

reviewed the deaths, serious hematological events, serious skin events, congenital abnormalities, and episodes of renal calculi for the sponsor. We review these in the order presented by but there is one case of pancytopenia that is listed under the leukopenia category.

(1) Deaths

Five deaths were reviewed by . They consisted of an 81 year old woman with interstitial pneumonia; a 19 year old man who committed suicide; a 71 year old man with leukopenia and thrombocytopenia and concurrent methicillin- resistant staphylococcal pneumonia (discussed below); a 37 year old man who developed toxic epidermal necrolysis (TEN), and a 64 year old woman with Stevens-Johnson syndrome (SJS) who died after a complicated hospital course (despite recovering from the SJS).

(2) Serious Hematological Reactions

Twenty-five patients with serious hematological AEs were reviewed by . Three of these were reported in the 120 day safety update.

(a) *Pancytopenia/Aplastic Anemia*

There were 3 cases of pancytopenia and 2 cases of aplastic anemia reviewed by . As mentioned earlier, there were no AEs in the summary of the PMS data that were coded as pancytopenia or aplastic anemia. Thus, even the events were recoded or these are different events.

One pancytopenia (91-103) developed prior to initiation of zonisamide and a second case (9960236-J1) developed within seven days of initiation of zonisamide and began to improve within two days of discontinuation. A third patient identified as having aplastic anemia was found to have a bone marrow biopsy consistent with multiple myeloma. All three of these are unlikely to have been caused by zonisamide.

Two cases are summarized below that developed in association with zonisamide use. Neither case was well described clinically, and in the second case, states that the patient did not stop zonisamide until after recovery was occurring. However, this information was not on the AE report and we don't know its source.

Patient 94-010501: A 56-year-old woman initiated zonisamide as monotherapy for seizures. After 4 weeks, she developed a fever, rash, a low WBC, low platelet count and anemia. She was hospitalized and treated with GSF and steroids. The bone marrow examination showed "marrow depression". One week after latter, a repeat bone marrow biopsy showed "improvement". In the AE report, the patient still had abnormal counts several months after the event.

Patient 95-071002: A 3-year-old male taking valproic acid and nitrazepam for seizures had zonisamide added to his AED regimen. Five months later, during a hospitalization to improve seizure control, his hemoglobin was 7.8 mg/dl, WBC 5,460 cells/mm³, and platelet 150,000 cells/mm³. (The AE report indicated that prior to the hospitalization, all three cell lines had been abnormal and were improving at hospitalization. The lowest platelet count was 23,000.) According to [redacted] zonisamide was stopped after a bone marrow examination at the hospitalization was found to be consistent with aplastic anemia. The blood counts gradually improved.

Given our current level of knowledge about the cases, the first case seems more consistent with aplastic anemia. More detail would be helpful for both cases, particularly the second. We don't know the exact findings from the bone marrow

(b) *Leukopenia/ Granulocytopenia/ Neutropenia/ Agranulocytosis*

Fifteen cases of leukopenia, granulocytopenia, neutropenia, or agranulocytosis were reviewed by [redacted] in the ISS. We are not sure what definitions of agranulocytosis and granulocytopenia were used by [redacted] in this review.

(i) *Agranulocytosis*

Of the six reports of agranulocytosis, one occurred in a patient taking concomitant ticlopidine (black box warning for agranulocytosis) whose recovery period coincided more closely with the withdrawal of ticlopidine.

Patient 94-012101 developed a WBC of 800 cells/mm³ three weeks after starting zonisamide; however, he had a concurrent methicillin-resistant staphylococcal pneumonitis, and it is unclear which event occurred first.

The most compelling case of agranulocytosis occurred in patient 94-082203 where agranulocytosis recurred upon rechallenge. However, the event was also associated with other organ system involvement perhaps suggesting a different disease process.

A 27-year-old female received zonisamide for seizures. Six weeks after starting the drug, she developed a rash, fever, abnormal liver functions, and a low WBC count. Zonisamide was discontinued. On rechallenge, the rash and low WBC count reappeared, accompanied by an eosinophilia.

Three other patients (90-105, 91-018, 9960542-J1) had episodes of agranulocytosis that were possibly attributable to zonisamide. There were no deaths and all patients recovered.

