CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-789

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 11, 1998

FROM: Paul Leber, M.D.
Director, Division of Neuropharmacological Drug Products

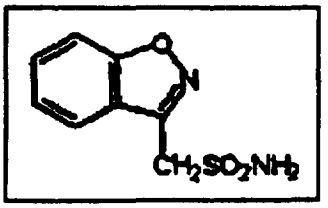
SUBJECT: Approvable action: NDA 20-789 (zonisamide)

TO: File NDA 20-789
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the Division's Review Team's recommendation that Athena's pending NDA 20-789, which allows for zonisamide's marketing as "adjunctive therapy in the treatment of partial seizures in adults with epilepsy," be declared approvable. This NDA has a PDUFA date of 3/19/98.

The primary clinical efficacy review was undertaken by James Sherry M.D., Ph.D. (2/27/98). The statistical clinical review was conducted by Dr. Todd Sahlroot (2/18/98). The safety assessment was carried out by a safety review team (Drs. Knudsen, Racoosin and Sevka) led by Greg Burkhart, M.D., M.S. (2/24/98). An overall summary of the findings that bear on the approvable action is provided by Russell Katz, M.D., Deputy Division Director and Neurology Team leader. (2/22/98)

The drug substance



Zonisamide is 1,2-benzisoxazole-3-methanesulfonamide was first synthesized in 1972. Although it is identified as a carbonic anhydrase

inhibitor[1], this action is not currently believed to account for zonisamide's anti-epileptic effects which are similar to those exhibited by phenytoin, carbamazepine and valproate.

Preclinical findings

Zonisamide was determined to be teratogenic in studies of mice, rats and dogs. It also impairs reproductive performance.

Zonisamide was not found to be tumorigenic in either mice or rats, but it does increase mutation frequency in CH lung cells. It was not found to be mutagenic or clastogenic in several other in vitro and in vivo assay systems, however.

Pharmacokinetics

Peak plasma levels of zonisamide are attained within 4 to 6 hours of the oral administration of the capsule formulation. Because of its high affinity for RBC's, almost 90% of zonisamide in the blood is bound to or resides within RBCs. Only 40% of zonisamide is protein bound, however.

Zonisamide is extensively metabolized; N-acetyl zonisamide [NAZ] and 2-sulfamoylacetyl phenol(SMAP), the latter is formed as a result of a CYP 450 3A4 mediated reduction of NAZ, are major metabolites.

The oral clearance of zonisamide from plasma is about 10 to 15 ml/min and the corresponding elimination half life from plasma is about 63 hours. Renal clearance is 3.5/ml/min. Clearance from RBC's, however, is considerably slower, (circa 2 ml/min; half life of 105 hours).

Plasma and blood levels following multiple dose use are, as expected, considerably higher than those found after the administration of a single dose. The ability to predict plasma and red cell levels in repeated use is complicated; plasma and red cell clearance, volume distributions, and red

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[1] This is of interest because acetazolamide, (aka Diamox®), another sulfonamide inhibitor of carbonic anhydrase, has anticonvulsant effects that are said to be mediated through this inhibition (i.e., leads to a reduction in CNS pH).

cell binding change as a function of time, or daily dose, or some combination of the two.

Zonisamide does not induce its own metabolism nor has its administration been found to have an effect on CYP 450 activity. The clearance of zonisamide, however, is increased by the co-administration not only of enzyme inducing AEDs (phenytoin and carbamazepine), but by valproate.

Effectiveness in use

The sponsor has provided reports of 3, parallel, placebo controlled 'add-on' studies that bear on the effectiveness of zonisamide in the management of epileptic patients who experience partial onset seizures with or without secondary generalization. Two of the studies, 912-US and 912-EUR, evaluated zonisamide under a forced escalation flexible dose regimen that was adjusted on the basis of realized zonisamide plasma levels; the third study, 922, employed a complicated dose escalation paradigm that allowed for a fixed dose comparison over at least a portion of its double blind phase.

The estimate of treatment effect in each study is presented in terms of the between treatment (i.e, drug vs placebo) difference in the percent reduction in median seizure frequency between a baseline (pre-randomization) period and a period corresponding to all or to some lesser part of each study's randomized, blinded, comparison phase.

Percent median reduction is expressed in terms of events per 28 day interval of observation. It is calculated as: **(100 • { [median frequency in randomized phase-median frequency in baseline phase]/ median frequency baseline phase}).** This metric is asymmetric in that **maximum improvement** (i.e., complete seizure suppression) is associated with at most a **100 percent reduction (i.e., minus 100%)** in seizure frequency, while there is no upper limit on the percentage increase that is associated with an increase in seizure frequency.

The experimental designs employed, however, are open to questions about

the preferred way in which to estimate a treatment effect from the data they generate. Ordinarily, regulatory assessments focus primarily upon analyses that consider all patients randomized (so-called "intent to treat" analyses.) Whether or not this approach should be taken when, as in the current examples, a study design employs a titration phase during which subjects are assigned to a less than effective dose of a drug is arguable.

Specifically, in evaluating a study that employs a titration phase, a case can be made for basing the estimate of treatment effect on differences found within the subset of patients randomized who actually attain their assigned dose of AED and remain on it throughout the study's maintenance comparison phase. An estimate of treatment effect derived from this subset seems more likely to capture the true effect of a drug than one that is based on data generated, even if only in part, from a period (titration phase) when the AED of interest is being purposely[2] administered at a subtherapeutic dose.

If the regulatory goal is to determine in a proof of principle sense whether or not a drug has the capacity to act as an AED, is it not most appropriate to rely on the analysis strategy that has the greatest 'sensitivity' to detect the drug's effect if, in fact, one does exist?

The merits of the case for analysis of an "evaluable subset" so defined are self-evident, but even when such subset analyses are specified in a study's protocol, they may have serious limitations. Specifically, any analysis that considers but a subset of the sample randomized is at risk of providing a 'biased' estimate of treatment effect when the likelihood of a subject being excluded from (or included in) the subset being analyzed is in whole or in part affected by the subject's ultimate response/outcome (i.e., if censoring is informative).

I have gone to some length to review this issue because in the course of his excellent review (2/18/98), Dr. Salhroot emphasizes the need to treat the results of subset analyses of the kind described with caution. My

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[2] In an effort to reduce the incidence and/or severity of drug induced untoward effects.

purpose here is to make clear in the record that I am not only mindful of his concerns, but share them. In the present case, however, I believe there is no reason to suspect that informative censoring occurred. Moreover, even in Study 922, the study among the 3 RCTS with the highest rate of premature discontinuations, analyses employing conservative imputation schemes for missing subjects for the most part attained statistical significance (vide infra).

The Clinical Trials

912-US

Study 912-US was a 12 week long trial 'add-on' placebo controlled trial conducted with 152 patients with complex partial seizures (history of at least 4 such seizures per month while being treated with one or two other AEDs). It was carried out at 4 sites.

Prior to randomization, a cadre of potential subjects were screened in an 8 to 12 week baseline observational phase to determine whether they met criteria for randomization and to quantitate their seizure activity. Zonisamide randomized subjects were dosed under a regimen intended to bring subjects from an initial 100 mg/day dose to 400 mg a day by week 3 (i.e., a two week titration phase). Based upon plasma level data monitored by a clinician otherwise uninvolved in the conduct of the study, additional dose adjustments were subsequently made to maintain zonisamide plasma levels within the 20 to 30 ug/ml range; dummy adjustments were made for placebo assigned patients.

The primary outcome assessment was based on the percentage change in frequency of partial and complex partial seizures between the baseline period and the last 8 weeks of the double blind trial (i.e., seizure frequency during weeks 5 through 12). Estimates of seizure frequency and type were based on information recorded by patients in diaries.

Of the 152 patients randomized, 141 were available for this analysis. Among 69 zonisamide subjects in this analysis, a reduction of 29.5% in the median frequency of partial seizures was observed; among the 72 placebo subjects, there was a 1.5% increment in median seizure frequency.

