

Patient 1276-05044 (Study 021A): SAE - Hyponatremia, Hypochloremia, Non-Cardiogenic Chest pain, Apathy, Constipation

A 39 year old female, with history of previous non-cardiac chest pain and hyponatremia, on carbamazepine and lamotrigine, was hospitalized for atypical chest pain while on 2400mg of rufinamide that was started 6 days earlier. MI was ruled out (negative cardiac enzymes) and following this event patient recovered fully. ~ 6 weeks later, she stopped taking only Rufinamide on her own. She was discontinued from the study on administrative grounds. The following day she was hospitalized for constipation and loss of interest. Labs revealed multiple abnormalities- sodium (129 mEq/l), chloride (94 mEq/l), hematocrit (33%) and hemoglobin (10.8 g/dl). She was treated and discharged with improvement clinically and in the lab parameters.

Reviewer Comments

The causes for the metabolic abnormalities were possibly multi-factorial, with carbamazepine most likely responsible for hyponatremia in this patient with history of hyponatremia (baseline value not mentioned). However, in conjunction with the second SAE case of hyponatremia described below (Patient 0008-01168) and the changes in labs, i.e., - a) shifts in sodium from normal baseline to low post-treatment in the all double-blind subgroup (rufinamide = 26 [2.1%] and placebo = 11 [1.7%]), b) shifts in sodium from normal baseline to low post-treatment in the adult double-blind subgroup (see below) (rufinamide = 19 [2.6%] and placebo = 6 [2.1%]), whether rufinamide was contributory in some way to hyponatremia cannot be excluded. Similar changes in chloride (means or shifts) in this all double-blind subgroup were not seen.

It is recommended that the possibility of the association of the occurrence of hyponatremia while on Rufinamide treatment be included in the label as indicated below- see below under comments for patient 00081-01168 with hyponatremia.

Patient 1284-5033 (Study 0021E): SAE- Hyponatremia

This 54-year-old Caucasian female patient entered double-blind study 021A with a diagnosis of inadequately controlled partial seizures. The patient was randomly assigned to receive rufinamide during the double-blind Phase of study 021A. She completed 91 days of double-blind treatment. The patient then entered the extension phase and began receiving open-label treatment on 06-Mar-98. Concomitant AEDs during the Extension phase included phenytoin, lamotrigine, Keppra (levetiracetam), Trileptal (oxcarbazepine), and Zonegran (zonisamide). The patient also received vagal nerve stimulation to treat epilepsy. Concomitant non-AED medications during the extension phase included Tylenol, Advil, Carafate, atenolol, and Pravachol. Her serum sodium level on 06-Apr-09 [sic] (confirmed on Sep 11, 2006 via a TCON when clarification was sought that the actual date is 06-Apr-98) was 143 mmol/L (normal range, 125-154 mmol/L).

On ~~1~~ the patient was admitted to hospital for elective medication adjustment. She was started on oxcarbazepine 300 mg BID. On 19-Mar-2001, the oxcarbazepine dosage was increased to 450 mg BID. On 20-Mar-2001 (Day 1111 of the Extension Phase), while receiving rufinamide 3200 mg/day, the patient experienced mild nausea, mild vomiting, and moderate sleepiness; due to these events, oxcarbazepine was discontinued. On the same day, serum sodium results (values were not provided) revealed the need for increased fluid restriction.

b(6)

Hydrochlorothiazide, previously taken in combination with captopril, was discontinued at this time. The events of nausea, vomiting, and sleepiness were resolved on 22-Mar-01, and the serious event of hyponatremia was completely resolved on 23-Mar-01 (serum sodium level at this was not provided). Hyponatremia was not the reason for hospitalization, but was considered to be medically significant. In a follow-up report, the investigator confirmed that nausea, vomiting, and sleepiness were symptoms of hyponatremia. In the investigator's opinion, the serious adverse event of hyponatremia was moderate in intensity and unrelated to study medication. The event was suspected to be related to oxcarbazepine therapy and the hydrochlorothiazide/captopril combination. The patient continued study medication following the event and completed the study.

Reviewer Comments

Sufficient information has not been provided that would justify the investigator's impression of the lack of a relationship. Sodium levels that were critical for review were not provided. Further, the chronology of the dates was incorrect (serum sodium level on April 6, 09....?). This was brought to the sponsor's attention during the Sep 11, 2006 TCON when the location of this case within the NDA submission was sought. This was clarified and the actual date was Apr 98. Barring these aspects, the severity of hyponatremia could not be determined.

Patient 0008-01168 (Study AE/ET1): SAE - Hyponatremia

This 61-year-old male patient entered the double-blind phase of the study AE/ET1 with a diagnosis of inadequately controlled partial seizures. Active medical condition other than epilepsy present at enrollment included congenital goiter and prostatic disorder (since 05-Jan-94). The patient was randomly assigned to receive rufinamide during the Double-blind Phase of study AE/ET1. He then entered the extension phase and began receiving open-label rufinamide treatment on 18-Jun-94. The only concomitant non-AED medication recorded during the Extension Phase was paracetamol. Concomitant AED therapy included carbamazepine, clonazepam, and vigabatrin throughout the extension phase; the patient also received clobazam and diazepam to treat prolonged seizures.

The patient had two events of hyponatremia during the Double-blind Phase. The second event continued into the extension phase. The patient demonstrated no clinical symptoms consistent with hyponatremia. His serum sodium level was 126 mmol/L (normal range, 135-145 mmol/L) on 31-May-94 (18 days before the start of open-label rufinamide), 143 mmol/L on 03-Jun-94 (15 days before the start of open-label rufinamide); 124 mmol/L on 14-Jun-94 (4 days before the start of open-label rufinamide), and 140 mmol/L on 01-Aug-94 while receiving 800 mg/day of open-label rufinamide. In the investigator's opinion, the hyponatremia was suspected to be related to study medication.

Reviewer Comments

This patient had asymptomatic hyponatremia both during the double-blind phase and open-label phase and while concomitantly receiving carbamazepine and other medications. However, in conjunction with the second SAE case of hyponatremia described above (Patient 0008-01168) and the changes in labs, i.e., - a) shifts in sodium from normal baseline to low post-treatment in the all double-blind subgroup (rufinamide = 26 [2.1%] and placebo = 11 [1.7%]), b) shifts in sodium from normal baseline to low post-treatment in the adult double-blind subgroup (see

below) (rufinamide = 19 [2.6%] and placebo = 6 [2.1%]), whether rufinamide was contributory in some way to hyponatremia cannot be excluded.

It is recommended that the greater incidence of shifts in serum sodium from a normal baseline to lower values post treatment with rufinamide compared to placebo that occurred in clinical trials should be mentioned in the precautions section of the label under laboratory tests. It is recommended that the concerns of the possibility of the occurrence of asymptomatic hyponatremia that was considered serious in the two patients who were also receiving carbamazepine be included in the precautions section of the label under laboratory tests.

