

The sponsor also provided some information on the patients with abnormal creatinine values in the RCTs. These turned out to be laboratory errors. (These errors may have been the basis for the recoding of the laboratory database.)

Finally, there were no cases of renal failure or reports of altered renal function in the NDA, the JAC or the PS. There were a few cases of renal failure reported in the JPME but they did not appear to be unexplained cases of primary renal failure.

Hepatic Events

In reviewing the NDA laboratory data, we noted a consistent increase in alkaline phosphatase but not in SGPT. Because of the liver failure cases reported in the JPME, we asked for a careful review of liver events in all data sources. To meet this request the sponsor screened the database for laboratory outliers as well as clinical events suggestive of hepatic events. While not specially stated by the sponsor, I assume that the laboratory data for SGPT were also recoded along with that for creatinine and BUN. Hence, I would have been interested in seeing the RCT analysis repeated – not just searching for outliers. In any case, the sponsor found 1 patient that they defined as having a serious event in the NDA. This patient had elevated liver enzymes detected 25 days after zonisamide had been stopped. No reasons for discontinuation were given. The patient was hospitalized because of the increased enzymes and for increased seizure activity. I am not certain whether there were any cases of elevated ALT or AGT along with elevated bilirubin.

In the JAC, there was 1 patient (10142) who possibly had fulminant hepatic failure that recovered before death or transplant. There was also evidence that alkaline phosphatase was systematically increased in the JAC and PS without any increase in SGPT. No serious events were identified in the PS or RS, and there were 5 serious cases in the JPME, according to the sponsor. One of these was a death, but most cases were complicated by other serious events relating to the skin or hematological system, and several were also taking valproic acid.

In short, the extensive nature of the JPME along with the complicated nature of the reported cases of hepatic failure doesn't suggest a signal for primary hepatic failure. However, I believe we need to make sure that the corrected laboratory data do not show a systematic increase in liver enzymes, and if so, whether any patients experienced a concurrent increase in bilirubin. More recently, agency reviewers have been focusing on affirmative findings of elevated bilirubin for drugs that affect liver enzymes as indicating a significant risk for fulminant hepatic failure. The alkaline phosphatase increase appears convincingly related to zonisamide but unexplained.

Hematological Events

Based upon the sponsor's review of the NDA, there is 1 case of agranulocytosis and no cases of aplastic anemia (1/1168 PYs). There were 4 cases defined as having agranulocytosis in the JAC, but only 1 seems to meet standard definition (1/718). There

was probably 1 case in the PS (1/ in an unknown amount of time). This experience is suggesting that the rate is about 1 per 1000 PYs quite a bit above the reported background rates.

There were 2 good cases reported in JPME, one of which was a 15-year old patient who developed agranulocytosis and a concurrent infection 5 weeks after starting zonisamide.

Thus, the response to the AE letter, has clarified the hematological risks showing that agranulocytosis is probably a risk associated with zonisamide use.

Serious Skin Rash

The response to the AE letter confirms that serious skin rash is a risk when taking zonisamide. There may have been 1 case of SJS in the NDA (#921/5652/1483), as pointed out by Dr. Tresley. There were no observed cases in either the JAC or the PS. In the JPME, there were 41 cases of SJS and 5 TEN and 4 called Lyell syndrome giving a reporting rate of about 4 per 100,000 PYs (50/1.3 million [I added 200,000 PYs since IMS data were not available for 1998]). Five of these events resulted in death giving a reported rate for death due to rash of about 4 per million person-years. The sponsor did not discuss the effect of dose and duration of use of rash occurrence.

CNS toxicity

As requested the sponsor systematically recoded CNS events for both drug and placebo. (Dr. Tresley states in his view that the sponsor recoded event only for drug. However, placebo rates are given in the corresponding table.) They also examined dose and timing but the findings were difficult to interpret.

Renal Stones

The sponsor calculated the incidence of renal stones in the NDA confirming that zonisamide probably causes stone occurrence. The rate in the NDA was about 6 per 1000 PYs while the rate in the general population is about 1 per 1000 PYs.

While we did not specially request that they compute rates stratified by duration of use, this description would be more meaningful in labeling since most stones occurred with long term use. There was one case of renal failure possibly caused by a stone reported in the JPME.

ECG data

While ECGs were performed in some studies, ECG interval data were not entered into a database. Abnormal findings reported on ECGs were entered as adverse events. In reviewing these, there were no striking findings.

Pregnancy Experience

In Dr. Tresley's review, he computes an incidence of birth defects concluding that it is higher than expected. However, he appears to have combined the retrospective and prospective reports, which would not provide a valid incidence rate since retrospective reports are essentially a numerator without the corresponding denominator.

I could not separate the retrospective from the prospective reports; hence I could not compute the incidence using just the prospectively reported pregnancies.

Safety Update

In general, there were no new major safety issues identified in the safety update. There were 15 cases of oligohydrosis with 1 developing symptoms of heat stroke that have been reported. We need to ask the sponsor to review these events in detail.

Labeling

We asked the sponsor to analyze the RCTs separately so that we could decide about pooling the data. Instead they pooled two of the RCTs and split out the CNS events.

Discussion/Recommendation

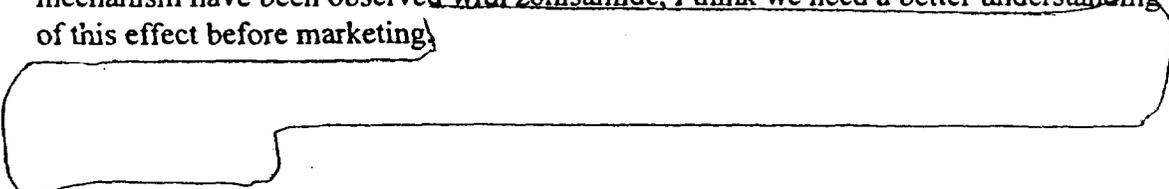
The sponsor's response to the AE letter tried to address all the concerns raised in the letter. In particular, they provided a study report for the PS and a summary of the JAC experience that materially expanded our understanding of these two data sources. While I generally agree with Dr. Tresley in the sense that the NDA is relatively small, it clearly meets the ICH guidelines. In addition, the experience in the JAC (1008 patients) definitely adds to our overall experience. The experience in PS will probably count as well although we do need to clarify a few issues about that data source. Thus, I don't agree with Dr. Tresley's recommendation that we need more experience to define the risks. (He recommended an additional safety study of 3000 patients before approval.) Although there certainly are a number of issues that still require clarification and significant risks may emerge from these additional analyzes, I think we are getting a pretty good picture of the risks associated with zonisamide use.