The 'p' value for this difference was 0.0004. Other data analyses, including one that attempted to provide an "intent to treat" perspective, provided similar positive results. Although no formal check was made to exclude the possibility of informative censoring, the possibility is ignorable because even when Dr. Salhroot imputed "the observed placebo maximum for all subjects with missing data irrespective of treatment assignment," the result remained statistically significant.

For subjects completing the study, the dose of zonisamide ranged from < 200 mg/day to more than 600 mg/day.

Developing a recommended dosing regimen for zonisamide from the dosing regimen used in this trial is difficult, if not impossible. This is, at least in part, a consequence of the fact that following the two week forced titration phase, subsequent dose adjustments were made based on attained plasma levels (i.e., to bring and/or hold plasma levels within a presumed "therapeutic" range of values.) While this method of dosing may well have contributed to the effective use of zonisamide in the trial, it is unclear how this experience can be used to design a regimen for dosing in the absence of plasma level monitoring.

912-EUR

Study 912-EUR is essentially identical in design to 912 US. The sponsor, however, had not wanted to submit its results to the NDA because it determined the study to be less than reliable in regard to its conduct and execution. Nonetheless, because the study was, despite its declared defects, a source of randomized controlled trial evidence bearing on the effectiveness of zonisamide, I asked that the study be reported in the NDA.

The study was conducted at some 10 centers. Subjects (N =144) were randomized to placebo (n = 71) or zonisamide (n = 73). Although the no statistically significant treatment differences were obtained, the results trended in favor of zonisamide. Although it is not obvious what factors beyond chance caused this study to fail to replicate the results of 912 US, its failure, given the corroborative positive findings of Study 922, is largely unimportant from a regulatory perspective.

Study 922

Study 922 was conducted at 20 centers. A total of 203 subjects with partial onset seizures were randomized. To qualify for entry, a subject, over a 4 week placebo baseline period, had to satisfy criteria for minimum seizure frequency rates. The study employed a complicated 3 arm, unbalanced group, design[3] that was intended to allow a placebo controlled comparison of the effects of 100 mg, 200 mg, and 400 mg a day of zonisamide. The drug dose versus placebo comparisons allowed by the design confound time on treatment with attained dose, however.

Patients were randomized to placebo or to one of two forced escalation regimens[4] that brought subjects to a fixed dose of 400 mg a day by the end of week 7 of the 12 week long placebo controlled comparison phase. The two active treatment escalation arms differed in the time allowed to elapse before the dose was advanced from the initial dose of 100 mg/day to 200 mg/day. (5 weeks for those in regimen **B1**, and 1 week for those in regimen **B2**; dosing over weeks 7 to 12 was identical in both active treatment arms.

Outcome assessment was based on counts of seizures, classified by clinical type, as recorded by patients in diaries.

As discussed in the introduction to this section, there are many possible approaches to the analysis of the data adduced in a study of this design. During pre-NDA discussions, the Division urged the sponsor to base its primary analysis of the study on a comparison of the placebo vs. combined active drug groups over the 5 week interval (wks 8-12) during which all subjects assigned to active treatment were to be receiving 400 mg a day of zonisamide. This analysis, as acknowledged above, could produce a biased estimate of treatment effect if there were informative censoring over the first 7 weeks of the study.

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[3] Figure 1 of Todd Sahlroot's 2/18/98 review provides a graphic depiction of the trial design.

That potential risk acknowledged, the agency's suggested analysis, identified as "primary" by the sponsor in its submission, attains highly significant results favorable to zonisamide for all seizures (p = 0.01) and/or all partial seizures (p = 0.009) for the 40% vs. 9% difference in reduction in median seizure frequency. (see Table 3, population 1 in Dr. Salhroot's review)

Dr. Sahlroot observes that these positive findings derive from a comparison of only 84% of the subjects randomized in the trial. While a true 'intent to treat' analysis is not possible, Dr. Sahlroot makes the point that what is described as the analysis of Population 4 (all randomized subjects contribute scores normalized without making adjustment for the extent of the time over which they were actually observed during weeks 1 to 12) is about as close to an intent to treat analysis as one can get here. This analysis provides a statistically significant result (p=0.025). A final note of support for the affirmative interpretation of the study derives from an examination of the seizure frequency rates for the "dropout cohorts" in this study (see Figure 2 of Dr. Salhroot's review). These provide no indication that an informative censoring process accounts for the study's positive findings, and, in fact, raise the possibility that the effect of treatment might actually be under-estimated by the 'primary' analysis.

Of added interest, weeks 2 through 6 (5 weeks in toto) of the placebo controlled portion of the study allow a comparison of the efficacy of 200 mg a day a of zonisamide versus placebo and weeks 1 through 5 allow a comparison of 100 mg/day versus placebo. These comparisons support a conclusion that does of zonisamide as low as a 100 mg a day are as effective as a daily dose of 400 mg /day (based on the effect sizes presented in table on the top of page 5 of Dr. Katz's review).

Conclusion about efficacy

The findings of Studies 922 and 912 US provide substantial evidence of zonisamide's effectiveness in adjunctive use as a treatment for partial onset seizures in adults. The evidence adduced documents that daily doses from 100 to 400 mg are effective, but leaves unanswered the extent to which daily dose affects the proportion of patients likely to attain a

clinically satisfactory response.

SAFETY

Background

Although zonisamide has been marketed in Japan since 1989 and Korea since 1992, the post-marketing monitoring systems in place in those countries are of unknown provenance and reliability. Moreover, a substantive proportion of the information submitted to the NDA concerning that foreign experience consists of a review of Japanese PMS reports conducted by [redacted]
Dr. Burkhart finds the IRG review wanting from several perspectives (see page 34 and 35 of Dr. Burkhart's safety review). Also disquieting to Dr. Burkhart is the likely possibility that potentially important clinical information available to the [redacted] reviewer was not included in the reports made to Athena's NDA.

Because of this concern, the Division recommends that final approval of this application be conditioned upon the firm's submission of a comprehensive review of the information that has been reported from PMS experience in Japan.

Also, inexplicably, Athena's NDA fails to provide reports on some 1000 or so patients who participated in studies used to support the product's approval in Japan. Again, the Division believes that final action on this NDA should be delayed until a full accounting of the experience with this cohort is reported to the Athena NDA (see page 42 and 43 of Dr. Burkhart's review for details).

For the reasons just related, it seem fair to assert that what we can currently assert we know of zonisamide's risks derives primarily from reports of experience gained in the 1600 or so subjects who participated in its premarketing development in the US and Europe. This information, importantly, was not all collected by [redacted] the sponsor that carried out the 3 new effectiveness trials reported upon in the Athena NDA. In fact, a substantive proportion of the clinical evidence derives from

experience gathered at the behest of the original commercial sponsor, [redacted] That firm had abandoned zonisamide in 1987 because of concerns that its use was associated with an unreasonably high incidence of renal calculi. At the time [redacted] elected to suspend clinical testing, some 260 or so patients were active participants in 5 ongoing controlled clinical trials.

The source and extent of clinical experience relied upon by the Division's Review Team

The safety team's review document (2/24/98) written by Dr. Burkhart enumerates the sources of clinical safety data relied upon. Some 1600 or so individuals have been exposed to at least one dose of the drug. There are about 1400 patients/subjects with some kind of multi/repeat dose exposure. Among this latter subset, about 1000 form the sponsor's primary data base; of these, some 269 participated as subjects in one of the sponsor's 3 placebo controlled efficacy trials.

The duration of exposure to zonisamide exceeds 6 months in slightly over 500 of the 1000 patients within the primary safety data base; almost 350 of these patients have been treated for a year or more.

As to dose and duration of exposure, about 300 patients have been exposed for a year or more to 400 mg/day, the highest daily dose recommended for use in the draft product labeling being proposed by the Division.