Treatment Emergent General Chemistry Lab Changes in All Subgroups Combined

Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were comparable to those seen in the double-blind studies (Ref: Sponsor's Appendix I, Table 8.1.1-4). A majority of the patients in each treatment group had no shifts relative to the normal range between baseline and the last post-baseline evaluation. The percentages of patients with upward or downward shifts from normal were similar to those seen in the double-blind studies, as shown in Sponsor's Table 8.4-4, ISS. The lack of a placebo arm made meaningful interpretations difficult.

Clinically notable increases or decreases occurred in $\leq 7.4\%$ of the patients (Ref: Sponsor's Appendix I, Table 8.3.1-4). Listings of all patients with clinically notable values for low bicarbonate, low chloride, low sodium, and either high or low uric acid was submitted in Sponsor's Appendix I, Table 8.6-12. Adverse events related to general chemistry parameters occurred in $<1\%$ of the rufinamide-treated patients (Ref: Sponsor's Appendix I, Table 6.10.1-1).

Three patients who had serious adverse events of hyponatremia (0008-01168 in Study AE/ET1, 1276-05044 in Study 021A and 0001-01631 in Study AE/ET1E), and one patient had a serious adverse event of hypochloremia (1276-05044 in Study 021A). One patient discontinued due to hyponatremia (0001-01631 in Study AE/ET1E). Each of these patients received carbamazepine as a concomitant AED. Patients 0008-01168 and 1276-05044 were discussed above under all double-blind subgroup and patient 0001-01631 is discussed below.

Patient 0001-01631 (Study AE/ET1E): SAE - Hyponatremia + Discontinuation

This 30-year-old female patient entered the double-blind phase of the study AE/ET1 with a diagnosis of inadequately controlled partial seizures. No medical history was recorded at study entry, and the only active medical condition other than epilepsy present at enrollment was urinary tract infection. The patient was randomly assigned to receive placebo during the double-blind phase of study AE/ET1. She then entered the extension phase and began receiving open-label rufinamide treatment on 04-Jul-94. Non-AED concomitant medications recorded during the Extension Phase included aspirin plus C, Calmurid (topical hydrocortisone), heptaminol, povidone-iodine, Urogenin, domperidone, norfloxacin, paracetamol, hexamidine, roxithromycin, Sofrasolone o.r.l., acetylsalicylic acid, cefatrizine, colludol, unspecified cough syrup, ipratropium bromide, mebeverine, multivitamins, yeast dried, cefadroxil, Endrine "Wyeth", oxytetracycline, nifurtoinol, amoxicillin/clavulanic acid, ascorbic acid, tilia spp. extract, benzoxonium, bisacodyl, dimethoxanate, doxycycline, fusafungine, omnibionta, strepsils, pyralvex, and cefaclor; concomitant AED therapy included carbamazepine, clobazam, and valproate throughout the extension Phase.

On _____ of rufinamide therapy), while receiving 1200 mg/day of rufinamide, the patient was admitted to the hospital with a history of dizziness, confusion, and a general deterioration in health for 3 days. A diagnosis of pneumonia was made and the patient was found to be hyponatremic (the test was performed during hospitalization and *the results are unavailable*). Sodium levels had been normal on 26- Jan-98. It was also determined that the patient had received an overdose of carbamazepine and valproate (levels were not available), which was attributed to poor patient compliance. The dose of carbamazepine was reduced (dose reduction unknown) and rufinamide was stopped due to the events, with the last dose taken on the day of admission _____. The patient was discharged from the hospital on _____ having made a complete recovery according to the sponsor.

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Reviewer Comments

While multi-factorial causes were possibly responsible for hyponatremia, the extent of the role that rufinamide may have played is unknown and not determinable. In the absence of sufficient relevant details such as blood levels, baseline levels, etc., for correlation, it is speculative to exclude rufinamide as a cause for hyponatremia although the onset of events was on day _____ of rufinamide treatment and serum sodium was reported to be normal 2 months prior to the event onset.

See comments, including label recommendations, above under description of patients 0008-01168 in Study AE/ET1 and 1276-05044 in Study 021A who experienced hyponatremia.

Treatment Emergent General Chemistry Lab Changes in Adult Double-blind Subgroup

Mean Changes

Sponsor's Table 8.4-5, ISS, displayed mean values for general chemistry parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2 visits. Mean changes were small and were generally comparable in the rufinamide and placebo groups. The rufinamide group had a larger mean change in uric acid (-17.0 $\mu\text{mol/L}$) than the placebo group (0.7 $\mu\text{mol/L}$), but both changes were small. Discernable differences that were clinically meaningful, however, were not seen.

Shift Table Changes

The numbers of patients with shifts in general chemistry parameters, relative to the normal range, was summarized in Sponsor's Table 8.4-6, ISS. The table showed that the majority of patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation. The percentages of patients with upward or downward shifts from normal were similar in the two treatment groups. Discernable differences that were clinically meaningful, however, were not seen.

Clinically Notable Changes

The incidence of patients with normal values for general chemistry parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.4-7, ISS for the double-blind studies in adults with partial seizures. The rates were generally similar in the two treatment groups. Discernable differences that were clinically meaningful, however, were not seen.

One patient who had serious adverse events of hyponatremia and hypochloremia (1276-05044 in Study 021A) was described and discussed above under all double-blind subgroup. This patient did not discontinue due to these events.

Treatment Emergent General Chemistry Lab Changes in Adult Double-blind with Open-label Extension Subgroup

Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were comparable to those seen in the double-blind studies (Ref: Sponsor's Appendix I, Table 8.1.1-49). The largest mean change was in uric acid (-17.3 $\mu\text{mol/L}$). A majority of the patients had no shifts relative to the normal range between baseline and the last post-baseline evaluation (Ref: Sponsor's Appendix I, Table 8.4.10-4). Twelve percent of the patients had downward shifts in chloride. For the remaining parameters, downward or upward shifts occurred in <9% of the patients. Clinically notable increases or decreases in general chemistry parameters occurred in <5% of the patients (Ref: Sponsor's Appendix I, Table 8.3.1.49).

Three patients had serious adverse events of hyponatremia (0008-01168 in Study AE/ET1, 0001-01631 in Study AE/ET1E, 1276-05044 in Study 021A), and one patient had a serious adverse event of hypochloremia (1276-05044 in Study 021A). One patient discontinued due to hyponatremia (0001-01631 in Study AE/ET1E). All patients were described and discussed above under all double-blind subgroup.

Treatment Emergent General Chemistry Lab Changes in Mono-therapy Double-blind Subgroup

Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were generally comparable in the rufinamide and placebo groups (Ref: Sponsor's Appendix I, Table 8.1.1-34). The placebo group had a larger mean change in uric acid (13.2 $\mu\text{mol/L}$) than the rufinamide group (-4.7 $\mu\text{mol/L}$). A majority of the patients in each treatment group had no shifts relative to the normal range between baseline and the last post-baseline evaluation. The percentages of patients with upward or downward shifts from normal were generally similar in the two treatment groups (Ref: Sponsor's Appendix I, Table 8.4.7-4). Higher percentages of patients in the rufinamide group than the placebo group had upward shifts in calcium (6.7% versus 0%). Clinically notable increases in potassium occurred in 15 (7.8%) rufinamide-treated patients and no placebo-treated patients (Ref: Sponsor's Appendix I, Table 8.3.1-34). All other clinically notable values occurred in comparable percentages of patients in the 2 treatment groups.