Zonisamide, which is a sulfonamide, is clearly associated with a significant risk for serious skin rash. While no confirmed cases of SJS or TEN were observed in the NDA, JAC or PS, 50 life-threatening skin rashes were reported in the JPME giving a rate of about 4 per 100,000 PYs of use and a reported death rate of about 4 per million PYs. Since there is bound to be some degree of under-reporting, the rate of rash and corresponding death could both be substantially higher. In the NDA, the rate of serious rash was at out 2-3 per 1000 PYs.

Zonisamide use also appears to be associated with a risk for agranulocytosis at a rate of about 1 per 1000 PYs. As with other AEDs, there appears to be a significant risk for CNS toxicity. Zonisamide appears to affect renal function although this effect is ill defined at present, and finally, the occurrence of renal stones is clearly greater with zonisamide use. In fact, my guess is that use beyond 1 year in the NDA, may have had a rate as high as 1 per 10 PYs for renal calculi, but the data have not yet been analyzed by the sponsor to compute this rate.

The effect of zonisamide on creatinine/BUN is interesting and of significant concern particularly since the sponsor appears to have concluded that the drug affects the GFR and zonisamide is intended for long-term use. As in most NDAs, there is limited long-term experience and certainly none that systematically analyzes renal function. Likewise, while there is extensive post-marketing experience, I do not believe that chronic effects resulting after long-term use are likely to be spontaneously reported.

While it is true, that no serious renal events not attributable to renal stones or another mechanism have been observed with zonisamide, I think we need a better understanding of this effect before marketing.



In addition to further consideration of the renal effects of zonisamide, there are additional issues requiring clarification. First, since the sponsor has shown that the original laboratory database was not valid for creatinine and BUN, we have to assume that all the laboratory data are flawed making the original NDA analysis suspect. Thus, I think the entire analysis needs to be repeated, with specific emphasis on the liver enzymes.

A second issue is the apparent absence of ECG interval data. In the development program, abnormal findings on the ECGs that were conducted were treated as any other adverse event, but actual ECG data were never entered into a database. Hence, in my opinion, I think the sponsor should either enter the ECG data from the most recent RCT or conduct an additional study. This effort could be conducted as a phase 4 commitment.

As we observed in the NDA, there was significant increase in alkaline phosphatase during zonisamide use in both the JAC and in the PS. Thus, the finding is real and unexplained. After conducting the additional analyses of the laboratory database, the sponsor needs to consider and address this finding proposing appropriate labeling to describe the effect.

In summary and assuming that the efficacy of lower doses is not an approval issue, I recommend issuing another approvable letter requesting further clarifications as listed below. (Upon receiving their response, we will need to consult with cardio-renal.) Assuming that zonisamide is eventually approved, I think warning statements will be necessary in labeling, based upon what we now know, for serious skin rash,

agranulocytosis and CNS toxicity. We will also need to consider the possibility of recommending periodic WBC counts in labeling.

While it is dangerous to compare across drugs, the number of risks associated with zonisamide appear to exceed that seen with other recently approved AEDs - raising concern about its approval as first line treatment. Certainly if it has a pronounced effect on GFR, an argument could be made for not approving it until there are data showing it worked in non-responders, or perhaps not approving it at all.

Finally, we should also consider asking the sponsor to follow a large number (3000) of US patients if zonisamide is eventually approved. From a well defined large cohort we may get a good description of the totality morbidity and mortality associated with its use.

Additional Questions

- 1) You have apparently concluded that zonisamide has an effect on the GFR. Is this correct? Please provide a more detailed analysis of the RCT data. Did patients have progressive increases in creatinine/BUN like those patients in the study 810-824? Please separately analyze patients with long-term use in the NDA for renal AEs. Please ask your renal consultant to provide a more detailed discussion of this issue than is included in his second consultative report. It appears that he has concluded that the GFR is affected because both BUN and creatinine increase with zonisamide. Also ask the renal consultant to review the renal events reported from post-marketing experience in Japan. Finally, propose a study to examine this effect in more detail, possibly as a phase 4 commitment. Given that zonisamide use has significant risks for serious skin rash and agranulocytosis, studying a large (3000) population of US users would be prudent. One could also select 100 patients or so from this cohort in whom to study renal function.
- 2) Since you discovered many errors in the laboratory database that resulted in additional findings that were not seen in the NDA (statistically significant increases in BUN and creatinine), please reanalyze the entire laboratory database for mean change and outliers. For hepatic enzymes specifically, focus the outlier analysis on 3 times the upper limit of normal, and list all patients for drug and placebo who had increases of 3 times the upper limit of normal along with the corresponding bilirubin levels. This listing should be conducted separately for the RCTs and then the open experience and also for the JAC and the PS.
- 3) While you conducted a thorough search and analysis of the skin rash in the NDA, there appeared to be no discussion of the effect of dose or the duration of use on the risk for rash. Please provide such a discussion for all experience including that in the JPME. Also, your initial screen found 66 patients for review, but you were able to retrieve 61 of their CRFs. Where are the remaining 5 patients' CRFs. Your search was also limited to the "primary database". Why is that?
- 4) In your evaluation of hematological events, you defined agranulocytosis too broadly by allowing patients with moderate-severe leukopenia to be counted. Use a standard definition from the literature (i.e., <600 neutrophil count) and provide a listing of

cases from the NDA and from all Japanese experience. Include the duration of use and dose up to the time of the event. Use these findings to modify the description of the risk for agranulocytosis in labeling. Consider whether periodic WBC counts should be recommended in labeling.

