The sponsor has also performed a rat fertility study and a rabbit embryo-fetal toxicity study. These studies were considered adequate and produced positive findings that would not preclude approval.

Finally, the sponsor performed additional neurohistopathologic examination of the brain in the rat juvenile study, and found no treatment related abnormalities. They have also agreed to perform a dog juvenile study in Phase 4.

Tradename and carton and container questions

Dr. Lee of DMEPA has concluded that the current proposed tradename, Banzel, could be potentially confused with the name [redacted] is the proposed name for an investigational drug currently being developed under an IND. If the rufinamide NDA is approved before an NDA for [redacted] Banzel will be considered acceptable. b(4)

Comments

As described earlier, based on our original review of this NDA, we had concluded that, although the data submitted suggested anti-partial seizure activity of rufinamide, the effects were considered to be unusually small, inconsistent, and an appropriate dose was difficult to identify. [redacted] We had also concluded that Study 22, in patients with LGS, was clearly positive at the one dose studied (3200 mg/day), but that the evidence taken as a whole did not support approval for that indication. b(4)

The sponsor has not, as recommended in the Approval letter, performed a new study in patients with partial seizures, but instead has provided additional analyses and arguments to attempt to establish substantial evidence of effectiveness for rufinamide for this indication.

I do not find these arguments convincing. Although they have provided numerous analyses that yield statistically significant differences for all doses

above 200 mg/day and placebo, they have failed to establish, for the reasons stated above, any convincing dose response in this dose range. The effects seen were, in fact, quite small, and they have not provided evidence that this is not so. Although a number of the studies that were negative were done under slightly different conditions than in the proposed indication of adjunctive therapy for partial seizures in adults (negative studies examined rufinamide's effects as monotherapy, in pediatric patients with partial seizures, and in adults with generalized tonic-clonic seizures), and these differences could **possibly** explain the results, b(4)

With regard to Lennox-Gastaut Syndrome, however, I believe, upon further reflection, that the sponsor has presented substantial evidence of effectiveness for this indication.

Although we had originally concluded that the evidence was not adequate to support such a claim, and Dr. Hershkowitz reaches this same conclusion after having reviewed the sponsor's re-submission, I think that the sponsor has provided substantial evidence of effectiveness, as provided by a single adequate and well-controlled trial and confirmatory evidence. b(4)

First, the study is clearly and overwhelmingly positive, robust to numerous analyses. This is an unequivocal conclusion (even in the face of the previously mentioned baseline imbalance in seizure frequency). I now also believe that the data in the application, taken as a whole, provide evidence that rufinamide has anti-seizure activity. I note, in this regard, the sponsor's additional analyses of Studies ET1 and 21A, which, in addition to the results as originally presented, further suggest anti-seizure activity,

Lennox-Gastaut Syndrome is a devastating seizure syndrome, and although other drugs carry this indication, as noted by Dr. Hershkowitz, these drugs are not without significant toxicities, and additional therapies are clearly needed for this condition. I agree that the sponsor has provided no dose response data in this indication; however, the safety experience at the one dose studied demonstrates its tolerability, and is acceptable, in my view. I had previously argued (my memo of 9/15/06) that if a

single positive study in partial seizures and a single positive study in LGS could support an approval for LGS.

b(4)

I believe it is entirely reasonable to consider the data as confirmatory, as that word is commonly understood, to the clear positive finding in Study 22.

For this reason, then, we recommend that rufinamide be approved as adjunctive treatment for patients with Lennox-Gastaut Syndrome. We have included a draft package insert to which the company and the division have agreed.

Russell Katz, M.D.

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/s/

Russell Katz
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MEDICAL OFFICER