Treatment Emergent General Chemistry Lab Changes in LGS Double-blind Subgroup

Bicarbonate and cholesterol were not measured in the LGS study.

Mean Changes

Sponsor's Table 8.4-8, ISS, displayed mean values for general chemistry parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2 visits. Mean changes were small and were generally comparable in the rufinamide and placebo

groups. The change in uric acid was larger in the rufinamide group (66.9 $\mu\text{mol/L}$) than in the placebo group (32.8 $\mu\text{mol/L}$).

Reviewer comments

The significance of the greater change in uric acid with rufinamide compared to placebo is not unknown.

Shift Table Changes

The numbers of patients with shifts in general chemistry parameters, relative to the normal range, was summarized in Sponsor's Table 8.4-9, ISS. The table showed that the majority of patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation. The percentages of patients with upward or downward shifts from normal were generally similar in the two treatment groups. A higher percentage of patients in the rufinamide group (12.2%) than the placebo group (4.7%) had downward shifts in calcium.

Clinically Notable Changes

The incidence of patients with normal values for general chemistry parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.4-10, ISS for the LGS study. No patient in either group had clinically notable values for chloride or sodium. For the remaining parameters, 0 to 3 patients per treatment group had clinically notable values.

There were no serious adverse events related to general chemistry parameters, and no discontinuations due to such events, in either treatment group.

Treatment Emergent General Chemistry Lab Changes in LGS Double-blind with Open-label Extension Subgroup

Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were generally comparable to those seen in the double-blind studies (Ref: Sponsor's Appendix I, Table 8.1.1-14). In contrast to the results in the double-blind studies, uric acid showed a mean decrease (-10.9 $\mu\text{mol/L}$) in this population. A majority of the patients in each treatment group had no shifts relative to the normal range between baseline and the last post-baseline evaluation (Ref: Sponsor's Appendix I, Table 8.4.5-4). No patient had clinically notable values for chloride (Ref: Sponsor's Appendix I, Table 8.3.1-14). Twenty-one (16.5%) of 127 patients had increases in calcium, 21 (16.7%) of 126 patients had increases in glucose (fasting blood tests were generally not required), and 26 (20.5%) of 127 patients had increases in uric acid (no patients had clinically notable decreases in uric acid). Other clinically notable increases or decreases occurred in $\leq 7.4\%$ of the patients. The higher rates relative to the Double-blind Phase reflect the longer duration of exposure in this population. There were no serious adverse events related to general chemistry parameters, and no discontinuations due to such events.

Treatment Emergent General Chemistry Lab Changes in Pediatric Double-blind Subgroup

Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were comparable in the rufinamide and placebo groups (Ref: Sponsor's Appendix

I, Table 8.1.1- 24). A majority of the patients in each treatment group had no shifts relative to the normal range between baseline and the last post-baseline evaluation. The percentages of patients with upward or downward shifts from normal were similar in the two treatment groups (Sponsor's Appendix I, Table 8.4.2-4). No patient in either group had clinically notable values for bicarbonate, chloride, or sodium (Ref; Sponsor's Appendix I, Table 8.3.1-24). For the remaining parameters, the percentages of patients with clinically notable values were similar for the rufinamide and placebo groups. There were no serious adverse events related to general chemistry parameters, and no discontinuations due to such events, in either treatment group.

Treatment Emergent General Chemistry Lab Changes in Pediatric Double-blind with Open-label Extension Subgroup

Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were comparable to those seen in the double-blind studies (Ref: Sponsor's Appendix I, Table 8.1.1-19). A majority of the patients had no shifts relative to the normal range between baseline and the last post-baseline evaluation (Ref: Sponsor's Appendix I, Table 8.4.4-4). No patient had clinically notable values for bicarbonate or chloride (Ref: Sponsor's Appendix I, Table 8.3.1-19). Forty-four (13.6%) of 323 patients had increases in potassium. Other clinically notable increases or decreases occurred in $\leq 7.6\%$ of the patients. The higher rates relative to the Double-blind Phase reflect the longer duration of exposure in this population. There were no serious adverse events related to general chemistry parameters, and no discontinuations due to such events.

Treatment Emergent Thyroid Function Lab Changes

Reviewer Comments

An increased incidence of thyroid follicular adenomas was noted at dosages ≥ 60 mg/kg in the rat carcinogenicity study (thought to be species specific). As a result, the sponsor performed comprehensive thyroid monitoring tests (see Table 7.1.A). The parameters that were evaluated under this panel were Free Thyroxine (T4), T3 (T3 total), Thyroxine (T4 Total), and TSH. The number of patients who were evaluated varied depending on the assessed parameter, the analysis subgroup and the treatment (rufinamide or placebo). These numbers varied further between the rufinamide and placebo treatment groups for the same parameter. Further, in some subgroups, not all parameters were assessed. Free thyroxine and T3 were not measured in the LGS study. Thyroxine and TSH were the only thyroid parameters evaluated at both baseline and post-baseline in the mono-therapy substitution studies, and only in Study 016, which did not have a placebo group. Hence, the interpretation of the results required allowances for such variations in the denominators.

The data (mean changes) was presented using SI counts for all the parameters (normal Free Thyroxine SI units = 10-20 pmol/L [*sponsor 10.27 to 23.17*] [conventional units = 0.8-1.8ng/dl]), T3 SI units = 0.9-2.8 nmol/L [*sponsor 1.23 to 3.07*] [conventional units = 60-181 ng/dL]), Thyroxine (T4) SI units = 58-161 nmol/L [*sponsor 64.35 to 160.88*] [conventional units = 4.5-12.5 μ g/dL] and TSH SI units = 0.50-4.70 mIU/L [*sponsor 0.3 to 5*] [conventional units = 0.50-4.70 μ IU/L]). The results were presented as Mean Changes, Shift Table Changes and Clinically Notable Changes.

Treatment Emergent Thyroid Function Changes in All Double-blind Studies Subgroup

Mean Changes

Sponsor's Table 8.5-1, ISS, displayed mean values for thyroid laboratory parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2 visits. Because inclusion of data that were clearly in error made it impossible to interpret the mean values correctly, median values and ranges are also shown for thyroxine. The rufinamide group had a slightly larger median change in thyroxine than the placebo group (3.0 versus 0.0 nmol/L). Mean changes in the remaining parameters were small and were similar in the rufinamide and placebo groups. Discernable differences that were clinically meaningful were not seen.

Shift Table Changes

The numbers of patients with shifts in thyroid parameters, relative to the normal range, was summarized in Sponsor's Table 8.5-2, ISS for all treated patients with epilepsy (double-blind studies). The table showed that the majority of patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation. Thirty-four (2.7%) rufinamide-treated patients and 11 (1.7%) placebo-treated patients had shifts from normal baseline TSH to final values which were above the normal range during the double-blind Phase. An additional 26 (2.1%) and 14 (2.2%) patients, respectively, had shifts from baseline values above the normal range to normal values at the final evaluation during the Double-blind Phase.