In sum, the extent of clinical experience gained with zonisamide in respect to duration of exposure is sufficient by test of current agency guidance.

Adverse findings deserving identification and discussion

At the outset of the concluding section of his comprehensive safety review document, Dr. Burkhart notes (page 44), "the NDA for zonisamide has collected sufficient experience with its use to justify approval and there is no affirmative evidence of risk that would preclude such approval." I concur in his assessment, but, like Dr. Burkhart, I do have some observations for the record about a number of aspects of the safety

review and the review team's conclusions.

Harms that may be associated with zonisamide's use.

Patients with epilepsy undergoing treatment with a muli-AED drug regimen can present a complicated medical picture. Accordingly, it is difficult, indeed usually impossible, to distinguish between drug associated and drug caused adverse findings reported during experience gained outside of a controlled trial setting.

This is hardly surprising. Beyond the clinical events and abnormal findings that may represent a direct consequence and/or sequelae of epilepsy are the untoward effects that are the consequences and/or sequelae of chronic AED use. In the case of a patient suffering from one of the symptomatic epilepsies, an underlying medical condition may also be a source of observed adverse clinical events and outcomes.

Despite the uncertainties of adverse event causality assessment just described, drug product labeling is expected not only to enumerate the harms that have been reported in association with a drug's use, but to offer guidance as to those untoward clinical and laboratory findings that are likely to actually be due to the untoward pharmacological effects of the drug.

Labeling is also expected to provide, if at all possible, an accurate depiction of the harms (i.e,. their incidence, features, severity, natural evolution, and cofactors known to increase or decrease their risk of occurrence--dose, subject attributes, time at risk, drug use, etc.). Ideally, labeling will also provide information about factors/maneuvers that may affect either the incidence of the harm or the degree of injury caused.

Unfortunately, there is more often than not a gulf between the goals just described and what can actually be realized. Information obtained from clinical observers and patients tends to be incomplete and imprecise. In part this is a reflection of the fact that adverse event detection, description, reporting and tabulation is anything but a standardized

process. To the contrary, the process of adverse event detection, description, reporting and analysis is subject to a number of sources of variability that are beyond our capacity to control

Moreover, a proportion of important risks associated with the use of a drug are likely to remain unidentified even if premarket testing is comprehensive, either because these events occurred and were not recognized/reported, or because they did not occur even once. As is well known, the latter occurs not through anyone's fault, but because the relatively small sample of patients exposed during the course of a typical drug product's development cannot be relied upon to capture events that occur even regularly in one of every 200 or so patients exposed. The risk of non-detection of events increases considerably when an event occurs after a long latency, or occurs primarily in a subgroup of the population, particularly if that subgroup is under-represented in the clinical development cohort. It is against this background of uncertainty regarding the assessment of drug associated risk that my comments about the findings of the Division's review team's safety analysis must be viewed.

Enumeration by Organ system

Although it is impossible to know with surety all the harms that are associated with or likely to be caused by zonisamide, the following list, enumerated by organ system, represents those that I believe 1) are or are reasonably likely to have been caused by zonisamide or 2) seem important to identify and discuss so as to make clear in the record that the evidence for a causal link between their occurrence and exposure to zonisamide was considered, but found to fall short of that sufficient to allow even a tentative conclusion about the putatively causal linkage.

These two classes of harms (i.e, declared versus contemplated) are basically those that are typically given prominence in drug product labeling.

In the text that follows, adverse events reported from the 3 RCTs at a frequency of at least 1% among 269 zonisamide patients and at a rate that is 2 or more fold greater than that observed among the 230 placebo

randomized patients are identified by an asterisk.(*) [N.B. The rule applied is the one used by Dr. Burkhart to construct the table which appears on page 19 of his review.)

Body as a whole:

Deaths/SUDs

Twenty-three (23) zonisamide associated deaths have been reported to the NDA. The Patient-time for the cohort from which 21 of these deaths arose is available. The incidence of death within 30 days of zonisamide use is on the order of 1 per 100 PYs, and, not unexpected in light of incidence estimates available for other recently evaluated AEDs.

In the judgment of the safety review team, 6 deaths are sudden and unexpected; the SUD rate is, therefore, about 3/1000 PYs, a rate totally consistent with that calculated for other recently evaluated NDA's for AEDs.

In sum, there are no findings that suggest that zonisamide increases the risk of death or that it can cause death by an some unusual or unique mechanism.

Potential risks attributable to zonisamide's status as a sulfonamide

The review team has assumed that zonisamide, as a sulfonamide, possesses the capacity to induce the presumed immunologically mediated untoward reactions (e.g., serum sickness, SJS, etc.) long recognized to be associated with the use of drugs of this chemical class.

Overdose experience

Dr. Burkhart reports that 2 cases of overdose are described in the ISS; they recovered without evident sequelae after an interval during which they were described as being confused and sedated. Another patient was reported to have been in coma for several hours following an intentional overdose, The scantiness of the information provided precludes further

comment.

Skin & appendages:

In the RCTs, only one patient was reported as discontinuing treatment because of a serious rash. Although several other cases of serious rash were reported in the NDA, neither Stevens-Johnson Syndrome [SJS] or Toxic epidermal necrolysis [TEN] were observed in the pre-marketing cohort. There is a concern, however, that cases of vesiculobullous rash reported from PMS in Japan might be examples of SJS. Further information is required before these reports can be reliably evaluated.

In controlled trials reports of rash* were more common among zonisamide than among placebo randomized subjects

Neurological

Again, not surprising for a member of the AED class, there were several reports of worsening epilepsy (therapeutic failure, increased seizure frequency, status epilepticus, etc.)

Reports of ataxia*, dysarthria*, nystagmus* and diplopia* suggest that zonisamide may cause cerebellar impairment/ motor incoordination. There is a suggestion that the increased incidence of ataxia seen in RCTs is entirely accounted for by events suffered by elderly patients.

Reports of paresthesias* were more common among patients randomized to zonisamide than to placebo. A similar finding, incidentally, was reported for topiramate, a recently approved AED with known carbonic anhydrase inhibitory activity.

Reports of Dysgeusia* were more common among zonisamide than among placebo assigned patients.

For completeness, it should be mentioned that a patient randomized to zonisamide in Study 912 US suffered a stroke.

Psychiatric

Alterations in mental status are often reported in association with the use of AEDs. Among alterations reported with zonisamide are bradyphrenia, confusion*, somnolence, forgetfulness*, difficulty concentrating*, depression,* anxiety*, paranoia*, delirium, and hallucinations*, etc. Still other findings of less certain psychiatric origin, but often reported as such, are reports of irritability*, fatigue and anorexia.

In a number of instances, a full blown psychiatric diagnosis was made; 8 patients were identified as being depressed (there were 6 suicide attempts; one completed), another 8 patients had "paranoid episodes" and 12 others were coded as having had a psychotic episode. The latter two classes of events (psychosis and paranoia) were evidently considered serious as all but one of the patients so classified were "hospitalized."

While these putatively psychiatric adverse phenomena and episodes will be described in product labeling, it is important to be mindful that not only are the manifestations of epilepsy sometimes confused with psychiatric phenomena, but that epilepsy and psychiatric conditions occur together at a frequency that cannot entirely be explained by chance (or so it is widely believed).

Even more to the point from a regulatory risk assessment perspective, altered mental status has been reported frequently in association with the use of other recently approved AEDs.

Cardiovascular

Although there is no signal suggesting that the use of zonisamide is associated with a risk of cardiovascular injury, the effects of zonisamide on this system have not been evaluated as comprehensively as the review team would prefer. The limitations of the sponsor's review of the EKG findings is specifically cited by Dr. Burkhart (page 30 of his review).

Intermittent tachycardia was experienced by one zonisamide randomized patient in study 912 US

Pulmonary

Cough* was reported more often among zonisamide as among placebo patients participating in RCTs

Liver /GI

A patient randomized in Study 912 US developed cholestatic hepatitis; the condition is reported to have resolved in the face of continued exposure to the drug.