- 5) We have several questions about the experience in the prospective survey. Apparently, 271 patients who were enrolled in it did not CRFs. Please explain how this occurred. Were these patients not included because they dropped out of the study before 1 year? Compare the demographic characteristics of these 271 patients who did have CRFs with those who did. Why were there so few serious events identified in this study. What definition was used to define serious? Perhaps, a review of all AEs observed in the study would be meaningful. What was total amount of person-time in this study?
- 6) As requested in the first approvable letter, please show the RCT adverse event tables separately for each RCT. The CNS events that you have recoded should be included in each table not in a separate table. CNS events will still require a warning statement.
- 7) There seems to be a systematic increase in alkaline phosphatase in the NDA, and the JAC and PS without any suggestion that SGPT increases. Please explain the increase. Include an appropriate labeling statement describing this effect, and a suggestion for any further study necessary to examine the effect.
- 8) Apparently, ECG interval data have not been entered into a database. Please propose a phase 4 commitment to collect and analyze such data from the most recent RCT or perform an additional study to collect such data.
- 9) Please describe the pregnancy experience in the spontaneous reports separately for prospective and retrospectively reported events. A prospective report is one where the pregnancy is reported before any knowledge about fetal outcome. A retrospective report is one that is reported after fetal outcome is known.
- 10) Please compute the rate of urinary calculi for the experience after 6 months of use and then for that experience more than 12 months of use. Add these findings to labeling.
- 11) Describe and evaluate the cases of oligohydramnios that have reported in the JPME. Were there similar cases in the NDA or in the other Japanese experience.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: March 14, 2000

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

TO: File, NDA 20-789

&

Director
Office of Drug Evaluation I/HFD-100

SUBJECT: Recommendation for action on NDA 20-789, for the use of Zonegran (zonisamide) in adult patients with partial seizures

The Agency issued a second Approvable letter on 6/30/99 to Elan Pharmaceuticals, Inc., for NDA 20-789, for the use of zonisamide in the treatment of partial seizures in adults. In this Approvable letter, we asked the sponsor to complete a considerable amount of additional work, related to the following items:

- 1) Additional safety and effectiveness analyses, because the sponsor extensively revised the database due to errors in data entry in the original NDA
- 2) More detailed analyses of renal (including calculi) and hepatic function
- 3) More detailed analyses of serious rash
- 4) More detailed analyses of hematological adverse events
- 5) More detailed analyses of cases of oligohydrosis in pediatric patients
- 6) Additional, more minor, safety issues

In addition, we asked the sponsor to adopt specific dissolution specifications, and had 2 CMC comments, relating to storage condition statements and expiration dating.

The sponsor responded to the Approvable letter in a submission dated 9/27/99. In addition, there have been several other submissions, as well as meetings with the sponsor, including labeling negotiations. The sponsor's submissions have been reviewed by Dr. Burkhart, safety team leader (review dated 3/8/00), Dr. Lawrence, statistician (review dated 12/17/99), Dr. Mahmood, Office of Clinical Pharmacology and Biopharmaceutics (review dated 2/22/00), Dr. Oliver, chemist (reviews dated 12/2/99 and 12/6/99), and Dr. Throckmorton, nephrology consultant in HFD-110 (review dated 2/29/00). Following is a

very brief summary of the sponsor's responses to the more important issues, and the division's recommendation for action on the NDA.

Efficacy

The sponsor's re-analyses have not altered our original conclusions; the application still contains substantial evidence of effectiveness for zonisamide as adjunctive treatment in adults with partial seizures.

Safety

Renal function

As both Drs. Burkhart and Throckmorton note, zonisamide use is associated with a small, presumably non-clinically significant, increase in creatinine and BUN, which is most consistent with an effect on GFR. The increases seem, in general, to occur within the first 4 weeks of treatment initiation, and remain stable over time; the increases do not generally fall outside normal limits. While the changes were reversible after treatment discontinuation in a 4 week PK study, there is insufficient experience in long term use to be able to adequately characterize reversibility in this setting. There were no cases of renal failure attributed to these changes in the development program, although there were several hard to interpret cases of renal failure in the Japanese post marketing experience.

Zonisamide use is associated with the occurrence of renal stones. The incidence (including cases in which stones were recovered and cases in which evidence of stones was captured via sonography) is about 1.3% in the first 6 months of treatment, and about 5.5% with treatment beyond 6 months; there is no normative data on the background rates of asymptomatic stones as diagnosed by sonography in this population. The recovered stones were composed of calcium or urate salts; it is not known if increasing fluid intake decreases the risk of stone formation.

Hepatic function

As noted by Dr. Burkhart, there was no systematic effect on LFTs.

Rash

There were a total of 49 cases (7 deaths) of SJS or TEN in the Japanese post-marketing experience, yielding an incidence of 46/million patient years of exposure, a rate greater than background. There were no confirmed cases of SJS or TEN in any of the development programs, although 2.2% of zonisamide treated patients in US and European controlled trials discontinued treatment due to rash, compared to 0% of placebo patients.

Hematologic events

There were 2 cases of aplastic anemia in the Japanese post-marketing experience, a rate greater than background. There were no confirmed cases of aplastic anemia in any of the development programs. There were 2 confirmed cases of agranulocytosis in the US and European development programs.

Oligohydrosis

There were 13 cases of oligohydrosis in patients between the ages of 1-17 years old in the Japanese post-marketing experience; temperatures ranged from 37-42 degrees C. There is no normative background rate data for this event. Two patients were diagnosed with heat stroke. No cases were reported in adults. There was one such case in the Japanese development cohort.

Other

There were no other significant safety issues. It is worth noting that the sponsor has not submitted EKG interval data, although there are no reports of QT prolongation or torsades de pointes. As Dr. Burkhardt notes, the sudden death rate in this NDA is similar to that in NDAs for other AEDs. The sponsor is attempting to obtain interval data from the EKGs performed to date; failing this, they will perform a study designed to obtain this data. The EKG data will be obtained as a Phase 4 commitment.

Chemistry

The sponsor has responded to the chemistry concerns detailed in the second Approvable letter.

Biopharmaceutics

The sponsor has adopted the dissolution specifications outlined in the Approvable letter.

Labeling

The labeling accompanying this package is substantially different from that included with the second Approvable letter. The version of labeling in this package has been negotiated with the sponsor, most recently in a phone conversation held on 3/13/00. There have been preliminary discussions about the content of the patient package insert, but final agreement has not been reached on this document; Lisa Stockbridge and her colleagues in DDMAC are currently reviewing this document at the time of this memo. While there have been changes in most of the sections of labeling, the major changes in this version of labeling that differ from the draft labeling with the Approvable letter are described below:

Clinical Trials

There has been a re-arrangement of the tables displaying the results of the 3 controlled trials, although the data described have not substantially changed (there are a few minor changes in the results related to the sponsor's re-analyses).

Indications

This section has **not** changed substantially. In particular, there had been some discussion about indicating zonisamide as a second line treatment because of the panoply of adverse events associated with its use. However, upon reflection, the review team has concluded that the significant adverse event profile is not substantially different from other available AEDs (e.g., lamotrigine) which are not second line treatments, and that indicating zonisamide as a second line treatment, at this time, is not warranted.