Reviewer Comments

See label recommendations below and section 9.4 under label review.

Clinically Notable Changes

The results were similar with rufinamide and placebo for free thyroxine, thyroxine, and TSH (Sponsor's Table 8.5-3, ISS). Specifically, clinically notable decreases in TSH occurred in 2.1% of the rufinamide-treated patients and 1.5% of the placebo-treated patients. Clinically notable increases in TSH occurred in 1.8% and 1.5%, respectively. Clinically notable changes in T₃ occurred in 6 (12.2%) of 49 rufinamide-treated patients with data, including 1 patient with a decrease and 5 with increases. No patient in the placebo group had T₃ measured. The rufinamide and placebo groups had similar rates of clinically notable increases in free thyroxine (1.9% versus 1.7%) and thyroxine (0.3% versus 0.2%).

Hypothyroidism or primary hypothyroidism was an adverse event in 5 (0.3%) rufinamide-treated patients and 2 (0.3%) placebo-treated patients in this population. Thyroxine abnormal was reported as an adverse event in 0 and 1 (0.2%) patients, respectively.

Hypothyroidism was a serious adverse event in one rufinamide-treated patient is described below.

Patient 0003-01054 (Study AE/ET1): SAE

This patient a 23 year old male entered the trial with a diagnosis of partial seizures. He was receiving vigabatrin 3000 mg daily (started 01-Jul-92), sodium valproate 500 mg daily (started 01-Sep-92) and carbamazepine SR 1500 mg daily (started 01-Mar-93). There was no relevant previous medical history. Rufinamide 200 mg daily was started on 27-Sep-93. On 24-Nov-93,

approximately 2 months after initiation of rufinamide, the patient was diagnosed with asymptomatic hypothyreosis during a routine blood check. Thyroid function tests were normal until 24-Nov-93, in particular T4 (6.4pgdl on 27-Sep-93, 5.5pgdl on 25-Oct-93). A TRH test performed on 24-Nov-93 confirmed hypothyreosis (serum values: TSH 3.01 mu/L, T3 126 ng/dL and T4 3.5pgdl). At baseline TSH was 3.65 mu/L, T3 119 ng/dL and T4 5.0 WdL. Sonography carried out on 19-Jan-94 revealed a suprasternal thyroid with normal structure in both lobes; scintigraphy was normal. No biopsy was carried out. On evaluation of these results the endocrinologist to whom the patient had been referred did not consider that any treatment was indicated but recommended follow-up. On 19-Jan-94 thyroid function tests were again normal (T4 5.1pg/dL, T3 139 ng/dL and TSH 4.82 mu/L). The patient did not discontinue prematurely. The patient had a follow-up examination visit on 25-Apr-94 but subsequently informed the investigator that he would not return for any further visits.

Reviewer Comments

~ 2 months after initiation and while on 200 mg of rufinamide, based on routine follow-up labs (baseline TFTs being normal), hypothyroidism was confirmed. This was not accompanied with clinical signs or symptoms or glandular abnormalities as investigated by sonography and scintigraphy. Without further treatment or intervention (and perhaps while still on rufinamide since the patient did not discontinue prematurely) and in ~ 6-8 weeks, the TFTs normalized spontaneously.

As discussed above, thirty-four (2.7%) rufinamide-treated patients and 11 (1.7%) placebo-treated patients had shifts from normal baseline TSH to final values which were above the normal range during the double-blind Phase. As discussed below, the greater shifts with rufinamide, from normal TSH baseline to post TSH high in 16 rufinamide (7.5%) vs. 6 placebo (3.0%) and normal thyroxine and free thyroxine at baseline to post low thyroxine (free and total) values compared to placebo (total = 14 [6.6%] rufinamide patients vs. 11 [5.6%]), placebo were clinically meaningful in the pediatric double-blind subgroup. Further, the results in clinically notable changes in the pediatric double-blind subgroup were additionally, clinically meaningful (increase in TSH in 5 [3.2%] rufinamide patients vs. 3 (2.1) placebo patients and decrease in free thyroxine 12.5% rufinamide vs. 0 placebo).

The TFT lab abnormalities of greater incidence of elevated TSH and decrease in thyroxine (total and free) compared to placebo in the pediatric double-blind subgroup, in conjunction with the abnormalities in TFTs of the magnitude sufficient to qualify as a SAE in an adult patient as described above strongly suggests that rufinamide alters TFTs by an unknown mechanism. *It is recommended that the concerns of the possibility of the occurrence of asymptomatic TFT aberrations with the administration of rufinamide be included in the precautions section of the label under laboratory tests. These TFT related lab abnormalities should be included in the precaution section of the label under laboratory abnormalities.*

No patient discontinued treatment due to adverse events related to thyroid parameters.

Treatment Emergent Thyroid Functions Changes in All Subgroups Combined

Mean Changes

Sponsor's Table 8.5-4, ISS, displayed mean values for thyroid laboratory parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2

visits. According to the sponsor, median values and ranges were included for free thyroxine and thyroxine, because inclusion of data that were clearly in error made it impossible to interpret the mean values correctly. The results were similar to those seen in the double-blind studies. The absence of a placebo arm limited interpretations.

Shift Table Changes

The numbers of patients with shifts in thyroid parameters, relative to the normal range, was summarized in Sponsor's Table 8.5-5, ISS for all treated patients with epilepsy. Overall, 36 (1.8%) patients had TSH values that shifted from normal at baseline to above the normal range at the last post-baseline evaluation. An additional 32 (1.6%) had values that shifted from above the normal range at baseline to normal at the last post-baseline evaluation. Upward shifts in free thyroxine (0.2%) or thyroxine (0.8%) were infrequent.

The absence of a placebo arm limited interpretations.

Clinically Notable Changes

The rates of clinically notable values were somewhat higher than those seen in the double-blind studies, reflecting the longer duration of exposure and greater number of samples obtained in this population (Sponsor's Table 8.5-6, ISS). Decreases in thyroid parameters occurred in 20.0% of the patients for free thyroxine and 8.0% of the patients for thyroxine. The same percentages of patients had increases and decreases in TSH (both occurred in 2.8% of the patients). All patients in this population with clinically notable high values for TSH and/or clinically notable low values for thyroxine/free thyroxine was identified (Ref: Sponsor's Appendix I, Table 8.6-9). The table displayed, for each of these patients, demographic information, treatment information, and laboratory results for TSH, thyroxine, and free thyroxine (if available). However, *in the absence of a placebo arm and coupled with the mixed findings of equal incidences of TSH increase and decrease, free thyroxine decrease or T₃ increase, etc., the significance and meaning of these observed changes could not be grasped.*

Hypothyroidism or primary hypothyroidism as an AE occurred in 21 (1.0%) patients in this population. Thyroid disorder and thyroiditis each occurred in 1 (0.1%) patient (Ref; Sponsor's Appendix I, Table 6.10.1-1). Hypothyroidism was a serious adverse event in one patient (0003-01054 in Study AE/ET1) as described above with comments. No patient discontinued treatment due to adverse events related to thyroid parameters.