In Japan, there have been PMS reports of GGT, alkaline phosphatase and AST elevations

Anorexia is mentioned here, but was classified as a "psychiatric" phenomenon for reasons that may well be arbitrary.

In the placebo controlled trials, treatment with zonisamide was associated with increased reports of what can be considered minor GI complaints: "stomach" pain*, diarrhea*, and constipation*.

Renal

Stones

Nephrolithiasis is unequivocally associated with the use of zonisamide. In phase 1 testing, a patient developed hematuria and flank pain within days of discontinuing a 24 day course of 40 mg of zonisamide a day. According to Dr. Burkhart, in Study 922, which provided for more extensive ultrasound monitoring than Dainippon's other trials, stones were detected in 2 zonisamide, but no placebo randomized patients. The review also records that the firm identified 26 patients who had at least one serious clinical event linked to renal stone formation.

Incidentally, stone formation is also caused by topiramate, another AED with carbonic anhydrase inhibitory activity.

Renal failure, acute

A case of acute renal failure occurred, but this was not the result of primary renal disease, but was secondary to rhabdomyolysis that developed during an episode of prolonged status.

Unexplored findings that might predict a capacity to cause renal injury in extended use

Minor degrees of serum creatinine elevation (increases of about 25%) were recorded in an early clinical pharmacology study (810-924) that were subsequently reversible upon withdrawal of zonisamide. While these were not reported to be associated with any clinical manifestations or other adverse laboratory findings, they are troublesome in that we have no understanding of the mechanism responsible for them. Dr. Burkhart speculates that they might be due to a drug-lab test interaction and our letter to the firm (and labeling draft) asks the sponsor to evaluate this possibility. Other conceivable explanations exist but are hard to reconcile with the fact that elevated creatinine plasma levels were not reported in the RCT experience. In any event, whether or not a drug-lab test interaction is responsible for them, these changes deserve mention in product labeling. My latent concern is that they might represent a signal of subclinical renal injury (i.e., reduced GFR, tubular dysfunction, etc.).

Endocrine

There is no signal, but a thyroid nodule was discovered in a zonisamide randomized patient in Study 922

Hematologic

There are 3 patients reported to have had serious hematologic events; I cannot make an informed judgment about their importance or relationship to zonisamide.

Postmarketing reports from Japan raise a concern that zonisamide's use has been linked to a number of serious hematologic conditions.

GU

Male sexual dysfunction(not otherwise specified)* was reported by 3/269 zonisamide as compared to 0 of 230 placebo randomized patients.

Pregnancy

Nine pregnancies were reported in the ISS. Five ended with abortion (2 therapeutic, 3 spontaneous). Of the 4 that went to term, one produced a child with hypospadias. N.B. Zonisamide is a potent teratogen in preclinical studies.

Conclusions regarding Safety

A determination that a new drug is 'safe for use' is not a warrant that it is free of risk, but a judgment, based on experience typically limited to that gained during its development, that the harms reported in association with its use, taking into account the severity and course of the condition that is the target of treatment, and the nature and quality of alternative treatments available for the condition in the armamentarium, are reasonably acceptable for a drug product that has been shown to be effective in use as claimed.

Considered in this light, the evidence submitted and reviewed, although perhaps not detailed and complete enough to allow the drafting of final product labeling, is sufficient to justify an approvable action. A formal regulatory determination that zonisamide is safe for use, however, must await the firm's response to our requests for additional information regarding postmarketing experience with the drug in Japan, and clarifications by the sponsor of a number of other relatively minor matters.

Abuse Liability Assessment

By dint of the requirements of the Controlled Substance Act, zonisamide, as a CNS depressant, can be deemed to require evaluation for possible

scheduling under that Act as a drug that may be abused. The information required for that assessment has not yet been submitted.

Dosing regimen

As noted in the section discussing the findings of the 3 placebo controlled trials, there is evidence that zonisamide is effective at daily doses ranging from 100 mg to 400 mg. No study, however, provides an estimate of the proportion of patients exhibiting a satisfactory clinical response by dose. This limitation notwithstanding, Dr. Katz has proposed a dosing regimen that seems eminently reasonable to me.

Labeling and action letter.

The letter and attached draft labeling together describe the deficiencies identified in the application and the actions the sponsor must take to rectify them.

Recommendation

An approvable action letter for the NDA should be issued; a proposed draft for a letter, including a draft version of labeling, is attached.

/S/

Paul Leber, M.D.
3/11/98

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: March 19, 1998

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: Director
Office of Drug Evaluation I/HFD-100

SUBJECT: Response to your questions about draft labeling for NDA 20-789, Zonisamide

We have made most of the changes you have suggested in the draft labeling. You had several questions which are addressed below:

1) Clinical Pharmacology, Special Populations:

You suggest that the increase in AUC of 35% seen in patients with marked renal impairment would not require dosage adjustment. This increase in AUC was seen after a single dose; the actual increase in AUC in such patients at steady state is difficult to predict, but may be much greater than 35%. In addition, an increase of even 35% may be important. For these reasons, we are not including the portion of the statement that you have proposed.

2) Clinical Pharmacology, Clinical Studies:

You ask if the definition of the intent to treat population you have proposed is accurate; it is, and we are including it. This will also necessitate changing slightly the language you have proposed to describe the study. Specifically, you say that the primary comparison was for the combined treatment groups vs. Placebo "in weeks 8-12". Because the primary comparison included data from weeks 1-12, we have removed the language in quotes.

3) Warnings, Seizures on Withdrawal:

We had proposed that the drug be discontinued gradually; you suggest that because the T1/2 is 60 hours, this is not necessary. Perhaps, but, for

example, suppose that the patient is on a concomitant enzyme inducer; the T1/2 could be decreased by 50%. In addition, it is true that a gradual withdrawal of drug will always result in a less steep decline in plasma levels than if it is abruptly stopped. Because of these considerations, we have left the language as originally proposed.

4) Precautions, Laboratory Tests:

You have suggested that the language is either too vague (we should list the tests the prescriber should perform), or not vague enough (we should remove the statement entirely). This is a sticky problem, one we face frequently. In this case, for example, we don't believe that systematic laboratory surveillance was particularly well done. In any event, we are going to replace this statement with a note to sponsor asking them to draft a statement that is both clinically relevant and describes what we think we know about lab tests and zonisamide.

5) Dosage and Administration:

We had 2 contradictory statements about the time to reach steady state; one said 4 weeks for initial treatment, one said 2 weeks for dose adjustment. The time to SS is about 2 weeks under any circumstances, and this will be fixed.

We have also changed somewhat the recommended dosing regimen. In the draft we sent up (I wrote this part, not the sponsor), I tried to describe a possible dosing scheme, based on the clinical trials. The idea was to recommend a regimen we knew to be tolerated, and that would allow the practitioner to stop at either 100, 200, or 400 mg/day. We have changed it slightly to make clear that SS will be reached in about 2 weeks; this may help them decide whether or not to wait at the lower doses a little longer to see if the response improves.

6) Dosage and Administration, Patients with Renal or Hepatic Disease

You suggest that an increase of 35% in AUC in renally impaired patients may not be so ominous. Maybe not (maybe yes, too; I don't really know), but, as noted above, at steady state this increase may be magnified. For this reason, we are leaving it as we originally proposed

7) Dr. DeGeorge had several comments:

a) He believes that the drug should be categorized as Pregnancy Category D, because of the strong signal in animals, and because we want to put a brief description of the teratogenicity findings in the Warnings Section. Based on a conversation I had with him this AM, he believes that the regulations clearly permit the classification as D based on animal studies.

I have subsequently re-read the regulations which describe Pregnancy Category D. It **clearly** requires human data; there is no other possible interpretation I can convince myself makes sense. For this reason, we are leaving the drug Category C.

b) He believes that a statement about the lack of abnormal LFTs seen in animals with liver pathology should be included in the Animal Toxicology Section at the very end of labeling. Dr. Fisher has re-written this paragraph to more accurately reflect the data.