Warnings

There have been extensive changes to the sections on Serious Rash and Hematologic Events (as well as changes in the positioning of these sections), and a section on Oligohydrosis in pediatric patients has been added.

Precautions

There have been extensive changes to the sections on Kidney Stones and the effect of the drug on Renal Function. There have also been extensive changes to the Laboratory Tests section.

Adverse Reactions

This section has been extensively revised as per our instructions. In particular, the sponsor has combined data from all 3 controlled trials in one 2% ADR table (based on our review of the individual study results and our conclusion that these data were combinable).

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RECOMMENDATIONS

The attached Approval letter with attached labeling should be sent to the sponsor once agreement has been reached about the content and format of the patient package insert.

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/s/

Russell Katz, M.D.

Cc:
NDA 20-789
HFD-120
HFD-120/Katz/Kapcala/Ware/Oliver/Guzewska
HFD-860/Mahmood

APPEARS THIS WAY
ON ORIGINAL

Review of Clinical Data

Response to the Second Approvable Letter

NDA: 20-789
Sponsor: Elan
Drug: Zonisamide
Route of Administration: PO
Reviewer: Greg Burkhart, M.D., M.S.
Review Completion Date: March 8, 2000

13/1
3-8-00

Summary

Two approvable letters have been issued for the zonisamide NDA with the review team concluding that zonisamide is effective in treating partial seizures. There is also significant concern that zonisamide can cause life-threatening skin and hematological events. In the post-marketing experience from Japan (JPME), the reporting rates for SJS, TEN, aplastic anemia and agranulocytosis exceed generally accepted background rates with 5 reported deaths from SJS/TEN in an estimated 1 million person-years (PYs) of use. There were no cases of SJS, TEN, aplastic anemia or agranulocytosis in the NDA or Japanese approval databases (JAC) which when combined had about 2000 PYs of experience. There was, however, one case of severe neutropenia (neutrophil count < 600 without any clinical symptoms) observed in the NDA database.

Zonisamide use is also associated with other clinically significant AEs. As with several other approved AEDs, it can cause CNS toxicity resulting in hospitalization or drug discontinuation. Like other carbonic anhydrase inhibitors, its use is associated with formation of urinary calculi. In the NDA, about 3 per 100 patients per year were diagnosed with a calculus of the urinary system. The rate was greatest in the second 6 months of use and a significant number of the patients participating in the NDA were monitored with sonography to detect urinary calculi.

Zonisamide also caused slight but statistically significant increases in creatinine and BUN in the RCTs. No patients in the RCTs, however, had clinically significant increases and no cases of unexpected renal failure were observed in the NDA. Drs. Young (sponsor's consultant) and Throckmorton (HFD-110) who are nephrologists, have concluded that the small effects on creatinine and BUN are also certainly attributable to a reduction in the glomerular filtration rate (GFR).

In the RCTs, the effect on creatinine/BUN is observable within 4 weeks of starting zonisamide and, in a PK study in which exposure lasted 30 days, creatinine/Bun promptly returned to normal upon zonisamide discontinuation. In my opinion, the database was too small to address reversibility after longer use with only 18 patients having follow-up data after drug discontinuation. Based upon analysis of the RCTs and their extensions, the effect is probably not progressive although the number of patients with sufficient data at each time point was limited. While there have been several potential cases of renal failure identified in the JPME, the cases are difficult to evaluate given the limited clinical detail.

Finally, the sponsor did not enter interval data from the ECGs that were performed in the US RCT into a database. Thus, there is no analysis of the effect, if any, of zonisamide on QT interval duration. There were no ECG events suggestive of QT prolongation or TDP, and sudden death rates in the zonisamide NDA were similar to those seen in other AED NDAs. To address the issue, the sponsor has proposed conducting a phase 4 clinical study to collect such data, but is considering collecting the QT data from the existing ECGs in the US RCT.

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Background

The FDA issued the first AE letter for the zonisamide NDA on March 19, 1998 and a second AE letter on June 30, 1999. The second letter requested clarification and additional analysis of two significant issues before zonisamide could be approved.

First, it appeared to agency reviewers based upon data contained in the first response that the sponsor had identified data entry errors for creatinine and BUN. When these errors were corrected, a re-analysis showed that both increased systematically with drug exposure, a different result from that presented in the NDA. The first response did not discuss this issue in detail nor was it clear whether this problem extended to the rest of the laboratory dataset. Hence, the second AE letter asked the sponsor to examine the validity of the full laboratory dataset, and if necessary, conduct a complete reanalysis.

The second issue requiring further discussion and analysis concerns zonisamide's effect upon renal function. In the first response, the sponsor's renal consultant initially concluded that zonisamide did not affect the glomerular filtration rate (GFR). However, after he considered the new analyzes based upon the corrected creatinine/BUN data, he recommended labeling and monitoring that in effect stated that zonisamide caused a decrease in the GFR - he did not outline his reasoning in detail (see my 6/7/99 review). There was also no discussion about whether the decrease in GFR was progressive, reversible or whether patients were at a higher risk for chronic or acute renal failure. The second AE letter asked for a full evaluation and discussion of this issue since a significant effect on renal function could impact zonisamide's approval.

There were additional questions in the second AE letter mostly focused on clarifications of existing data. The most important was a request for a new analysis of the risk of urinary calculi after 1 year of use, and an analysis of ECG interval data since none was presented in the NDA.

Athena submitting a response to the second AE letter on September 27, 1999 and I completed review of the safety issues on March 3, 2000. Dr. Throckmorton, a nephrologist from HFD-110, has also reviewed the data pertaining to renal function.

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Safety Issues

I will review the safety issues starting with the validity of the laboratory dataset and the effect of zonisamide upon renal function, which represent the bulk of new information contained in the second response. I have attached the sponsor's tables and figures to the end of my review.

1) Laboratory Dataset Validity

In the second AE letter, we asked the sponsor to explain the changes made to the laboratory dataset that resulted in different findings on analysis of the BUN data. According to the sponsor, there was no recoding of the laboratory dataset. The changes in the BUN analysis that were reported in the first response occurred because of a change in the definition of "baseline". Apparently, the original CRO had used the incorrect baseline values in the first analysis.

In any case, the sponsor proceeded to evaluate the validity of the data. The sponsor sampled data and showed that the overall error rate was about a 2% with "outliers", similar to that in the rest of the database.