Treatment Emergent Thyroid Functions Changes in Adult Double-blind Subgroup

Mean Changes

Sponsor's Table 8.5-7, ISS, displayed mean values for thyroid laboratory parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2 visits. Mean changes in all parameters were small and were similar in the rufinamide and placebo groups. *Discernable differences that were clinically meaningful were not seen.*

Shift Table Changes

The numbers of patients with shifts in thyroid parameters, relative to the normal range, was summarized in Sponsor's Table 8.5-8, ISS, for adults in double-blind studies. The table showed that the majority of patients in both treatment groups had no shifts relative to the normal range

between baseline and the last post-baseline evaluation. Upward and downward shifts from normal occurred in similar percentages of patients in the 2 treatment groups. Because the observed changes were inconsistent with respect to a match for a hypo or hyper thyroid profile and further the rufinamide shifts were sometimes lower than placebo. Discernable differences that were clinically meaningful were not seen.

Clinically Notable Changes

Clinically notable values occurred in similar percentages of patients in the rufinamide and placebo groups in the population of adults with partial seizures who received study drug in double-blind studies (Sponsor's Table 8.5-9, ISS). Because the observed changes were inconsistent with respect to a match for a hypo or hyper thyroid profile and further the rufinamide shifts were sometimes lower than placebo. Discernable differences that were clinically meaningful were not seen.

Hypothyroidism was a serious adverse event in one patient (0003-01054 in Study AE/ET1) as described above with comments. No patient discontinued treatment due to adverse events related to thyroid parameters.

Treatment Emergent Thyroid Functions Changes in Adult Double-blind with Open-label Extension Subgroup

Mean changes in all parameters were small and were similar to those seen in the double-blind studies (Ref: Sponsor's Appendix I, Table 8.1.1-50). Downward shifts in thyroxine relative to the normal range occurred in 8.0% of the patients, whereas downward shifts in the remaining parameters occurred in <3% of the patients (Ref: Sponsor's Appendix I, Table 8.4.10-5). Upward shifts relative to the normal range occurred in <2% of the patients for all thyroid parameters. Clinically notable increases and decreases in TSH occurred in similar percentages of patients (3.3% and 3.5%, respectively). Clinically notable changes in the remaining thyroid parameters occurred at rates similar to those seen during the double-blind studies (Ref: Sponsor's Appendix I, Table 8.3.1-50). As noted above, hypothyroidism was a serious adverse event in one patient (0003-01054 in Study AE/ET1). No patient discontinued treatment due to adverse events related to thyroid parameters.

Treatment Emergent Thyroid Functions Changes in Mono-therapy Double-blind Subgroup

Thyroxine and TSH were the only thyroid parameters evaluated at both baseline and post-baseline in the mono-therapy substitution studies, and only in Study 016, which did not have a placebo group. There was a mean increase in thyroxine of 133 nmol/L in the rufinamide-treated patients in this population, and a decrease (-0.5 mU/L) in TSH (Ref: Sponsor's Appendix I, Table 8.1.1-35). Fewer than 2% of the rufinamide-treated patients had upward or downward shifts from normal in free thyroxine, thyroxine, or TSH (Ref: Sponsor's Appendix I, Table 8.4.7-5). Clinically notable increases in thyroxine occurred in 1.5% of the patients; no patients had clinically notable decreases. Clinically notable increases in TSH occurred in 0.8% of the patients, and clinically notable decreases occurred in 2.3% (Ref: Sponsor's Appendix I, Table 8.3.1-35).

Treatment Emergent Thyroid Functions Changes in LGS Double-blind Subgroup

Free thyroxine and T₃ were not measured in the LGS study. Hence the value that one could place on the results from a partial thyroid profile analyses was limited.

Mean Changes

Sponsor's Table 8.5-10, ISS, displays mean values for thyroid laboratory parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2 visits. Mean changes in the 2 parameters evaluated in this study were small and were similar in the rufinamide and placebo groups. While the changes were greater for the rufinamide arm compared to the placebo, *meaningful interpretations were limited by the thyroid panel being incomplete and secondly by small sample size.*

Shift Table Changes

The numbers of patients with shifts in thyroid parameters, relative to the normal range, was summarized in Sponsor's Table 8.5-11, ISS, for the double-blind, adjunctive therapy study in LGS. The table showed that the majority of patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation. Eight (10.8%) rufinamide-treated patients and 2 (3.1%) placebo-treated patients had upward shifts from normal baseline TSH to final values during the double-blind Phase which were above the normal range. The corresponding shifts in thyroxine however were greater in the placebo group. *Meaningful interpretations were limited by the thyroid panel being incomplete, the small sample size and mixed results.*

Clinically Notable Changes

As shown in Sponsor's Table 8.5-12, ISS, clinically notable decreases in thyroxine occurred in 3 (5.1%) rufinamide-treated patients and one (1.8%) placebo-treated patients. Clinically notable increases in TSH occurred in 1 (1.7%) rufinamide-treated patient and no placebo-treated patient. There were no other clinically notable values. *Meaningful interpretations were limited by the thyroid panel being incomplete and secondly by small sample size.*

No patient in either treatment group had a serious adverse event related to thyroid parameters, nor did any patient discontinue treatment due to such an event.

Treatment Emergent Thyroid Functions Changes in LGS Double-blind with Open-label Extension Subgroup

Mean change in thyroxine and TSH (the only 2 parameters evaluated in this study) were small and were similar to those seen in the double-blind study (Ref: Sponsor's Appendix I, Table 8.1.1-15). Approximately half of the patients (68 of 131) did not have thyroid parameters measured at both baseline and post-baseline (Ref: Sponsor's Appendix I, Table 8.4.5-5). Eight (5.9%) patients had a shift from normal to above the normal range for TSH, and 1 (0.7%) had an upward shift in thyroxine. Clinically notable decreases in thyroxine occurred in 3 (4.8%) patients, and clinically notable increases in TSH occurred in 1 (1.6%) patient. There were no other clinically notable values (Ref: Sponsor's Appendix I, Table 8.3.1-15). No patient had a serious adverse event related to thyroid parameters, nor did any patient discontinue treatment due to such an event.

Treatment Emergent Thyroid Functions Changes in Pediatric Double-blind Subgroup

T₃ was not measured in the pediatric studies.

Mean Changes

Sponsor's Table 8.5-13, ISS, displayed mean values for thyroid laboratory parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2 visits. According to the sponsor, median values and ranges were shown for thyroxine, because inclusion of data that were clearly in error made it impossible to interpret the mean values correctly otherwise. The median change in thyroxine was larger in the rufinamide group (5.8 nmol/L) than in the placebo group (0.0 nmol/L). Mean changes in TSH were small and were similar in the 2 groups.

Shift Table Changes

The numbers of patients with shifts in thyroid parameters, relative to the normal range, was summarized in Sponsor's Table 8.5-14, ISS for the double-blind studies in pediatric patients. A majority of the patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation. Downward shifts in thyroxine occurred in 6.6% of the rufinamide-treated patients and 5.6% of the placebo-treated patients; upward shifts occurred in 0.9% and 0.5%, respectively. Downward shifts in TSH occurred in 0% of the rufinamide-treated patients and 0.5% of the placebo-treated patients; upward shifts occurred in 7.5% and 3.0%, respectively. These greater shifts with rufinamide, from normal TSH baseline to post TSH high and normal thyroxine and free thyroxine at baseline to post low thyroxine (free and total) values compared to placebo, *were clinically meaningful in these pediatric double-blind subgroup.*

Reviewer comments

See label recommendation above under all double-blind subgroup and section 9.4 label review.