/S/

Russell Katz, M.D.

Cc:
NDA 20-789
HFD-120
HFD-120/Katz/Leber/Ware/Sherry/Burkhart

MEMORANDUM

DATE: February 22, 1998

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-789

SUBJECT: Supervisory Review of NDA 20-789, for the use of Zonisamide to Treat Partial Seizures

BACKGROUND

NDA 20-789, for the use of Zonisamide, a sulfonamide carbonic anhydrase inhibitor, as a treatment for partial seizures, was submitted on 3/27/97 by Athena Neurosciences, Inc.

The clinical effectiveness portion of the NDA has been reviewed by Dr. James Sherry of the Division (review dated 2/27/98) and Dr. J. Todd Sahlroot of the Division of Biometrics (review dated 2/18/98). The clinical safety data has been reviewed by various members of the Division's Safety Team (review by Dr. Greg Burkhart dated 2/13/98). In addition, the application has been reviewed by Dr. Fisher, pharmacologist (review dated 1/20/98), Dr. Scarpetti, chemist (review dated 1/29/98), and Dr. Mahmood, biopharmaceuticist (review dated 12/12/97).

In this memo, I will briefly review the relevant clinical data, and present my recommendation for action.

EFFECTIVENESS

The sponsor has submitted the results of 3 randomized controlled trials that they believe support the conclusion that Zonisamide is effective as a treatment for partial seizures. Two of the studies, 912-US and 912 EUR were sponsored by [redacted] and the third, 922 US was sponsored by [redacted] The sponsor originally proposed not to submit the results of 912-EUR because they believed that it did not meet GRP standards; however, the Division requested that a study report be submitted for this study.

STUDY 922

This was a randomized, placebo controlled, fixed multi-dose, double blind, multi-center, add-on trial in patients with complex partial or partial onset seizures with a motor component, with or without secondary generalization.

All patients were enrolled into a 4-week single blind placebo phase, after which, if they met seizure frequency criteria they were randomized to one of three treatment groups (all daily doses greater than 100 mg were given as BID dosing):

Group A-12 weeks of Placebo

Group B_1-5 Weeks of 100 mg/day,1 week of 200 mg/day, 1 week of 300 mg/day, followed by 5 weeks of 400 mg/day.

Group B_2-1 week of 100 mg/day, 5 weeks of 200 mg/day, 1 week of 300 mg/day, followed by 5 weeks of 400 mg/day.

(See Dr. Sherry's review, page 27, for a graphical representation of this design).

The last 5 weeks of the trial were considered the "controlled" portion, in which Groups B_1 and B_2 received 400 mg/day (arrived at via different titration schemes), and Group A received placebo.

The protocol specified analysis plan was complicated. The primary parameter to be analyzed was the median percent change from baseline in 28 day partial seizure frequency. There were to be 3 primary comparisons:

1) To evaluate the effect of 100 mg, Group B_1 was to be compared to Group A during Weeks 1-5

2) To evaluate the effects of 200 mg, Group B_2 was to be compared to Group A during Weeks 2-6

3) To evaluate the effects of 400 mg, the combined B Groups were to be compared to Group A during Weeks 8-12

Prior to the blind having been broken, Drs. Hoberman and Sahlroot of Biometrics met with the sponsor to discuss various approaches to the data. As a result of this meeting, several populations to be analyzed were agreed upon (the designations, however, were those of the sponsor):

1) **Primary**-Week 8-12 data, excluding patients who dropped prior to Week 8. This analysis evaluated 400 mg/day, utilizing combined data from Groups B_1 and B_2 compared to placebo.

2) **Data Sensitivity**-Week 8-12 data with data from patients who dropped out prior to Week 8 imputed, using unspecified Worst Case assumptions

3) **Intent to Treat**- All Week 1-12 data

4) **Efficacy Evaluable**-Week 8-12 data only for patients with at least 2 weeks of treatment, excluding patients with major protocol violations

Apparently, no agreement on the primary methods of analyses was reached at the meeting. In the NDA, all analyses performed were 2 way ANOVA (terms for treatment, center, treatment*center interaction term).

RESULTS

A total of 203 patients were randomized at 20 centers in the US. The following chart displays the disposition of patients (taken from Dr. Sahlroot's review, Table 2):

	Group A	Group B Combined
Randomized	85	118
Completed Wk 12	72 (85%)	95 (81%)
Completed Wk 7	73 (86%)	102 (86%)

As can be seen, 86% of patients in both treatment groups entered the "controlled" portion of the trial. The following table displays the results of the primary analysis (taken from sponsor's Table 10; Dr. Sahlroot's review, Table 3) As described earlier, the first 2 rows of the table examine Weeks 8-12, the last row examines Weeks 1-12:

	Group A		**Group B Combined**		**P-value**
	N	Med % Change	N	Med % Change	
Primary	72	-9.0	98	-40.5	0.009
Data Sensitivity	85	-2.6	117	-29.0	0.009
Intent to Treat	84	-4.0	113	-22.9	0.027

The worst case imputation scheme used by the sponsor to analyze the Data Sensitivity cohort (row 2) was not in the protocol. The analysis they presented imputed the group maximum percentage increase from baseline for all patients who dropped out from that particular group. Maximums were 572, 128, and 600 for Groups A, B_1, and B_2, respectively. As noted by Dr. Sahlroot, this procedure is not conservative, and when he imputed the Group A maximum to all dropouts, the resulting P-value was 0.07.

The following results were seen for the comparisons of Groups B_1 and B_2 individually to Group A (taken from Sponsor's Table 11, Dr. Sahlroot's Table 4):

		Group A		Group B_1	P-value
	N	Med % Change	N	Med % Change	
Wk 1-5	80	-8.3	56	-24.7	0.04

		Group A		Group B_2	P-value
	N	Med % Change	N	Med % Change	
Wk 1-6	82	-4.0	55	-20.4	0.003

STUDY 912-US

This was a randomized, double blind, placebo controlled, titration design, multi-center, add-on trial in patients with refractory complex partial seizures (CPS).

Patients receiving 1 or 2 of the following AEDs (PHT, CBZ, PB, PRM) with a history of at least 4 CPS/month and no more than 8 generalized tonic-clonic seizures for the 4 months prior to study were eligible to be enrolled into the Baseline Phase. The Baseline Phase lasted between 8-12 weeks: patients with at least 15 seizures in the first 4 weeks or 30 seizures at 8 weeks were randomized after 8 weeks; patients not meeting these criteria were randomized after 12 weeks. The purpose of these additional 4 weeks of baseline was unclear.

The Treatment Phase lasted 12 weeks. The initial dose was 7 mg/kg/day, and was determined on the basis of the dose that was to give a trough plasma level of between 20-30 mcg/ml. The target doses were to be 400-600 mg/day, given q 12 hours. However, due to adverse events, the protocol was amended to provide for slower titration: the initial dose was changed to 1.5 mg/kg to be titrated to 7 mg/kg/day over 28 days. The dose of Zonisamide could be adjusted by a non-blinded investigator in order to increase the trough level to a maximum of 40 mcg/ml or the dose to a maximum of 20 mg/kg/day. In the trial, this translated to a dose

titration scheme of 100 mg/day for the first week, 200 mg/day for the second week, and 400 mg/day for the third and fourth weeks, after which the dose could be increased to the maximum allowable.

The protocol did not define the primary outcome measure or analysis. Drs. Hoberman and Sahlroot agreed with the sponsor in a pre-NDA meeting that the following 4 populations would be analyzed (this was the same meeting previously mentioned; again, the specific designations were those of the sponsor):

1) Primary-Week 5-12 data excluding data from patients who dropped out before Week 5

2) Worst Case-Week 5-12 data, imputing for patients who dropped out before Week 5 the maximum percent increase for their treatment group

3) Intent to Treat-All post-randomization data

4) Evaluable-Patients with at least 2 weeks of treatment after Week 5. These populations are analogous to those analyzed in 922.