(ii) Granulocytopenia

Of three patients identified in the PMS data as having granulocytopenia, 2 cases (90-115, 91-112101) were temporally associated with zonisamide use and had no other explanatory factors. A third case of granulocytopenia (95-090602) was temporally associated with zonisamide (WBC down to 500 cells/mm³) but it occurred in conjunction with symptoms of a viral infection and monocytosis. Recovery occurred within one week of stopping the drug.

(iii) Leukopenia/neutropenia

The one case of neutropenia (92-111202) occurred in a patient on zonisamide for an unknown duration, six weeks after the addition of phenytoin.

Of the five patients identified with leukopenia, three had concomitant thrombocytopenia. One patient (93-022502) had thrombocytopenia preceding the initiation of zonisamide; worsening thrombocytopenia and leukopenia developed 10 days after the initiation of zonisamide concurrent with clinical deterioration and subsequent death from methicillin-resistant staphylococcal pneumonitis.

A 2 year old male (93-052102) developed thrombocytopenia and leukopenia one month after starting zonisamide. He eventually developed anemia and had a bone marrow that showed no megakaryocytes, 19,000 nucleated cells and 83% lymphocytes. No interpretation of the marrow findings was provided. He eventually recovered.

A third patient (93-020802) developed mild leukopenia while on zonisamide, but recovered within four days of stopping therapy; the time course was more consistent with withdrawal of a concomitant penicillin-derived antibiotic. A fourth patient (9960221-J1) developed leukopenia after 3-5 weeks of zonisamide, but the WBC began to drop four days after the initiation of radiotherapy for a brain tumor. A fifth patient (94-080904) developed mild leukopenia and thrombocytopenia associated with a generalized rash that was likely related to zonisamide because the rash recurred upon rechallenge.

(c) *Thrombocytopenia*

Of five case reports of thrombocytopenia, three were accompanied by leukopenia and were discussed above (93-022502, 93-052102, 94-080904). Two other cases occurred

shortly after zonisamide initiation and resolved after it was discontinued (89-198, 90-022). The most severe case is summarized below.

Patient 89-198: A 72-year-old male with a history of psychiatric disorders had zonisamide added to a regimen of five other medications (not specified). About 3 weeks later, he developed oral bleeding and persistent bleeding following an injury. The patient was found to have thrombocytopenia and zonisamide was stopped. The patient recovered following treatment with dexamethasone and platelet transfusion.

(3) Serious Dermatological Reactions

There 40 patients identified by [redacted] as having serious dermatological events in the PMS data (13 from the 120 day safety update). Of the 40 case reports, [redacted] classified 8 as TEN, 31 as SJS, and one was coded as hypersensitivity (originally coded as SJS by the investigator).

A significant problem with the [redacted] review was that the clinical summaries of the cases did not specifically mention whether patients were concomitantly using lamotrigine. We have noted that several spontaneous reports from Japan of serious skin rash with lamotrigine have reported concomitant zonisamide use.

(a) TEN

Of the eight reports of TEN, one patient (94-060302) had been taking zonisamide for two years and developed TEN 3 weeks after a course of ampicillin. There was too little clinical data to evaluate another case 99-50050-J1.

Four cases (92-032701, 95-040306, 95-040307, 95-100602) were exposed to multiple concomitant medications. The 2 summarized below developed serious skin reaction classified by [redacted] as TEN while only exposed to zonisamide.

Patient 93-092901: A 74-year-old female initiated zonisamide monotherapy to prevent seizures following a chronic subdural hematoma. She developed a skin eruption considered to be Lyell's Syndrome (TEN) one month later. Treated in hospital with IV steroids. Rash resolved 2 weeks latter. No mention of permanent injury, skin grafting etc.

Patient 9960153-J1: A 13 year old female initiated zonisamide for epilepsy. One month later she developed TEN. The diagnosis was confirmed by skin biopsy and a lymphocyte

stimulation test was positive for zonisamide. The patient survived.