Clinically Notable Changes

As shown in Sponsor's Table 8.5-15, ISS, the results were similar for rufinamide and placebo. Specifically, 5 (3.2%) rufinamide-treated patients and 3 (2.1%) placebo-treated patients had clinically notable increases in TSH and 4 rufinamide (2.4%) and 1 placebo-treated patient (0.6%) had clinically notable decreases in thyroxine (total). *These results in clinically notable changes in the pediatric double-blind subgroup coupled with those noted in the shifts were additionally, clinically meaningful.*

Hypothyroidism or primary hypothyroidism was an adverse event in one (0.5%) rufinamide-treated patient and one (0.5%) placebo-treated patient in this population. Neither of these were serious adverse events or adverse events leading to discontinuation of treatment.

Reviewer Comments

See label recommendation above under all double-blind subgroup.

Treatment Emergent Thyroid Functions Changes in Pediatric Double-blind with Open-label Extension Subgroup

Mean changes in free thyroxine, thyroxine, and TSH were small and were similar to those seen in the double-blind studies (Ref: Sponsor's Appendix I, Table 8.1.1-20). Approximately half of the patients did not have thyroid parameters measured at both baseline and post-baseline. Of those who did, 16 (4.1%) had upward shifts in TSH and 2 (0.5%) had upward shifts in thyroxine (Ref: Sponsor's Appendix I, Table 8.4.4-5). The incidences of clinically notable values were similar to those seen in the double-blind studies (Ref: Sponsor's Appendix I, Table 8.3.1-20). No patient had a serious adverse event related to thyroid parameters, nor did any patient discontinue treatment due to such an event.

Treatment Emergent Thyroid Functions Changes in Diabetic neuropathy and Healthy Volunteer Subgroup

Diabetic neuropathy Subgroup

Descriptive statistics showed that mean changes in laboratory parameters were similar in rufinamide- and placebo-treated patients in Study 0201. Comparable percentages of patients in the two groups had clinically notable values for laboratory parameters and shifts from within to outside the normal ranges. Sponsor's Appendix I, Tables 8.1.1-36 to 8.1.1-40 (mean values), 8.3.1-36 to 8.3.1-40 (clinically notable values), and 8.4.8-1 to 8.4.8-5 (shift tables) reflected these changes.

Healthy Volunteer Subgroup

There were no notable changes in laboratory parameters in any of the studies in healthy volunteers (Ref: Sponsor's Appendix I, Tables 8.1.1-51, 8.3.1-51, and 8.4.11-1). No subjects discontinued study drug due to laboratory abnormalities (Ref: Sponsor's Appendix I, Table 7.4.2-5).

TREATMENT EMERGENT CARDIAC (QTC/ECG) FINDINGS

The primary findings of concern stemmed from the thorough QT studies that revealed a QT shortening with rufinamide that was noted at all doses starting at the lowest dose and that further shortened with increasing doses. The methods, analyses and results were discussed by Dr. Lisa Jones (safety team). Because QT shortening, like QT prolongation, can lead to serious cardiac fatal arrhythmias and that rufinamide is the first anticonvulsant to carry this trait, discussions on the general understanding (Ref: <http://ghr.nlm.nih.gov/gene=kcnq1>; <http://ghr.nlm.nih.gov/gene=kcnh2>) of QT shortening and its impact will ensue under the premise that QT shortening with rufinamide is an established finding.

QT changes are typically related to potassium voltage-gated channels and the KCNQ1 genes and or the KCNH2 genes regulate these channels. KCNQ1 is also known by other names such as ATRF1, IKs producing slow voltage-gated potassium channel alpha subunit KvLQT1, KCNA8, KCNA9, KCNQ1_HUMAN, KQT-like 1, Kv1.9, Kv7.1, KVLQT1, and LQT1. KCNH2 (subfamily H [eag-related], member 2) is also known by other names such as Eag related protein 1, ERG1, Ether-a-go-go related gene potassium channel 1, HERG, HERG1, human ether a-go-go-related gene, KCNH2_HUMAN, Kv11.1, and LQT2.

The KCNQ1 and KCNH2 genes belong to a large family of genes that provide instructions for making potassium channels, transport positively charged potassium atoms (ions) into and out of cells and play a key role in a cell's ability to generate and transmit electrical signals. In cardiac muscle, the channels are involved in recharging the muscle after each contraction to maintain a regular heartbeat.

Mutations in the KCNQ1 or the KCNH2 gene results in the production of short and nonfunctional versions of the respective proteins which cannot be used to build potassium channels. Other mutations alter a small number of protein building blocks (amino acids) which alters the normal structure and function of the channels. More than 140 disorder-causing mutations have been identified with KCNH2.

Depending on the affected organ/site at which there is altered potassium channel disorder, and the types of mutation, several clinical syndromes are described, amongst which is the short QT syndrome. An inability of cells in the inner ear and cardiac muscle to properly transport potassium ions leads to the hearing loss and abnormal heart rhythm (arrhythmia) found in Jervell and Lange-Nielsen syndrome. In another disorder, such disruption in the flow of potassium ions in cardiac muscle results in the irregular heartbeat, risk of fainting (syncope) and sudden death characteristic of Romano-Ward syndrome. Mutations in the KCNH2 gene are thought to be the second most common cause (after mutations in the KCNQ1 gene) of Romano-Ward syndrome. Other mutations in the KCNQ1 gene are responsible for several other heart rhythm abnormalities that include familial atrial fibrillation, short QT syndrome, sudden infant death syndrome (SIDS), and acquired long QT syndrome.

In familial atrial fibrillation, stroke and sudden death can occur due to increase the flow of potassium ions through the channel formed by the KCNQ1 protein.

Short QT syndrome is characterized by an abnormal heart rhythm that increases the risk of cardiac arrest and sudden death. The identified mutation changes a single amino acid in the KCNQ1 protein. Specifically, it replaces the amino acid valine with the amino acid leucine at protein position 307 (written as Val307Leu or V307L). This change disrupts the usual function of ion channels made with the KCNQ1 protein, increasing the channels' activity. By allowing more potassium ions to flow out of cardiac muscle cells, the V307L mutation is likely responsible for the changes in heart rhythm often found in short QT syndrome.

Likewise, mutations in the KCNH2 gene are also associated with short QT syndrome. In a small number of families with short QT syndrome, researchers have identified a mutation that replaces the amino acid asparagine with the amino acid lysine at position 588 of the KCNH2 protein (written as Asn588Lys or N588K). This switch in amino acids disrupts the usual function of ion channels made with the KCNH2 protein, increasing the channels' activity. By allowing more potassium ions to flow out of cardiac muscle cells, the N588K mutation is likely responsible for the changes in heart rhythm often found in short QT syndrome.