2) Zonisamide's potential effect on renal function

In the first AE letter, the agency asked the sponsor to investigate an apparent increase in creatinine in subjects participating in study 924, a pharmacokinetic study of 200 and 400 mg conducted in 24 healthy volunteers over 30 days. A figure plotting mean creatinine and BUN values by day of study is included in the appendix. The last time point shown was collected several days after zonisamide was discontinued. While there is a clear increase in mean creatinine with time that returns to baseline at follow-up, there is no change in BUN, in my opinion. None of the patients in this study had clinically significant increases in BUN or creatinine.

This finding in study 924 was consistent with the findings from the first analysis of the RCT data in which there was a small but statistically significant increase in creatinine in the zonisamide group. While there was also a slight increase in BUN, it did not reach statistical significance. As in study 924, none of the patients in the RCTs developed clinically significant increases in creatinine or BUN, and the only case of renal failure in the NDA occurred in a patient with preceding rhabdomyolysis.

To investigate the finding, the sponsor first conducted a study that excluded any effect of zonisamide on the creatinine assay. After not finding any effect, the sponsor asked Dr. Young, a consulting nephrologist, to consider the issue. Based upon the initial analyses, he concluded that zonisamide most likely affected the tubular secretion of creatinine. His reasoning was based upon the fact that BUN did not increase concurrently with creatinine making it very unlikely that there was reduction in the GFR. Dr. Young also pointed out

that a number of drugs affect the tubular secretion of creatinine and that the effect has no clinical significance.

Dr. Young changed his interpretation after the new analysis of the RCT data showed that zonisamide caused small but statistically significant increases in both creatinine and BUN. Tables A and B in the appendix were taken from Dr. Young's third report included with the second response and summarize the RCT data analysis. In 912US and 922, there is a small statistically compelling increase in mean creatinine with the evidence weaker for mean BUN. The statistical evidence for BUN is stronger when focusing on the percentages of patients with greater than a 30% increase. While the change in creatinine and BUN with zonisamide in study 912E was about the same magnitude, there was 1 patient assigned placebo who had large increases in both parameters.

I also examined several categorical definitions for on-study and change from baseline in creatinine and BUN. In my opinion, there is significant evidence that both creatinine and BUN increase systematically with zonisamide use, although the effect is small. I also checked the degree of correlation between the change from baseline in creatinine and the change from baseline in BUN. There was statistical evidence of a weak correlation (R^2 about 4%), but not surprisingly it was present in both placebo and zonisamide. There was also some correlation between lower baseline creatinine values and a larger change in creatinine while on-study. The R^2 was about 7% ($p=.0002$) in the zonisamide group. Of course, this effect could reflect a greater exposure in patients with low body weight since creatinine generally decreases with body weight.

Given the statistical decrease in phosphorus and statistical increases in chloride and alkaline phosphatase that we had previously noted, I checked to see if these changes correlated with the increases in creatinine/BUN. As pointed out by Dr. Throckmorton, decreases in phosphorus and increase in chloride could reflect a renal tubular acidosis. Carbonic anhydrase inhibitors also induce such changes. However, I found no relationship.

When creatinine is plotted by time in the RCTs and study 924, the increase in creatinine/BUN is observable very early certainly within 4 weeks of starting the drug. The effect of dose is more difficult to evaluate since the drug was titrated and these studies are relatively short in duration. In study 921, a 2 year open label safety study, the effect was observed early and in my opinion, there was evidence of dose response (see Figures in appendix).

Both Drs. Young and Throckmorton consider the increase in creatinine and BUN to almost certainly be due to a decrease in the GFR. Dr Young goes further to conclude that the effect is likely to be so small that an actual study of the GFR could miss it given the variability the methods available to study GFR.

Dr. Young's provides a good discussion of the potential clinical significance of the effect in the most recent submission. He reasons that the small effect on GFR is clinically

unimportant so long as it is reversible, not progressive with long term treatment, and not associated with an increased rate of acute renal failure. Dr Young then went on to examine the evidence for each of these points.

To address the question of progression, the sponsor plotted creatinine and BUN against time in 912US, 922, 921 and 921 extension. Study 921 extension enrolled patients from study 921 and 922 and includes data on a small number (about 50) of patients after 4 years of zonisamide use.

I created the following tables to summarize the experience in study 921 and to complement the sponsor's plots of these data. Of the 193 patients enrolled in this study, 128 had data available at 1 year and 58 had data at 2 years of follow-up.

On study creatinine and BUN by week in study 921				
creatinine/BUN				
Study Week (N)	Mean	Medium	Min	Max
Baseline (193)	0.83/12.1			
Week 4 (142)	0.91/12.5			
Week 8 (160)	0.91/12.3			
Week 12 (157)	0.92/12.5			
Week 16 (140)	0.93/12.0			
Week 24 (128)	0.95/12.6			
Week 52 (128)	0.98/13.5			
Week 80 (77)	0.93/13.5			
Week 104 (58)	0.92/13.9			

Change from baseline in creatinine and BUN by week in study 921			
(% change in creatinine/% change in BUN)			
Study Week (N)	Mean	Medium	Max
Baseline (193)	0/0		
Week 4 (142)	11/7		
Week 8 (160)	12/5		
Week 12 (157)	13/6		
Week 16 (140)	16/6		
Week 24 (128)	16/7		
Week 52 (128)	24/19		
Week 80 (77)	16/22		
Week 104 (58)	15/21		

Overall, the findings are similar to those from the RCTs and 924. There is a small increase in creatinine and BUN that is observable after 4 weeks of use. The peak increase

in both creatinine and BUN occurred at 52 weeks. At this time point, 90% of patients had an increase compared to their baseline value. The largest value was an 80 % increase over baseline with the upper 10th percentile defined at a 54% increase.

Interpreting temporal changes in data in which the number of patients decreases significantly with time can be complex. To get a better picture of what was happening from long-term use, I defined 4 cohorts of patients by cumulative time of exposure in study 921. I identified all patients with at least 6 months, 12 months, 18 months or 24 months of exposure and plotted their creatinine by time. These plots confirmed that the effect on GFR was persistent but it clearly was not progressive in study 921. Of course, the number of patients included at the latter time points is fairly small.

I also identified the patients with the largest changes at each time point to see what happened to their creatinines/BUN values with longer use. In all patients when follow-up, the values decreased. None of the dropouts had events that were renal function related as best we could tell.

The experience in study *921 extension* supported the findings in study 921. However, the number of patients was relatively small. At 3 years, there were 66 patients and at 4 years there were 50 patients.