(b) SJS

Of the 31 cases of SJS, the description of the rash in two cases was not consistent with SJS or did not contain enough information to determine whether it was SJS. While there was limited clinical data for all the cases, there were 9 cases that were compelling (5 monotherapy, 4 add-on therapy) in which zonisamide use was associated with rash occurrence that was consistent with SJS. However, as noted before, the extent of concomitant lamotrigine use in these cases was not discussed by [redacted]

(4) Congenital Abnormalities

Twenty-two children (including one set of twins) born to 21 mothers were reviewed for evidence of congenital abnormalities by [redacted] in the NDA. In the NDA, 13 births were spontaneously reported, six came from the prospective survey, and three came from the general survey. Of the 13 spontaneously reported births, one baby (a twin) was born with an atrial septal defect. The mother had been taking phenytoin and valproic acid in addition to zonisamide; the other twin had no congenital abnormalities. Of the 6 births in the prospective survey cohort, one baby was aborted at 16 weeks and noted to have anencephaly (it is not clear from the report whether the abortion was spontaneous or elective). The mother was taking phenytoin concomitantly. Of the 3 births in the general survey cohort, one baby was aborted in the fourth month (it is not clear from the report whether the abortion was spontaneous or elective). Its condition was unknown. The mother was taking phenobarbital concomitantly.

Two additional cases of congenital abnormalities were described in the 120 day safety update. The source of the reports (spontaneous, general survey, or prospective survey) is not provided. One baby had facial and extremity features consistent with the fetal anti-epileptic drug syndrome. Its mother was taking primidone, valproic acid, carbamazepine, phenobarbital, and diazepam in addition to zonisamide. The second case described a baby with chordee (downward bowing of the penis as a result of hypospadias), birthmarks over the hip and left ankle, and obstruction of the nasolacrimal duct. The report did not disclose whether the mother was on concomitant anti-epileptic drugs.

(5) Nephrolithiasis

In the 120 day safety update, a report was included of a patient who developed renal calculi while on zonisamide therapy. It is not disclosed whether this was a spontaneous report, or part of the general or prospective surveys.

Patient 9950054-J1: A 33 year old man was treated with a low dose of zonisamide for 14 months for post-traumatic epilepsy. His dose was increased to 400 mg/ day and 3.5 months later the patient developed renal colic. The patient had bilateral calculi and ultimately developed anuria with a creatinine of 9.9 ug/ml. The patient was treated with lithodialysis, lithotripsy, and recovered his renal function. The stones were composed of calcium phosphate.

4. Discussion of PMS Experience

In the *Propective Survey*, the sponsor has described the experience of 1512 patients who were prospectively followed. Assuming that this study was capable by design of observing serious AE occurrence, its findings could be informative. Thus, we should clarify its methodology and findings. Based upon the description in the ISS, there was 1 serious rash and 1 case of granulocytopenia neither of which was well described in the submission. There was 1 birth reported where the infant (fetus) had anencephaly. Since the study is ongoing, an update may be informative.

The details of the design of the *Retrospective Survey* of 3906 exposed patients was also not clearly described in the submission, but on face, it would seem to be an unlikely source of valid data. If physicians voluntarily enrolled patients retrospectively there may have been significant selection bias to enter patients who had tolerated zonisamide. Nevertheless, there were at least 2 cases of serious skin rash found in patients included in this survey.

The sponsor also provided a summary of serious AEs that have been spontaneously reported in Japan. There were compelling cases of serious skin rashes some consistent with TEN, and serious cases of hematological events with one probable case of aplastic anemia and several probable cases of agranulocytosis. These cases were difficult to evaluate because of uncertainty in the source of much of the data and limited clinical details in most cases.

The sponsor provided 2 estimates of the extent of zonisamide use in-Japan. One was based upon shipping weights [redacted] and another was based upon IMS data [redacted]. However, the methods used for either estimate were not clearly described. In addition, the number of prescriptions, while part of the IMS data, were not provided. Thus, we were not able to make our own estimates of zonisamide exposure in Japan.

B. Experience in the Japanese Development Program

The *Japanese Approval Cohort* of 1008 patients (605 adults and 403 children) appears to have been a completely separate set of patients from those in the NDA population.

The only information in the NDA on the cohort was the translated clinical summary that was provided to the Japanese regulatory authorities by Dainippon.

While the summary was not particularly helpful at enumerating patients with specific events, it did report that there were 9 (0.9%) patients who discontinued treatment because of low WBC counts. Six others (0.6%) discontinued treatment because of elevated liver enzyme tests.

C. Literature Reports

The sponsor did a computer-based search of the published literature for the period January 1, 1970 - December 31, 1995 . Overall, the events reported in the literature were consistent with those observed in the development program or from the Japanese PMS experience.

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IV. Conclusion

In my opinion, 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. However, there are a number of issues that need to be clarified before marketing.