Certain drugs, including medications used to treat arrhythmias, infections, seizures, and psychotic disorders, can lead to a drug-induced long QT known as acquired long QT syndrome. A small percentage of cases of acquired long QT syndrome occur in people who have an underlying mutation in the KCNQ1 or the KCNH2 gene.

The exact mechanism of how rufinamide causes QT shortening is unknown. The risks associated with QT shortening (risks are essentially similar to those associated with QT

prolongation) such as fatal cardiac arrhythmias or AE suggestive of serious cardiac events were not seen in the rufinamide clinical trials. Although QT shortening is probably not directly related to the sodium ion channels, it is conceivable that perhaps the hitherto approved sodium ion channel anticonvulsants, if formally tested via a TQT study (Thorough QT study), may also exhibit QT shortening via the same and hitherto unknown mechanism as rufinamide. While such speculation appears to tone-down the QT shortening characteristic that seems to be unique to rufinamide, the concerns of the greater cardiac risks in people who have underlying mutations for potassium ion channels is only further amplified, particularly if such congenital QT abnormalities are associated with seizures.

As noted in the literature, cases of congenital long QT syndrome are associated with seizures both in children and adults (childhood- C. A. Horn, R. H. Beekman, M. Dick 2nd and S. J. Lacina, <http://archpedi.ama-assn.org/cgi/content/abstract/140/7/659>; Seizures and the Long-QT Syndrome- Annals of Emergency Medicine, Volume 28, Issue 5, Pages 556-560 M. Bell, R. Kozak; adults - D P J Hunt and K Tang, <http://emj.bmjournals.com/cgi>). Both syndromes described above, viz., Jervell and Lange-Nielsen syndrome and Romano-Ward syndrome are also associated with seizures (Sundaram MB, McMeekin JD, Gulamhusein S.Can J Neurol Sci. 1986 Aug;13(3):262-3) in which both short QT and long QT are seen.

Short and long QT are similar from the perspective that they seem to be genotypically (although the location for KCNQ1 is chromosome 11p15.5 and for KCNH2 it is 7q35-q36) and phenotypically comparable in that ultimately in both, altered genetics affect the potassium channels and both present with similar features within the spectrum of which are cardiac arrhythmias. Similar syndromes are caused by these genes and their phenotypic expressions are also similar. Within this spectrum, both QT shortening and prolongation have been identified. Therefore, such co-existence of congenital QT abnormalities (whether QT is prolonged or shortened) and seizures raises a different level of concern when one considers treating such seizures with a drug like rufinamide that can further affect QT.

These issues need further discussions with the sponsor. *Although premature, eventually, a warning in the label about short QT and rufinamide and the risks in patients with congenital QT abnormalities should be provided. An ECG prior to initiation with rufinamide to exclude QT abnormalities is recommended and needs to be included in the label.* See risk-benefit below.

Treatment emergent findings in relation to Vital Signs, Physical Examination, Tolerance, Abuse and Dependence, Effects of Withdrawal and Rebound and Drug Overdose are discussed in the respective sections in the review.

C) RISK-BENEFIT ASSESSMENTS

Epilepsy is a serious medical condition that presently has several choices of approved therapies (drugs and others) in its armamentarium as options. While chemically, rufinamide claims uniqueness, mechanistically it is similar to one of the several approved sodium ion channel targeting drugs. The specific indication that the sponsor seeks to market rufinamide for is neither unique nor is an unmet medical need. The benefit that rufinamide can provide is yet to be established.

Independent of the lack of established benefit or the lack of uniqueness with respect to the claim or the intended population or the benefit that rufinamide can offer over the currently available treatments, as noted, there were safety findings of concern rendering rufinamide a safety profile

that requires further considerations. These findings of concern were sudden deaths, CNS/Neuropsychiatric AE, Rash and hypersensitivity reactions, status epilepticus, laboratory changes related to TFTs, leucopenia and neutropenia, thrombocytopenia, hyperthermia, vomiting, and QT shortening. Further, while it was not possible to determine whether rufinamide was directly responsible for some of the noted events, its involvement by virtue of association could not be excluded. It should be noted that for some of approved agents, as indicated in the respective labels, some events were considered significant by virtue of just an association, e.g., hyperthermia. Given the overall comparability between rufinamide and some of the approved agents in relation to the mechanism of action, sought indication, intended population, etc., the question was if the safety profile of rufinamide (based on the observed findings or via association) was different and or riskier than the approved drugs.

As indicated in the respective sections, the rufinamide safety findings of concern were compared to several approved agents to determine the extent of comparability in the safety profiles. Table 1.3.3.B identifies these major safety findings of concern and provides a comparative overview of the safety profile by comparing rufinamide with the others as a group for the same adverse event (s). It is clear from Table 1.3.3.B that rufinamide generally appears to be qualitatively and quantitatively (frequency not shown in this table—see respective sections and frequency information was not always available) similar with respect to all but one of the listed findings, namely, QT shortening.

SAFETY TABLE 1.3.3.B OVERVIEW OF MAJOR AEs COMPARED			
Safety Finding	Rufinamide	Others ^{A B}	Comments
SUDEP	x	x	See Table 7.1.1.D
CNS/Neuropsychiatric Spectrum	x	x	See note below
Rash	x	x	See Table 7.1.3.3.B
Hypersensitivity Reaction	x	x	
Status Epilepticus	x	x	See Table 7.1.3.3.C
Lab ^C	x	x	See note below
Hyperthermia	x	x	See note below
Hematology ^D	x	x	See note below
QT Shortening	x	No ^E	See review
Ref: PDR 2006, Tables 7.1.1.D, 7.1.3.3.B, 7.1.3.3.C			
Note:			
A = Others include one or more approved drugs. Not all drugs caused each of the listed events.			
B = Finding listed as Warning (W) or Precaution (P).			
C = May involve hyponatremia and or LFT changes and or TFT changes.			
D = May involve anemia and or leucopenia and or neutropenia and or thrombocytopenia.			
E = PR prolongation in Lyrica			
CNS/Neuropsychiatric = Trileptal (P), Valproic Acid (W), Zonegran (W), Gabitril (W), Neurontin (W), Lyrica (P), Keppra (W), Topamax (W),			
Lab = Trileptal (W), Tegretol (P), Topamax (W)			
Hyperthermia = Zonegran (W), Topamax (W)			
Hematology = Valproic acid (W), Zonegran (W), Lamictal (W), Tegretol (P), Keppra (P)			

None of the approved agents cause QT shortening. The exact mechanism of how rufinamide causes QT shortening is unknown. Although QT shortening is probably not directly related to the sodium ion channels, it is conceivable that perhaps the hitherto approved sodium ion channel anticonvulsants, if formally tested via a TQT study (Thorough QT study), may also exhibit QT shortening via the same and hitherto unknown mechanism as rufinamide. While such

speculation appears to tone-down the QT shortening characteristic that seems to be unique to rufinamide, the concerns of the greater cardiac risks in people who have underlying mutations for potassium ion channels is only further amplified, particularly if such congenital QT abnormalities are associated with seizures.