In the NDA, the declared primary outcome measure was the Percent Change from Baseline during Weeks 5-12 for PS (SP+CP) and CPS; this was not stated explicitly in the protocol. The analyses performed were those used in 922.

RESULTS

A total of 152 patients were randomized at 4 US centers. The following displays the patient flow (taken from Dr. Sahlroot's Table 6, sponsor's Tables 7 and 8):

	Zonisamide	Placebo
Randomized	78	74
Completed Wk 12	62 (79%)	67 (91%)
Completed Wk 4	69	72

The following table displays the results of the primary outcome (adapted from Dr. Sahlroot's Table 7) for all partial seizures:

	Zonisamide		Placebo		P-value
	N	Med % Change	N	Med % Change	
Primary	69	-29.5	72	+1.8	0.0004
Worst Case	78	-22.9	74	+4.6	0.034
Intent to Treat	78	-25.4	74	+2.2	0.0003

Recall that the analyses represented by the first 2 rows examine data from Weeks 5-12, while the last row represents data from Weeks 1-12.

The following table examines the results for all Complex Partial Seizures (adapted from Dr. Sahlroot's Table 8, sponsor's Table 14):

	Zonisamide		Placebo		P-value
	N	Med % Change	N	Med % Change	
Primary	69	-29.6	70	-1.2	0.002
Worst Case	78	-19.2	72	+1.1	0.08
Intent to Treat	78	-25.2	72	-1.9	0.0004

The sponsor reports all 3 comparisons as statistically significant.

Dose

As noted earlier, the dose in this trial was permitted to be titrated to achieve a maximum trough level and/or a maximum dose/kg limit. As a

result, final doses reached were as high as 900 mg/day, and the maximum plasma trough level achieved was 40.4 mcg/ml.

In an attempt to examine the effectiveness of Zonisamide by dose, Dr. Sherry presents (Table 10, page 19 of his review) a breakdown of median percent change in seizure frequency during Weeks 5-12 according to a dichotomized dose range (a maximum dose of equal to or less than 400 mg/day or greater than 400 mg/day). The results are displayed below:

	<400 mg/day		**>400 mg/day**	
	N	Med % Change	N	Med % Change
Zonisamide	26	-27.1	52	-30.6
Placebo	9	-58.7	65	+6.1

As can be seen, many more patients were treated with a maximum dose of greater than 400 mg/day than whose maximum dose was 400 mg/day or less. It is not clear how long the maximum dose (on which this classification was based) was given during Weeks 5-12. No further analysis of response by dose was provided.

APPEARS THIS WAY
ON ORIGINAL

STUDY 912-EUR

This trial utilized the same protocol as 912-US with the one important exception being that the dose was given as a single daily dose. However, the sponsor indicated that the results of their audit suggested that the trial did not conform to GCP guidelines (e.g., lack of informed consent in some patients, lack of prospective baseline, etc). Nonetheless, the Division asked the sponsor to submit a complete study report.

APPEARS THIS WAY
ON ORIGINAL

Results

A total of 144 patients were randomized at 10 European centers. The following displays patient flow (adapted from Dr. Sahlroot's Table 10, sponsor's tables 6 and 7):

	Zonisamide	Placebo
Randomized	73	71
Completed Wk 12	61 (84%)	68 (96%)
Completed Wk 4	70	70

The following table displays the results of the primary outcome (adapted from Dr. Sahlroot's Table 11) for all partial seizures:

	Zonisamide		Placebo		P-value
	N	Med % Change	N	Med % Change	
Primary	69	-20.0	70	+0.3	0.21
Worst Case	72	-17.5	71	+4.5	0.23
Intent to Treat	72	-24.8	71	+2.9	0.12
Evaluable	65	-20.5	67	+4.5	0.04

Recall that the analyses represented by the first 2 rows examine data from Weeks 5-12, while the third row represents data from Weeks 1-12.

The following table examines the results for all Complex Partial Seizures (adapted from Dr. Sahlroot's Table 12, sponsor's Table 14):

	Zonisamide		Placebo		P-value
	N	Med % Change	N	Med % Change	
Primary	69	-20.0	70	+3.9	0.16
Worst Case	72	-17.5	71	+11.7	0.19
Intent to Treat	72	-24.8	71	+2.9	0.11
Evaluable	65	-20.5	66	+3.9	0.027

Dose

In this trial, doses ranged up to 1000 mg/day (the dose of the 75% quartile was 400 mg/day). The maximum plasma trough level recorded was 56 mcg/ml.

SAFETY

The NDA contains data for 1572 unique individuals who received at least one dose of Zonisamide. As noted earlier, the development of this drug was first undertaken by [redacted] who subsequently discontinued development because of concern over renal calculi.

Because of these issues, the current sponsor has divided the safety database into 2 portions: the Primary safety database contains the experience from the controlled trials and their extensions, and includes 976 patients. The Supplementary database contains data from Phase 1 studies, studies in indications other than epilepsy, and patients who were in studies that were discontinued.

In addition, Zonisamide has been marketed in Japan since 1989, and Korea since 1992. There exist 3 sources of post-marketing data from these

countries; 1) a retrospective survey of 3906 patients exposed to Zonisamide, 2) a prospective study of 1512 patients, which is still on-going, and 3) spontaneous reports. Finally, the submission to the Japanese regulatory authority contained experience in 1008 patients studied, of course, prospectively.

For the foreign data described in the paragraph above, only limited information (e.g., summaries) is supplied.

Exposure

Of the 976 patients in the primary safety database, 512 were exposed for 6 months or longer. Most of this exposure was at a dose of at least 400 mg/day. A total of 343 patients were exposed for at least 1 year, with 296 (86%) receiving a daily dose of at least 400 mg.

Deaths

At the time the NDA was submitted, the sponsor reported the occurrence of 22 deaths (21 Zonisamide, 1 placebo). In the controlled trials, there were no deaths on zonisamide and 1 on placebo.

The safety update includes information on 2 additional deaths.

Of the total of 23 Zonisamide deaths, 20 occurred while the patient was still receiving treatment or within 30 days of discontinuation of treatment.

Of these 20 deaths, 4 were in patients in the Supplementary database. Subtracting these and the 2 deaths reported in the SU, a total of 14 deaths were reported in the NDA for the Primary Safety database.

As noted in Dr. Burkhart's review, this results in an all cause mortality rate of 1.4/100 Patient-years (given the sponsor's estimate of 1000 PYs of exposure in the primary database).

Dr. Burkhart's review of the clinical data for these deaths suggests that none were related to events referable to the hematologic, dermatologic,

renal, or hepatic systems.

Of these deaths, 6 could have been considered Sudden Unexplained Deaths in Epilepsy (SUDEs). Of these, 3 occurred in the Primary database, giving a rate of 3/1000 PYs, a rate consistent with other recently approved AEDs.

Examination of the other deaths revealed that many were possibly related to specific seizure events or not otherwise likely to have been related to treatment (e.g., pneumonia, accidents, cancer, etc.).

Withdrawals

The individual study reports of the controlled trials were examined for the nature of withdrawals in these trials due to adverse events.

According to Dr. Burkhart's review, there was little difference in the rate of dropouts due to adverse events between drug and placebo in Study 922, although the exact proportion of such patients in the Zonisamide group who discontinued before the end of Week 12 is unclear (apparently the number of such placebo patients is 7/85 -8.2%).

In Studies 912-US and EUR, there were greater proportions of dropouts due to adverse events on Zonisamide compared to placebo (for example, in the US study, 10% of Zonisamide patients left the trial by day 21, compared to 10% having left the placebo group by Day 64).

The COSTART terms most commonly reported as being responsible for patient withdrawal in the controlled trials were somnolence, ataxia, fatigue, anorexia, irritability, dizziness, forgetfulness, trouble concentrating, and confusion. One patient withdrew due to a rash. There were no reports of hematologic, renal, or hepatic events leading to withdrawal in the controlled trials.