The PMS experience from Japan suggests that zonisamide use may be associated with agranulocytosis, SJS and TEN, and possibly aplastic anemia. Although the risks for these events do not appear to be high enough to preclude approval, we do need more information about the cases and well as a better estimate of the extent of Japanese post-marketing use. In addition, while there were no cases of aplastic anemia, agranulocytosis, SJS or TEN in the NDA, there were several reports of cases that require some clarification. Likewise, the experience of the *Japanese Approval Cohort* and the *Prospective Survey* conducted in Japan may both provide risk estimates or at least cap the risk for some serious AEs because they may both have well defined denominators and valid follow-up.

Based upon the experience in the NDA, the use of zonisamide can be expected to be associated with broad range of AEs that seem to occur in a dose dependent fashion, particularly CNS events such as somnolence, ataxia, confusion etc. Its overall safety profile is similar to that observed with topiramate and Diamox. Like topiramate, renal calculi were observed in the zonisamide development cohort, but not in controlled trials. Zonisamide use was also associated with increases in liver enzymes, decreases in WBC counts and increases in creatinine. We found no cases of liver failure, agranulocytosis, aplastic anemia, SJS or TEN. There was one case of renal failure that appear to develop secondary to rhamdomyolysis that occurred after status.

The slight mean increase in creatinine that was observed in the RCTs with zonisamide was also observed in a PK study, and while we could find no events suggestive of a decline in renal function, we need some explanation for this finding. Having the sponsor provide a more detailed discussion-of the issue along with a careful review of all other data, including PMS data, may be helpful.

There was one major deficiency in the presentation of the safety experience in the NDA. There was no systematic presentation of the ECG experience. While ECG data does not appear to have been collected for study 922, the most recent RCT, it may have been collected for US912. According to its protocol, ECG data should have been collected at the end of the double blind period. However, when we examined the patient specific listings of ECG data for this study, we were unsure whether the data was pre-treatment, on-treatment or both. There also seems to have been ECG data collected in some phase 1 studies.

Across the development program there were several events that were suggestive of allergic response and perhaps angioedema although we could find no events that were coded as such. Thus, it may also be helpful if the sponsor searches their databases for such events. Since zonisamide is a sulfonamide, it would not be too surprising if such events occurred occasionally. Since all the studies excluded patients with history of allergic-type reactions to sulfonamides, the labeling, if zonisamide is approved, should probably include a similar contraindication, in my opinion.

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V. Suggested Follow UP Issues

A. *Japanese Approval Cohort of 1008*

A full description of the 1008 patients who were the basis for Japanese approval could be informative. Dainippon could respond by providing a patient listing of all dropout and serious AEs. Narratives would be most useful for events in the hematological, hepatic, skin or renal systems. Some description of the extent of use would be helpful in evaluating the observed events.

B. *Prospective and Retrospective Surveys in Japan*

A full study report for the *Prospective Survey* that elucidated its methods and detailed its findings is necessary to determine its value. Dainippon should specifically provide a patient listing of all dropout and serious AEs. Narratives would be most useful for events in the hematological, hepatic, renal or skin systems. Since this was an ongoing study updating the extent of use may be larger than that reported in the NDA.

Similar concerns exist for the *Retrospective Survey* although its findings are unlikely to be that helpful.

C. *Spontaneous Reporting from Japan*

1. Clinical Reports

The clinical information provided for many AEs seemed to be in at least two different places in the NDA. For example, in some cases the information provided by the reviewer differed from that in the AE report. Dainippon could provide full narratives that include all clinical data and follow-up for serious skin rashes, hematological, renal and hepatic events. Many cases appeared to have incomplete follow-up. Please update as possible. For the serious skin reactions, there was little discussion of concomitant lamotrigine use.

2. Estimated Use from Japan

We do not understand the derivation of either estimate of Japanese use. In addition to explaining the methods, providing the actual prescription fill data for Japan coinciding with the dates of the safety update would be helpful.

D. NDA Clarification

1. Specific Patients

a) Laboratory

Individual study reports for the 3 RCTs indicate that 3 patients had clinically significant increases in creatinine. One appears to have been laboratory error. We could not find the other two patients.

The effect of zonisamide on creatinine is unclear. Providing an explanation and evaluation of all pertinent data on renal function would be informative including a review of PMS data.

There was also one patient reported to have thrombocytopenia in whom we could not locate any data (JPZ 3201).

There was also a patient listed in an individual study report of laboratory outliers as having a Hg of 3.9. We could not locate the patient or any information on the laboratory value.