Since study 924 showed that the effect on creatinine/BUN was reversible after 30 days of use, the sponsor identified patients with longer use who had follow-up data. However, only 18 patients could be found. All of these had decreases after discontinuation.

Finally, Dr. Young found no patients who developed unexplained renal failure in the NDA. Overall, there were no cases in about 1200 PYs of use. For use after the first year, there were no cases in 540 PYs which would exclude rates greater than 1 per 140 patients per year after the first year of use.

Dr. Young reviewed 12 possible cases of renal failure in the Japanese experience. There were 6 cases reported by physicians in the Retrospective Survey giving a rate estimated by the sponsor as 1.7 per 1000 PYs of use. As I have discussed in previous reviews, the experience in the RS is difficult to interpret since it probably captured data on long-term users and the clinical details on the cases is very limited. Several of the cases appear to alternative explanations for the events.

The other 6 possible cases came from the JPME giving a reporting rate of about 6 per million PYs. The consultant provided 2 references on the rate of renal failure in the general population. One found that the rate was 120 per million and the other found 48 per million.

In my view there are several problems in trying to interpret the experience from spontaneous reports that could represent renal failure. First, the clinical detail of the events is very limited. Second, zonisamide is clearly associated with urinary stone

formation and rhabdomyolysis is not unusual in patients with epilepsy and it can be associated with renal failure. Finally, I don't believe that renal failure is an event that is likely to be reported for a drug unless it occurs relatively early after starting the drug. Thus, in my view the experience from Japan as it pertains to renal events is impossible to evaluate.

In summary, there are small but statistically significant increases in creatinine and BUN that probably indicate that zonisamide causes a small reduction in the GFR. The effect occurs early after starting zonisamide and is quickly reversible after short-term use. The reduction in GFR probably does not progress with long-term use in most patients. Reversibility after long-term use has not been sufficiently addressed. There were no patients with unexplained renal failure in the NDA database.

3) Hematological Events

In the AE letter we asked the sponsor to select a standard definition of agranulocytosis and re-analyze the NDA. They selected a ANC of $< 600 \text{ mm}^3$. The sponsor found 3 patients in the primary database who met this definition. In two patients the neutrophil counts appear to have been in error since they were only single measurements with normal values both before and after. The other patient appears to represent a real case of severe neutropenia with no symptoms and quick recovery on discontinuation.

There were no reported cases of agranulocytosis in the Japanese Approval Cohort, but neutrophil counts were not measured. There were 4 cases reported from post-marketing. One of these patients developed a fever and was hospitalized and treated with G-CSF. All 4 patients recovered after discontinuation. There are also 5 possible cases of aplastic anemia in the JPME but none in the NDA databases. The reporting rates for both agranulocytosis and aplastic anemia are higher than the generally accepted background rates. The sponsor had proposed labeling describing the potential risks which, in my opinion, is acceptable.

4) Serious Skin Rash

The sponsor conducted the evaluation of skin rash in the primary and supplementary databases. They were able to locate the 5 patients not reviewed in the first response. Nothing new emerged from this review. The dose/duration analysis suggested that the risk was mostly present early although about 14% of the events occurred after the first 12 weeks of use. There was no apparent relationship with dose, but because of the titration, dose is a more difficult issue to address.

5) Clarification of the Japanese Experience in the "Prospective Survey" and "Retrospective Survey"

The second AE letter asked for clarification of the PS design specifically about the 271 patients who did not have CRFs. According to the sponsor, these 271 patients were

eligible to participate in this study but chose not to enroll. The sponsor states that there were about 2890 PYs of experience in the PS.

6) AE Tables for the RCTs

The sponsor provided the AE tables separately by study. One would draw the same conclusions from each table, so I see no reason why we can't combine the data for inclusion in labeling.

7) Increase in Alkaline Phosphatase

The sponsor has no explanation for a systematic increase in alkaline phosphatase. However, as pointed out to by Dr. Boehm, this issue has been a concern with other AED drugs, as reflected by several publications.

8) Re-analysis of LFTs

There is no evidence of a systematic increase in ALT or AGT in the RCTs.

9) Urinary Calculi Rates by duration of use

The following table gives the rates of urinary calculi by duration of use for the experience in the primary database. The group A events are all symptomatic stone plus detected that were symptomatic usually by sonogram. The group B events are those symptomatic events that were confirmed plus all asymptomatic events as with group A.

Incidence of Urinary Stones by Duration of Use in the Primary Database			
	0-6 months of use	6-12 months of use	>12 months of use
<u>Group A</u>			
Number of patients	993	615	398
Number of Events	12	16	13
PYs	418	256	34
Rate (per 1000 PYs)	29	63	24
<u>Group B</u>			
Number of patients	993	615	398
Number of Events	11	12	13
PYs	418	256	534
Rate (per 1000 PYs)	26	50	24

One difficulty in interpreting the data in the table is that the size of the experience accrued after 12 months of use is more than I thought. In retrospect, this cell should have been split further so that we could see if the incidence peaks over a selected duration of

use. As is, one can conclude that the rate after the first 6 months of use is greater than earlier use.

10) Absence of ECG Interval data

According to the sponsor, the investigators considered any abnormalities noted on the interpretation of the ECGs as AEs. None of the interval data were entered. The sponsor has proposed a phase 4 study to collect the data, but is now considering collected the QT data from the original ECGs.

While it would be unusual to approve a drug without an analysis of ECG data, I don't believe the absence of such data is enough to preclude approval. There have been no events of QT prolongation or TDP. The sudden death rate in the zonisamide NDA is similar to that in other AED NDAs.

11) Pregnancy Experience

All of the experience in the NDA was based upon retrospective reports where fetal outcome was known.

12) Cases of oligohydrosis in pediatric use in Japan

Decreased sweating (13 cases) with 2 events resulting in heat stroke have been reported in the Japanese post-marketing experience. In addition, at least 5 surveys of pediatric practices have been published in the Japanese literature. Of the 309 patients in these surveys, 74 were reported as having decreased sweating with 14 of these confirmed by the clinician. I am not sure exactly how these surveys were conducted, but there is no control group and the age was somewhat beyond a typical pediatric population since the age ranged up to 30.3. I don't know the age of the cases.

The event is described in the Japanese product labeling as being related to zonisamide. Without comparative data on how common decreased sweating reports would be, one would have to rely upon interpreting the severe heat stroke reports. Since there are just 2 of these at present, perhaps a precaution is justifiable.