In the overall safety database, a total of 287 patients withdrew due to adverse events, the most common being "somnolence, fatigue and/or ataxia" (86), irritability (33), concentration loss or difficulty (31), and memory loss or other cognitive impairment (27).

In the overall database, there were several cases of withdrawals due to renal, dermatologic, or hematologic causes.

The reports of these cases were, according to the Safety review, often poorly documented with little to no follow-up.

The one case of a potentially serious hematologic event leading to withdrawal described in the safety review (page 17) was of a 16 year old female who had been treated with Zonisamide 200 mg/day for 166 days at which time her hemoglobin fell to 6.9 g/dL. No follow-up information was available. Because of a potential signal of aplastic anemia in the post-marketing database (see below), there was a concern that this case could have been potentially consistent with that diagnosis.

I have discussed this case with Dr. Burkhart, who tells me that, on further exploration of the database, it became clear that no other cell lines seemed to have been affected. For this reason, there is less concern that this represents a potential case of aplastic anemia.

Dermatologic Events Associated with Withdrawal

A total of 18 patients are described in the Safety review as having withdrawn due to a dermatological adverse event.

A total of 6 rashes were considered serious, with 4 resulting in hospitalization. Of the serious rashes, the safety review describes 3 which either resolved or were resolving upon discontinuation of Zonisamide (one of which was treated with prednisone, Benadryl, and Atarax). While the descriptions are sketchy, no case appears to be overtly likely to be SJS or TENS, although several involved the face and/or periorbital edema.

Many of the rashes were described as pruritic, some as maculopapular, urticaria, erythematous, and in some no description was included. Most if not all patients were receiving concomitant AEDs, and the time from treatment initiation with Zonisamide to rash ranged from 7-574 days (all within 132 days except the one at day 574).

Other Serious Adverse Events

Three hematologic events were characterized as serious by the sponsor. Dr. Burkhart describes 2 of the cases in his review (pages 13-14); for the third case (presumably a case of thrombocytopenia with a positive re-challenge), no description was available.

Of the 2 cases described in the safety review, details were available for one; a 38 year old man with neutropenia first documented on Day 38, with WBC as low as 2.1 X $10^3/mm^3$ on Day 43. Treatment was discontinued on Day 46, with a documented normal WBC count on Day 82. He was on a dose of 500 mg/day at the time of treatment discontinuation.

One serious case of hepatic injury was reported. This was a 23 year old man with an alkaline phosphatase seen to be rising prior to treatment which continued to rise to a maximum of 560 U/L on Day 9 of treatment, which subsequently continued to fall on treatment. Similarly, SGOT and SGPT rose to maxima of 100 and 122 on Days 9 and 7, respectively, which also reverted to normal while on treatment.

A case of renal failure was also reported as a serious adverse event, but examination of the case revealed that the event was likely related to a seizure and/or phenytoin toxicity; the patient recovered while still receiving treatment with Zonisamide.

Other Adverse Events

The most commonly reported (5% or greater) AEs in the 3 controlled trials were:

Adverse Event	Zonisamide (N=269)	Placebo (N=230)
Ataxia	17%	6%
Irritability	12%	5%
Diplopia	9%	4%
Trouble Concentrating	8%	1%
Dysarthria	8%	2%

Adverse Event	Zonisamide (N=269)	Placebo (N=230)
Stomach pain	7%	2%
Depression	7%	3%
Forgetfulness	7%	2%
Anxiety	6%	3%
Confusion	6%	1%
Diarrhea	5%	3%
Nystagmus	5%	3%
Paresthesia	5%	1%

Other AEs that occurred at least twice as frequently on drug compared to placebo include, in order of decreasing frequency: rash, constipation, dry mouth, paranoia, hallucination.

An examination of the AE patterns by individual study and various intervals (see Safety Review, Table 20, pp 20-23) reveals a large relative risk for diarrhea, stomach pain/irritation, dry mouth, cough, and skin laceration during Weeks 1-12 in Study 922.

Laboratory Data

In the controlled trials, there were significant decreases from baseline in the mean plasma phosphorous levels in the Zonisamide group (from 3.54 to 3.19) compared to the placebo group (from 3.53 to 3.56), as well as a larger percentage of patients with clinically significant decreases in the Zonisamide group compared to the placebo patients. No patient discontinued treatment or had a serious event related to these decreases.

There were also significant differences between Zonisamide (from [redacted] and placebo (from [redacted] in the change from baseline for creatinine and alkaline phosphatase (from [redacted] for Zonisamide and from [redacted] for placebo).

According to Dr. Burkhart's review, it appears that 3 patients had at least one value of creatinine that met the criterion for clinically significant elevation. Closer inspection of the data suggests that in only 2 patients were these values not isolated elevations.

Apparently, 2 Zonisamide treated patients developed thrombocytopenia (one had a platelet count of 119,000; no data were available for the other patient) compared to 0 placebo patients in controlled trials.

In Study 922, there were statistically significant differences between drug and placebo in the change from baseline in WBC (decrease), and alkaline phosphatase, creatinine, uric acid, and chloride (increases). None of these mean changes were clinically significant.

There were 117 Zonisamide patients for whom laboratory data were available. Of these, 9 (8%) had clinically significant leukopenia at Week 20 (the aponsor did not discuss changes seen at Week 12). None of these patients discontinued treatment. Dr. Burkhart describes 4 "typical"cases. In these cases, the WBC count was recorded to be as low as 2600; for 3 of these cases, there was no follow-up data available.

In general, for patients who prematurely discontinued treatment, the sponsor did not provide laboratory data at the time of discontinuation.

As noted by Dr. Burkhart, the sponsor states that the only 4 discontinuations due to abnormal lab values occurred in the Warner-Lambert experience. One was a 43 year old woman with an elevated alkaline phosphatase (maximum 323 IU/L), and the other 3 were 1) the 16 year old female discussed earlier (Hgb 6.9), 2) a 38 year old man with neutropenia (minimum value of 2100), and 3) a 67 year old woman with leukopenia (minimum WBC, with no further follow-up, of 2800), and 4) a 60 year old woman with leukopenia (minimum WBC count, without follow-up, of 2600).

Post-Marketing Data

As noted above, there are 3 sources of post-marketing data: 1) a retrospective survey, 2) a prospective survey, and 3) spontaneous reports.

Fcr each of these data sources, the sponsor provided 2 separate evaluations: 1) a discussion of events that were "unexpected" (i.e., not included in Japanese labeling), and 2) a report by the medical monitor for

IBRD-Rostrum Global (IRG).

As Dr. Burkhart describes, there were deficiencies in the description of the post-marketing data. For example, for the [redacted] report, it is unclear how the [redacted] monitor identified cases to review. This is evident by the fact that, for example, the monitor describes several cases of aplastic anemia, when the sponsor's listing of adverse events does not include any such cases. Further, the [redacted] monitor seemed to have additional data for particular cases that was not included elsewhere in the submission. These deficiencies notwithstanding, I will briefly describe the findings in the post-marketing database.

1) Retrospective Survey

This was a survey of 3,906 patients conducted between 1989-94. It is not clear who was included in the trial or why, other than this was a population of patients with partial or generalized seizures. Minimal information was collected, including concomitant AEDs and adverse events. The specific methodology utilized is not clear to me, and it is therefore difficult to assess the completeness of data capture.

The most common event reported was somnolence (6.5%), followed by anorexia (2.6%), "psychiatric disorder", nausea/vomiting (1.5%), slowness of thought (1.3%) and apathy (1.2%). There was a 1.1% incidence of reported "vesiculobullous rash".

2) Prospective Survey

This was a survey of 1512 patients followed prospectively from the start of treatment with Zonisamide. Enrollment began in 1989 at 20 centers, and is on-going. The specific decisions about enrollment (who, etc.) are not clearly stated, nor is the duration or nature of the follow-up.