How many patients who dropped out had a laboratory abnormality at dropout? If any please describe.

b) AEs

Many of the serious skin reactions that resulted in either dropout or a serious AE did not include follow-up for the event. Is there additional follow up?

Patient 912-201-358 had a moderately severe anemia. Any follow-up or other clinical details would be helpful. The last Hg of 6.9 was not in the tabulations and the corresponding WBC and platelet count was not reported.

What was the clinical nature of the gastrointestinal AEs that appear to be associated with zonisamide use.

Were any cases of angioedema observed in the NDA development program.

Study 922 had an increased rate of cough. Any follow-up or clinical details for these patients? Any explanation?

c) Renal Calculi in Studies 920, 921 and 922

We could not follow the presentation of the findings on renal calculi occurrence in these studies. Please separate the discussion into those that were clinically symptomatic, those asymptomatic but detected by ultrasound and patient with echogenic foci that were not considered to indicate stones. Separate patients with baseline findings from those with a normal baseline.

d) ECG Data

We could not locate a complete presentation of the ECG findings. Were ECGs conducted in the RCTs or phase I studies. Please provide a complete analysis of all ECG data separated by study. If no data exist in the NDA, did the Japanese active controls trials collect such data?

e) Overdose

Were there any overdoses in the NDA development program? If so please describe this experience.

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MEMORANDUM

DATE: June 29, 1999

FROM: Russell Katz, M.D.

/S/

TO: Robert Temple, M.D.

SUBJECT: Response to Questions Concerning Approvable Package for NDA 20-789

You have asked several questions in your revised Approvable letter and draft labeling for NDA 20-789 for Zonisamide.

LETTER

In the Effectiveness section, you have added a sentence stating that the sponsor has now concluded that 100 mg/day is an effective dose, and you have asked us if this is a new case that the sponsor is making.

In the draft label accompanying the 3/19/98 Approvable letter, the Dosing and Administration section stated (and still states in the current draft) that evidence suggests that doses of 100 mg/day and greater are effective. Further, in that original draft label, the Clinical Trials sub-section describes one of the RCTs that was designed to address the effectiveness of this dose, and the sponsor has performed analyses which suggest that this dose is effective. In short, the effectiveness of the 100 mg/day dose had been established at the first Approvable letter, so it is not new. As a result, we have removed your proposed sentence which suggested this was a new conclusion.

LABEL

PRECAUTIONS

Kidney Stones

You suggested that a paragraph describing the Japanese post-marketing experience was unhelpful and asked whether it could be omitted. It has been omitted.

Laboratory Tests

You noted that the proposed paragraph on Serum Creatinine was no longer correct. We have deleted that paragraph and added a Note to the Sponsor asking for a comprehensive section describing the results of the analyses requested in the Approvable letter.

Exposure

Regarding the extent of exposure, Dr. Tresley essentially makes two arguments. First, he concluded that the actual number of patients exposed in the NDA was 993 and not 1572 as we thought. Second, he considers the supporting clinical data from [redacted] too limited in detail to count as relevant experience.

In the NDA, the sponsor did make a number of errors in describing patient exposure. This description was complicated by the regulatory history of zonisamide during which one sponsor stopped all studies and another restarted development. The subset of data in the development program was referred to as the "supplementary" database in the NDA while the more recent experience was referred to as the "primary" database. Based upon our computations made during review of the NDA, we found that 1572 unique patients had been exposed to zonisamide (combining the supplementary and primary databases). However, we also asked the sponsor to check this number since there was some double counting of patients who participated in early single or multiple dose studies but also entered an RCT (a common problem in NDAs).

As it turns out, the 993 patients reported by Dr. Tresley is actually the correct number for the primary database. The correct total number of all unique patient exposures is 1597. As I described during review of the NDA, most long-term exposure was derived from the primary database with at least 512 patients exposed for longer than 6 months and 343 exposed for longer than 1 year. Hence, on face, the development program meets ICH guidelines.

Regarding the JPME, Dr. Tresley's states on page 2 of his memorandum that there were [redacted] scripts yielding approximately [redacted] patient-years (through 1997-I think). However, based upon the data in the response to the AE letter, this statement is clearly wrong. The actual number of prescriptions for zonisamide in the JPME through 1997 (IMS data) is over 12 million. The sponsor estimated that this use corresponds to about 1.06 million person-years through 1997, much more than we had suspected during review of the NDA. The estimate was based upon the estimated average length of use for each prescription in a calendar year which was derived from the estimated daily use apparently recorded by IMS in Japan. Apparently in Japan, hospitals and physicians fill prescriptions and in the first 3 years, prescriptions are limited to 15 days of use.