13) Safety Update

The safety update consists of data from 921-extension and a RCT ZNS-140. The update date is August 25, 1999. For ZNS-140, which is still blinded, we have deaths and serious AEs. There are no new events of concern and the safety profile of zonisamide remains the same.



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MEMORANDUM

DATE: 2.29.00

FROM: Douglas C. Throckmorton, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Shaw Chen, M.D., Ph.D., Team Leader
Robert Fenichel, M.D., Ph.D., Deputy Division Director
Division of Cardio-Renal Drug Products, HFD-110

TO: Jackie Ware, Regulatory Project Manager
Greg Burkhart, M.D., Medical Team Leader
Russell Katz, M.D., Division Director
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Potential renal toxicity of anti-seizure medication
NAME OF DRUG: Zonisamide
TRADE NAME: Zonegran
FORMULATION: PO

RELATED APPLICATIONS: N/A
APPROVED INDICATIONS: N/A
SPONSOR: Elan Pharmaceuticals

DOCUMENTS USED FOR REVIEW:

1. NDA 20-789 items:
 - a. Renal Report dated 9.27.99 and 12.29.98.
 - b. AE letter dated 3.19.99, 6.30.99.
 - c. Safety Review dated 2.24.99 and 6.7.99.
2. Response to FDA request, dated 1.10.00.
3. SAS files related to NDA 20-789.

DATE CONSULT RECEIVED: 10.27.99

DATE CONSULT COMPLETED: 2.23.00

1.0 BACKGROUND

Zonegran is an antiepileptic drug in the sulfonamide class. While its mechanism of action is not known, it may work through actions at sodium and calcium channels, suppressing neuronal hypersynchronization. Zonisamide is also a weak carbonic anhydrase inhibitor, requiring 100-1,000 time higher doses than acetazolamide to achieve equivalent inhibition *in vivo* in rats. Zonisamide is primarily excreted in the urine as parent drug or as glucuronide metabolite.

Three adverse events related to the kidney have been associated with zonisamide use in the clinical database: renal stone formation, increases in BUN/Crt, and acute renal failure. The purpose of this consult is to review the strength of that association and provide recommendations about the renal toxicities of zonisamide as they are now understood.

Handwritten notes and stamps: "/S/" and "2.29.00" are present in the right margin, along with a large scribble.

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2.0 ISSUES AND COMMENTS

I'll begin my memorandum with a series of conclusions, based on my review of the available materials.

- 1) First, zonisamide causes a small decline in glomerular filtration rate, manifest in the NDA population by an increase in the mean serum BUN and creatinine.
- 2) There is an association between zonisamide and renal stone formation, although the exact relative risk for stone formation in patients taking zonisamide cannot be determined given our lack of knowledge about the background rate of stone formation in patients with seizure disorders.
- 3) Finally, the available data demonstrate that severe renal injury occurs in the patient population with an underlying seizure disorder, but not that it occurs more frequently in patients taking zonisamide.

Overall, then, I agree with the overall interpretation of the available data as presented by the sponsor's consultant, although I differ with him on some of the conclusions one can draw from those data. What follows is my analysis of three pivotal components of the zonisamide NDA as they relate to the renal effects of zonisamide:

- 1) Changes in serum markers of renal function.
- 2) Formation of renal stones.
- 3) Clinically-relevant renal toxicities.

2.1 CHANGES IN SERUM MARKERS OF RENAL FUNCTION

BUN and Serum Creatinine

The sponsor and the FDA are in agreement that there is a small increase in the mean BUN and serum creatinine associated with zonisamide use. This pattern is most consistent with a true reduction in glomerular filtration rate (GFR), as has been seen in other drugs with known nephrotoxic potential such as non-steroidal anti-inflammatory drugs (NSAIDs). In a study of outpatients taking ibuprofen (an NSAID), long-term administration was associated with an increase in elevations of either BUN or creatinine in individual patients, although a smaller percentage of patients had elevations in both BUN and creatinine(1). The association between ibuprofen use and renal injury is well-known, with an estimated incidence of clinically-significant renal injury (e.g., acute renal failure, nephrotic syndrome, interstitial nephritis, papillary necrosis) of 1%(2). Similar data on elevations in BUN and creatinine are seen with celecoxib (a COX-2 inhibitor or selective NSAID), although the association between celecoxib use and serious renal injury has not yet been defined. What we don't know is whether there are drugs that lack nephrotoxic potential but cause increases in BUN and creatinine.

Evidence presented by the sponsor suggests that the observed increases in BUN and creatinine are not progressive with continued use of zonisamide, and these changes are reversible upon drug discontinuation. These conclusions are limited by the small number of patients we have with long-term follow-up (103 patients out to 2 years).

Other Lab Markers of Renal Injury

My own analyses of the SAS sets from trials 921, 921 and 922 suggest that there is a small decrease in the mean serum phosphate and increase in mean serum chloride. There are no clear increase in abnormalities related to either glomerular 'sieving' function (i.e., proteinuria) or markers of hematuria. The last marker is relevant as a crude marker for renal 'inflammation' or injury, such as one might see in Allergic Interstitial Nephritis (caused by sulfonamides as a class).

These analyses are limited by several factors, most prominently the small number of patients in the dataset and the small number of patients with long-term follow-up (see above). The changes in serum phosphate and chloride can either be interpreted as supporting an effect of zonisamide as a carbonic anhydrase inhibitor, or as supporting a toxic effect of zonisamide on the proximal tubule. We can't tell the difference from the available data.

2.2 FORMATION OF RENAL STONES

There seems to be little disagreement that zonisamide use is associated with renal stone formation. In a sense, this is the one renal 'effect' of zonisamide that is agreed to by all parties, although the exact rate of stone formation has not been determined (see Dr. Young's letter dated 12.18.98). The relevance of these data to the discussion of renal injury is twofold:

- 1) Recurrent stone formation is associated with risk of permanent renal injury, primarily from obstruction.
- 2) Renal stone formation can be the hallmark of specific forms of renal injury, including Renal Tubular Acidosis (see below).

2.2 CLINICALLY-RELEVANT RENAL TOXICITIES

The occurrence of clinically-significant renal events in the Japanese database during long-term zonisamide administration is provocative, and cannot be ignored. Given the methods that were used to collect that data, I view them as roughly correlating to our Medwatch post-marketing surveillance data, with all of its strengths and weaknesses. In this sense, they suggest that such significant renal events occur in this population (that is, patients with seizure disorders) without allowing us to conclude that they occur more frequently when the population takes zonisamide. The absence of reported renal injury in the U.S. and European experience (approximately 1000 person-years) suggests that renal injury occurring at a rate of approximately 1:300 has been excluded.