The most common reported AEs were somnolence (16.5%), anorexia (6.6%), abnormal SGPT/GGPT (4.1%), nausea/vomiting (3.5%), slowness of thought (3.3%),psychiatric disorder (3.2%), and irritability (3.2%). There was a 1.4% incidence of vesiculobullous rash.

Serious Adverse Events in the Post-Marketing Data

Sponsor's Table 8f-7 (included at the end of Dr. Burkhart's review) lists the serious ADRs reported in all 3 post-marketing data sources.

Most of the events of interest pertain to dermatologic and hematologic events, the vast majority of which arise from the Spontaneous reports. The Sponsor reported 14 cases of Stevens-Johnson syndrome (SJS), 2 cases of Toxic Epidermal Necrolysis (TEN), 1 case of Lyell syndrome, 2 cases of muco-cutaneo-ocular syndrome, a total of 3 cases of erythema multiforme, 2 cases of "erythema", and a total of 12 cases of "rash".

In addition, there were 5 cases of agranulocytosis, 3 cases of leukopenia,and 2 cases each of pancytopenia, decreased IgA, and granulocytopenia.

In addition, there were 7 spontaneous reports of hepatic function disorder

Dr. Burkhart's review discusses in detail cases of serious adverse events identified by the IRG monitor. As noted earlier, there are discrepancies in the number and type of serious AEs discussed by the IRG monitor and those identified by the sponsor (the latter of which are described in the first few paragraphs above). The following brief case summaries are taken from Dr. Burkhart's discussion, which, again, is based on the IRG review. In many cases, the IRG discussed a number of serious events that, upon review by Dr. Burkhart, appeared to be either not serious or not related to Zonisamide. I will discuss only those that appeared reasonably related to Zonisamide (or not clearly not related) and serious.

Deaths

The IRG discussed 5 deaths: 1) a patient with pneumonia, 2) a patient who committed suicide, 3) a 71 year old man with thrombocytopenia and leukopenia and pneumonia, 4) a 37 year old man with TEN, 5) a 64 year old woman with SJS.

Hematologic Events

Aplastic Anemia

A 56 year old woman developed a fever, rash, low WBC, low platelets, and anemia 4 weeks after initiation of Zonisamide. Bone marrow showed "marrow depression". She was treated with GSF and steroids. One week later, a bone marrow biopsy showed improvement. Counts were still abnormal several months later.

Agranulocytosis

A 27 year old woman developed fever, rash, abnormal LFTs, and a low WBC 6 weeks after starting Zonisamide. Drug was stopped, and a rechallenge resulted in rash, low WBC, and eosinophilia.

According to Dr. Burkhart, 3 more cases were possible related to Zonisamide. All patients recovered.

Granulocytopenia

There were 2 cases that were possibly related to Zonisamide without other identifiable cause. A third case occurred in conjunction with symptoms of a viral infection.

Leukopenia/neutropenia

Five patients were identified as having leukopenia, 3 of whom also had thrombocytopenia.

One of these patients had thrombocytopenia prior to treatment that worsened on Zonisamide. This patient died from staphylococcal pneumonia.

A second patient, a 2 year old boy, developed leukopenia and thrombocytopenia one month after initiation of treatment. He went on to develop anemia with a bone marrow with no megakaryocytes, 19,000 nucleated cells, and 83% lymphocytes; no formal interpretation of the

marrow was supplied. This patient recovered.

A third patient developed leukopenia and thrombocytopenia with a rash, the latter of which recurred on re-challenge.

One patient experienced neutropenia while on zonisamide, 6 weeks after starting treatment with phenytoin.

Thrombocytopenia

In addition to the cases described above, 2 more patients were reported to have had thrombocytopenia. According to Dr. Burkhart, the most severe was a 72 year old man who developed oral bleeding and persistent post-injury bleeding 3 weeks after the addition of zonisamide to a regimen of 5 other unspecified drugs. He had thrombocytopenia, and recovered following dexamethasone and platelet transfusion.

Serious Dermatological Events

The IRG monitor identified 31 cases of SJS, 8 cases of TEN, and 1 case of "hypersensitivity".

According to Dr. Burkhart, 2 cases of TEN occurred in patients taking no other concomitant medications. Both patients survived; one was treated with IV steroids.

Again, the cases of SJS were poorly described and/or documented, but Dr. Burkhart identified 9 "compelling" cases, 5 of which were with zonisamide given as monotherapy. Interestingly, as he points out, we do not know the extent of concomitant lamotrigine use.

The sponsor has supplied two estimates of the total exposure to zonisamide in Japan: 400,000 patient-years, and 600,000 patient-years. The methods used to derive these estimates was not clearly stated.

Additional experience

The sponsor has submitted the clinical summary of the experience in 1008 patients that they submitted to the Japanese regulatory authority which supported approval there. This presumably represents a prospectively followed cohort, but the summary submitted did not permit a detailed examination of these patients. As Dr. Burkhart notes, in this cohort, 9 patients were reported to have withdrawn secondary to decreased WBC, and 6 withdrew due to elevated LFTs.

SUMMARY

The sponsor has submitted the results of 3 adequate and well controlled trials capable by design of demonstrating the effectiveness of zonisamide as an adjunctive treatment for partial seizures in adults. In addition, they have submitted safety data in over 1500 patients, as well as post-marketing experience in Japan.

Two of the three trials have demonstrated statistically significant differences between zonisamide and placebo. These trials employed different dosing regimens. In one, 2 different titration schemes were utilized to achieve a target dose of 400 mg by Week 8. The first 5-6 weeks of this trial were used to examine the effects of 100 mg and 200 mg/day. The second trial examined a more rapid titration (2 weeks) after which patients reached 400 mg/day, after which they could have received higher doses. The third trial was of essentially identical design, but used once a day dosing.

It is unclear why the third trial failed to detect a statistically significant difference on its primary outcome. The sponsor asserts that there were problems with the conduct of the trial, although it is not clear to me exactly what the problems were or how they might have affected the outcome. Perhaps the once a day dosing played a role, but it bears emphasis that the estimate of the treatment effect was very close to that in the second study.

In any event, the evidence submitted establishes the effectiveness of the

drug. However, the dose that is effective is not clear. Study 922 establishes that 400 mg/day is an effective dose, but examination of the 100 mg/day and 200 mg/day doses suggests that these doses are effective as well (each of the 3 doses was maintained for a maximum of 5 weeks). Study 912US utilized a titration design; as a result, it is difficult to establish "the" effective dose in this trial, although the mean dose was apparently 475 mg. It might be useful to ask the sponsor to analyze the first 4 weeks of this trial, which would be of interest in determining if 400 mg/day was "effective".

As regards safety, the experience in the development program does not appear to suggest any reason that would preclude eventual approval, but the data are not reported in sufficient detail to be able to arrive at this conclusion definitively at this time. As Dr. Burkhart notes, there are a number of cases of potentially serious events that need further clarification as well as further follow-up. In addition, for example, the sponsor has submitted no EKG data that can be independently reviewed. A further example of the inadequacy of the presentation is related to the disparate numbers of cases of a given event given in various places in the application (for example, the [redacted] monitor's review of cases; we cannot tell which cases were identified for further examination, etc.) Another example is renal stones; the sponsor reports different rates of this event in different places in the application. In addition, the supplementary database should be considered in equivalent detail as the primary database, unless there is a compelling reason that this should not be done.

Of particular interest is the post-marketing experience, in which a number of cases of serious hematologic, dermatologic, and perhaps hepatic events occurred, but for which the submitted data are extremely sketchy. Further, there are at least 2 large prospectively followed cohorts (the prospective survey and the Japanese approval cohort) for which detailed data are not available. It would be important to receive detailed information about these cohorts (including the methodology of data capture, etc.) in order to fully evaluate the risks associated with treatment with zonisamide. Further, a complete explanation of the sponsor's various estimates of exposure should be submitted.