I also disagree with Dr. Tresley's conclusion that the sponsor provided nothing new about the JAC or PS. In fact, the sponsor described the experience in the JAC and the [redacted] in detail and also provided a summary of the JAC and a study report for the [redacted]. Both sets of experience appear to have been capable of capturing data on serious events if they occurred, but I do have some concerns about the [redacted] experience.

The PS enrolled patients from their first prescription and followed patients forward in time to evaluate long term safety. Physicians completed CRFs, which were collected on a

yearly basis. Of the 1793 patients entered into the study, 1522 had CRFs collected. Of the 1572 with CRFs, 885 used zonisamide for longer than 1 year and 928 were 15 years of age or less. Of these 1572 patients only 476 patients reported at least 1 AE (total 1087 AE reports). Of the 1087 reports, only 2 were described as serious. In addition, it wasn't clear exactly why 271 patients were missing CRFs. Thus, I have two concerns; that the definition of serious may have been inappropriate, and that the study may have excluding patients dropping out in the first year (the 271). The study's primary objective was to study long-term use.

Based upon the translated summary of the experience in the JAC, there was also substantial pediatric exposure in this dataset as well. Of the 1008 patients, 408 were less than 16 years of age with 111 followed for longer than 1 year. Of the 605 patients who were 16 years of age or older, 160 were followed for longer than 1 year. The summary also included AE lists and lab data. The bulk of the patient experience in the JAC was derived from open experience.

The response also provided a study summary for the so-called RS. As I suggested in my review of the NDA, the sponsor confirmed that the RS enrolled patients who were current users of zonisamide. Hence, the absence of any findings in the RS may not be relevant. Any affirmative findings should be considered, but not necessarily using the RS experience as a complete denominator. I would view the experience in the RS much like that from spontaneous reporting.

Renal Function

In the AE letter, we asked the sponsor to investigate and explain the systematic increase in creatinine observed in study 810-824 and to provide descriptions of the patients with an elevated creatinine the RCTs. To evaluate the former issue, the sponsor conducted a laboratory study to determine whether zonisamide affected the validity of Jaffe reaction, which is used to measure creatinine. No systematic effect on the assay was found. The sponsor then had an expert consultant evaluate the findings in the NDA to offer an opinion as to whether zonisamide affects renal function. He produced two written reports. The first was based upon the original data in the RCTs. He concluded that there was probably a systematic effect of zonisamide on the tubular secretion of creatinine, but that there was probably no effect on the GFR. His opinion was based upon the fact that BUN did not increase along with the creatinine. He viewed this effect as being of more academic interest considering it to have little clinical significance.

He then wrote a second report after the new CRO reanalyzed laboratory data because of a large number of errors in the original database. (We did not know that the extent of this problem after review of the NDA.). This new analysis now found statistically significant increases in both BUN and creatinine. Although he did give his reasoning in detail in the second report, he recommended adding a precaution to describe the effect. However, it was not clear whether or not he now considered the effect to now be on GFR.

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 [redacted] 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 [redacted] without any increase in SGPT. No serious events were identified in the [redacted] 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 [redacted] 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 [redacted] and a summary of the 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 [redacted] (1008 patients) definitely adds to our overall experience. The experience in [redacted] 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, [redacted] 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. We need to discuss this issue with our in-house renal consultants and determine whether a study of renal function could be reasonably conducted as a phase 4 commitment or whether this effect needs to be clearly defined 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 [redacted]. 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.

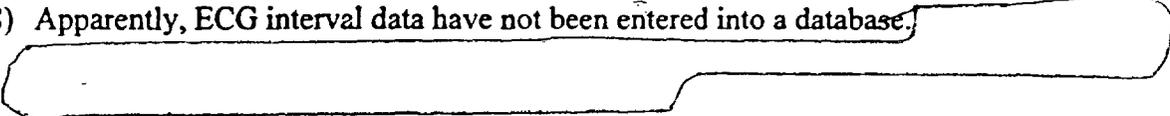
While it is dangerous to compare across drugs, the number of risks associated with zonisamide appear to exceed that seen with other recently approved AEDs - raising concern about its approval as first line treatment. Certainly if it has a pronounced effect on GFR, an argument could be made for not approving 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
- 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. 
- 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.