One feature of zonisamide that makes renal injury easier to postulate is that, based on what we know about zonisamide or compounds like it (*i.e.*, sulfonamides), there are at least three potential mechanisms for renal injury.

1) First, there is an association between stone formation and intra-renal precipitation, which can lead to long-term renal injury.

2) Second, there is a classic association between sulfonamides and acute interstitial nephritis (AIN). This is of particular relevance as one case of AIN was recently reported from Japan following zonisamide use.

3) Finally, a more speculative mechanism for renal injury that would tie together all of the disparate renal effects hinted at in the database would be a toxic effect on the renal tubule, leading to a Renal Tubular Acidosis (RTA). Support for this would be the decreases in serum phosphate and increased chloride (markers for proximal tubular injury) and stone formation, which classically occurs associated with distal renal tubular acidosis.

3.0 CONSULTANT RECOMMENDATIONS

Regarding the potential for renal toxicity, the zonisamide database is provocative for all of the reasons above, and suggests that, given sufficient data, zonisamide may prove to have nephrotoxic potential. Having said that, the available data are insufficient to conclude that zonisamide use is associated with an increased incidence of clinically-relevant renal injury. The data do demonstrate that zonisamide use is associated with a change in lab parameters (increased BUN, creatinine) that is common to agents known to have nephrotoxic effects. The data also allow us to propose mechanisms of renal injury that are consistent with the available data.

As has been proposed, description of the laboratory changes and the occurrence of renal stones to alert the clinician to the need for renal monitoring should be included in label, along with the observed cases of renal failure should be described as well. The U.S. and European data may also allow an estimate on the lower bounds for a rate of renal injury with zonisamide. One potential labeling, based on the class label used for all NSAIDs, is included in Appendix One below. My choice of NSAIDs as a template is based on the inclusion in that label of information about renal adverse events as well as language about suggested monitoring and prevention.

Based on the lack of severe renal injury reported in the U.S. and European databases to date, renal adverse events reported after marketing are likely to be quite rare. This fact, coupled with the complex nature of the patients illness who will take zonisamide, will obviously make detecting a signal for renal toxicity difficult in the post-marketing arena.

4.0 REFERENCES

1. Murray, M.D., D.C. Brater, S.I. Hui, and C.J. McDonald. 1990. Ibuprofen-associated renal impairment in a large general internal medicine practice. *American Journal of Medical Science* 299:(4)222-229.
2. Whelton, A. 1994. Nonsteroidal Anti-inflammatory Drugs: Effects on Kidney Function. In *Primer on Kidney Diseases*. A. Greenberg, editor. Academic Press, New York. 163-167.

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5.0 APPENDIX ONE: SUGGESTED LABELING

1. Add Warning that no information on the use of zonisamide in patients with advanced renal failure is available.

WARNINGS

Advanced Renal Disease

No information is available regarding the use of zonisamide in patients with advanced renal disease. Therefore, treatment with zonisamide is not recommended in these patients. If zonisamide must be initiated, close monitoring of the patient's renal function is advisable (see PRECAUTIONS—Renal Adverse Events).

2. Add Renal Adverse Events section to Precautions.

PRECAUTIONS

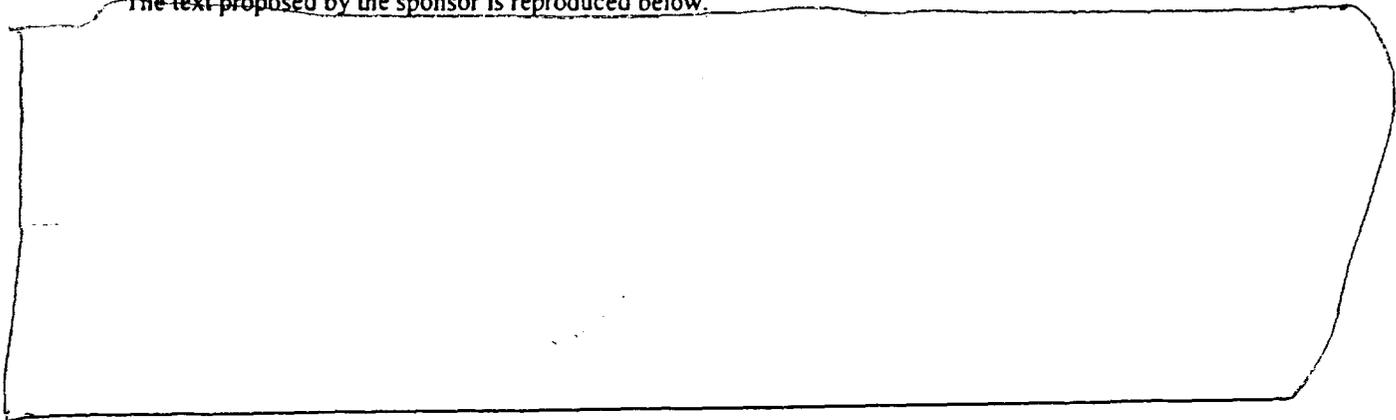
Renal Adverse Events

Renal injury, including acute renal failure, has been reported during long-term administration of zonisamide. Where follow-up data are available, discontinuation of zonisamide was followed by partial or complete recovery of renal function.

Caution should be used when initiating treatment with zonisamide in patients who are dehydrated. It is advisable to rehydrate patients first and then start therapy with zonisamide. Caution is also recommended in patients with pre-existing renal disease (see WARNINGS—Advanced Renal Disease).

3. Change the Laboratory Tests: Serum Creatinine/BUN section in PRECAUTIONS proposed by the sponsor.

The text proposed by the sponsor is reproduced below.



a The statement that 'measured concentrations remained stable during up to 5 years of zonisamide treatment' should be altered to reflect the small number of patients with follow-up beyond 2 years.

b. The statement that measured concentrations ... promptly normalized when the drug was discontinued' should be altered to eliminate 'promptly' and more adequately reflect the data on the timing of resolution.

c The sentences describing the cases of renal failure should not include the countries of origin, as this might be interpreted as implying variable standards of clinical relevance related to the countries. Data is to be interpreted on its own as good or bad, irrespective of the country of origin.

5. To Other Adverse Events Observed During Clinical Trials (page 14) of HFD-120 label.

Add renal failure, interstitial nephritis, oligo-anuria, and edema.

cc:

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