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Review of Clinical Data

Response to the Approvable Letter

NDA: 20-789
Sponsor: Athena
Drug: Zonisamide
Route of Administration: PO
Reviewer: Greg Burkhart, M.D., M.S.
Review Completion Date: June 7, 1999

/S/
6/7/99

On March 19, 1998 the agency issued an approvable (AE) letter for the zonisamide NDA with Athena responding to it on December 29, 1998. Dr Tresley reviewed the response in a 5/19/98 memorandum and recommended that the NDA be declared not approvable. My interpretation of the basis for this recommendation is that Dr. Tresley believes that the overall exposure is insufficient to affirm zonisamide's safety, and that there was insufficient evidence that the lower doses are effective.

I have also reviewed Athena's response in detail focusing on the safety issues that were described in my 2/14/98 review and the 3/19/98 AE letter. I have also considered Dr. Tresley's arguments as they pertain to safety. As I review the major risks that are associated with zonisamide use and describe where I think additional analyzes are still needed before marketing, I will also point out a number of factual errors made by Dr. Tresley in his review. Dr. Katz, in his memorandum, will also consider these issues along with the efficacy of lower doses.

Background

As reflected in the AE letter, there was convincing evidence in the NDA that zonisamide use was associated with a significant risk for serious skin rash. In the Japanese post-marketing experience (JPME), there were a number of life-threatening cases reported with several fatal cases of Steven's Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Since we were uncertain about the extent of exposure in Japan, the degree of estimated risk for SJS or TEN was not determinable although it appeared to be approaching 1 per 1000 patients per year, a risk similar to that with lamotrigine. In the 1572 patients included in the NDA we found no cases of SJS or TEN.

In addition to significant risk for serious skin rash, there was also evidence that zonisamide use was associated with significant risks for CNS toxicity and renal calculi.

As in other AED NDAs, the CNS events were somewhat vague and the terms used to code the events appeared artificial. Thus, we asked the sponsor to recode the CNS events. We also asked for computation of the incidence of renal stones.

While we found no cases of agranulocytosis, aplastic anemia or fulminant hepatic failure in the NDA, such cases were reported in the JPME. Hence we asked for careful search for these events in all data sources to confirm their absence. Finally, there were also a number of unclear issues regarding laboratory findings and selected adverse events, for which we asked for clarification. In particular, there was an unexplained systematic increase in creatinine in a PK/PD study with some suggestion that creatinine was also increased in the controlled studies. The proposed labeling attached to the AE letter also asked for separate analyzes of common events for each RCT.

While the NDA mentioned that there were additional denominator based experience in Japan (Japanese Approval Cohort [JAC], the Prospective Survey [PS], and the Retrospective Survey [RS] which is also called the general survey) this experience was not described. Hence, we asked the sponsor for a careful review of all serious medical events in this experience. The AE letter also asked for a detailed estimate of the extent of exposure in the JPSE, and for the study reports for the PS and RS and a translated summary of the experience in the JAC.

Response to the AE Letter

The response to the AE letter was well organized attempting to address the questions raised in the letter. In their effort to address some issues, the sponsor discovered that there a large number of errors in the NDA laboratory database. While not described in detail, the sponsor appears to have recoded all these data. However, it does not appear that all analyzes conducted in the NDA on this data were repeated. The sponsor also had 2 clinical experts consider the risk for skin rash and the effect of zonisamide on renal function.

In volume 2 the sponsor provided an integrated discussion of each issue across all data sources incorporating consultant viewpoints. A second volume summarized all Japanese experience separately for each data source. Finally, as we requested, the response contained a translated summary of the JAC, and study reports for the

The spontaneous reports were summarized up through 1998. However, use data in Japan was available through 1997. Thus, to compute reporting rates through I added about 200,000 PYs, roughly the same amount as in 1997.

Exposure

Regarding the extent of exposure, Dr. Tresley essentially makes two arguments. First, he concluded that the actual number of patients exposed in the NDA was 993 and not 1572 as we thought. Second, he considers the supporting clinical data from JAC and PS too limited in detail to count as relevant experience.

In the NDA, the sponsor did make a number of errors in describing patient exposure. This description was complicated by the regulatory history of zonisamide during which one sponsor stopped all studies and another restarted development. The subset of data in the development program was referred to as the "supplementary" database in the NDA while the more recent experience was referred to as the "primary" database. Based upon our computations made during review of the NDA, we found that 1572 unique patients had been exposed to zonisamide (combining the supplementary and primary databases). However, we also asked the sponsor to check this number since there was some double counting of patients who participated in early single or multiple dose studies but also entered an RCT (a common problem in NDAs).

As it turns out, the 993 patients reported by Dr. Tresley is actually the correct number for the primary database. The correct total number of all unique patient exposures is 1597. As I described during review of the NDA, most long-term exposure was derived from the primary database with at least 512 patients exposed for longer than 6 months and 343 exposed for longer than 1 year. Hence, on face, the development program meets ICH guidelines.

Regarding the JPME, Dr. Tresley's states on page 2 of his memorandum that there were [redacted] scripts yielding approximately [redacted] patient-years (through 1997-I think). However, based upon the data in the response to the AE letter, this statement is clearly wrong. The actual number of prescriptions for zonisamide in the JPME through 1997 (IMS data) is over 12 million. The sponsor estimated that this use corresponds to about [redacted] person-years through 1997, much more than we had suspected during review of the NDA. The estimate was based upon the estimated average length of use for each prescription in a calendar year which was derived from the estimated daily use apparently recorded by IMS in Japan. Apparently in Japan, hospitals and physicians fill prescriptions and in the first 3 years, prescriptions are limited to 15 days of use.

I also disagree with Dr. Tresley's conclusion that the sponsor provided nothing new about the JAC or PS. In fact, the sponsor described the experience in the JAC and the PS in detail and also provided a summary of the JAC and a study report for the PS. Both sets of experience appear to have been capable of capturing data on serious events if they occurred, but I do have some concerns about the PS experience.

The PS enrolled patients from their first prescription and followed patients forward in time to evaluate long term safety. Physicians completed CRFs, which were collected on a

yearly basis. Of the 1793 patients entered into the study, 1522 had CRFs collected. Of the 1572 with CRFs, 885 used zonisamide for longer than 1 year and 928 were 15 years of age or less. Of these 1572 patients only 476 patients reported at least 1 AE (total 1087 AE reports). Of the 1087 reports, only 2 were described as serious. In addition, it wasn't clear exactly why 271 patients were missing CRFs. Thus, I have two concerns; that the definition of serious may have been inappropriate, and that the study may have excluding patients dropping out in the first year (the 271). The study's primary objective was to study long-term use.

Based upon the translated summary of the experience in the JAC, there was also substantial pediatric exposure in this dataset as well. Of the 1008 patients, 408 were less than 16 years of age with 111 followed for longer than 1 year. Of the 605 patients who were 16 years of age or older, 160 were followed for longer than 1 year. The summary also included AE lists and lab data. The bulk of the patient experience in the JAC was derived from open experience.

The response also provided a study summary for the so-called RS. As I suggested in my review of the NDA, the sponsor confirmed that the RS enrolled patients who were current users of zonisamide. Hence, the absence of any findings in the RS may not be relevant. Any affirmative findings should be considered, but not necessarily using the RS experience as a complete denominator. I would view the experience in the RS much like that from spontaneous reporting.

Renal Function

In the AE letter, we asked the sponsor to investigate and explain the systematic increase in creatinine observed in study 810-824 and to provide descriptions of the patients with an elevated creatinine the RCTs. To evaluate the former issue, the sponsor conducted a laboratory study to determine whether zonisamide affected the validity of Jaffe reaction, which is used to measure creatinine. No systematic effect on the assay was found. The sponsor then had an expert consultant evaluate the findings in the NDA to offer an opinion as to whether zonisamide affects renal function. He produced two written reports. The first was based upon the original data in the RCTs. He concluded that there was probably a systematic effect of zonisamide on the tubular secretion of creatinine, but that there was probably no effect on the GFR. His opinion was based upon the fact that BUN did not increase along with the creatinine. He viewed this effect as being of more academic interest considering it to have little clinical significance.

He then wrote a second report after the new CRO reanalyzed laboratory data because of a large number of errors in the original database. (We did not know that the extent of this problem after review of the NDA.). This new analysis now found statistically significant increases in both BUN and creatinine. Although he did give his reasoning in detail in the second report, he recommended adding a precaution to describe the effect. However, it was not clear whether or not he now considered the effect to now be on GFR.