Short and long QT are similar from the perspective that they seem to be genotypically (although the location for KCNQ1 is chromosome 11p15.5 and for KCNH2 it is 7q35-q36) and phenotypically comparable in that, in both, altered genetics ultimately affect the potassium channels and both present with similar features within the spectrum of which are cardiac arrhythmias. Similar syndromes are caused by these genes and their phenotypic expressions are also similar. Within this spectrum, both QT shortening and prolongation have been identified. Therefore, such co-existence of congenital QT abnormalities (whether QT is prolonged or shortened) and seizures raises a different level of concern when one considers treating such seizures with a drug like rufinamide that can potentially further affect QT.

The pro-arrhythmic risks associated with QT shortening (risks are essentially similar to those associated with QT prolongation) such as fatal cardiac arrhythmias or AE suggestive of serious cardiac events were not seen in the rufinamide clinical trials. Therefore, if QT shortening can be considered a potential risk only in certain predisposed patients such as those with congenital underlying potassium channel abnormalities (who may have prolonged or shortened baseline QT) or others at risk (those on other QT affecting drugs), then it is conceivable that with appropriate history and ECG screening prior to rufinamide administration, one can exclude the exposure of such high risk population. Although premature, the concerns and the risks of QT shortening that is unique to rufinamide within its class can potentially be addressed in the label with appropriate warning and the need for screening to exclude baseline QT changes in certain predisposed populations.

V. CONCLUSIONS

While the overall exposure, safety monitoring and assessments in the adults were broadly adequate, assessments in the adolescent population and patients of African / Black and Hispanic /Latino races were limited. The sought indication in the adolescent population is therefore not justified. The risks and benefits in the African and Hispanic races have not been adequately evaluated.

The salient findings following exposure to rufinamide were related to the sudden deaths, rash, hypersensitivity, hyperthermia, CNS/neuropsychiatric, lab abnormalities, status epilepticus, and QT shortening. The various results discussed through out the review characterized these salient findings. All these adverse events (except QT shortening) that were qualitatively similar to the other approved agents (as noted in their respective package inserts) appeared to occur at a frequency that was estimated to be comparable to the approved agents (as shown in Table 1.3.3.B). Sometimes depending on the event and the extent of information presented such frequency estimates were either not available or were indeterminable to make a head to head comparison of the safety profile of rufinamide with other approved agents. However, overall, there was comparability in safety profiles between the approved class agents and rufinamide, except for the occurrence of QT shortening.

Rufinamide is the first antiepileptic with documented evidence to show that it shortens QT. The cardiac risks that are known to occur with QT shortening that are similar to those that occur with

1.3.5 Drug-Drug Interactions

See Section 8.2.

1.3.6 Special Populations

See Section 8.3.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Rufinamide) is a triazole derivative structurally unrelated to currently marketed antiepileptic drugs (AEDs). Rufinamide has the chemical name 1-[(2,6-difluorophenyl)methyl]-1*H*-1,2,3-triazole-4 carboxamide. It has an empirical formula of C₁₀H₈F₂N₄O and a molecular weight of 238.2. The drug substance is a white, crystalline, odorless and slightly bitter tasting neutral powder. Rufinamide is practically insoluble in water, slightly soluble in tetrahydrofuran and in methanol, and very slightly soluble in ethanol and in acetonitrile. The drug is available for oral administration in film-coated tablets containing 100, 200, and 400 mg of rufinamide.

2.2 Currently Available Treatment for Indications

There are several drugs approved for treatment in the US for the same indications. Reference to some of these drugs is made in this safety review in some sections (such as SUDEP death rate comparison, Rash/Hypersensitivity comparisons, CNS/Neuropsychiatric AE comparisons, etc.)

2.3 Availability of Proposed Active Ingredient in the United States

Not marketed in the US.

2.4 Important Issues With Pharmacologically Related Products

Those that are safety related such as CNS/Neurocognitive effects, Rash and Hypersensitivity Reactions, Sudden Deaths (SUDEP), Hyperthermia, etc. are discussed in the respective sections.

2.5 Presubmission Regulatory Activity

Regulatory Milestones Related to Safety

Rufinamide, an anticonvulsant, under NDA 021911 was resubmitted on November 17, 2005. It was initially submitted on September 8, 2005 and later withdrawn on November 2, 2005. According to the sponsor, since the original September 2005 submission did not contain electronic tumor frequency datasets for carcinogenicity studies, a refusal to file action by the

Agency was imminent. Subsequently, the sponsor re-submitted the NDA with the necessary information.

On March 13, 2006, the sponsor submitted a 4-month safety update.

On May 23, 2006, the sponsor submitted an amendment with request for a new name _____ since the previously proposed name of Inovelon was found unacceptable by the Agency (Division of Medication Errors and Technical Support identified a potential concern for _____)

b(4)

On June 23, 2006, the sponsor submitted a 95 page safety amendment document that provided corrections to the previously submitted numbers on AE and SAE. An amendment to the June 23, 2006 submission was made on August 17, 2006 further correcting these numbers.

The sponsor has formally submitted a request for deferral of pediatric studies for ages 0-4 years _____

b(4)

Rufinamide, according to the sponsor (Clinical overview, Module 2, 2.5.5.4, p. 78), is not marketed (registered) elsewhere and hence there is no post-marketing experience or post-market data.

According to the sponsor, Rufinamide was granted orphan designation on 8 October 2004 for the treatment of LGS.

2.6 Other Relevant Background Information

Drug Development

Rufinamide [1-(2,6-difluoro-phenyl)methyl-1H-1,2,3-triazole-4-carboxamide] is a triazole derivative, that according to the sponsor, is structurally unrelated to currently marketed AEDs. According to the sponsor, Rufinamide was profiled for anticonvulsant activity at the National Institutes of Health (NIH, Rockville, USA) and at Novartis. Based on in vitro studies, it was noted that rufinamide limited the frequency of firing of sodium-dependent action potentials in rat neurons, an effect that could contribute to blocking the spread of seizure activity from an epileptogenic focus. Further, the compound did not significantly interact with a number of neurotransmitter systems, including gamma-aminobutyric acid, benzodiazepine, monoaminergic and cholinergic binding sites, N-methyl-D-aspartate, and other excitatory amino acid binding sites (Module 2.6.2, Pharmacology Written Summary).

Ciba-Geigy in Europe initiated the earliest clinical studies with rufinamide, known at that time by the product name CGP 33101. Novartis, formed from the merger of Ciba-Geigy and Sandoz, continued the global development, using the product name RUF 331. Eisai Company, Ltd. acquired the rights to rufinamide from Novartis on 6 February 2004. Since that time, Eisai has been managing the development program.

The submitted data is meant to support Eisai's application for approval to market rufinamide film-coated tablets (100, 200, and 400 mg), under the trade name _____ (initially proposed trade name was INOVELON®), as adjunctive treatment of partial seizures in adults and of seizures associated with LGS. Eight double-blind, controlled studies were initiated to evaluate the safety and efficacy of rufinamide in epilepsy-related indications, including 1 study (021)

b(4)

summarized in 2 reports, 1 for the adult patients (021A) and 1 for the pediatric patients (021P). Seven studies were completed, and 1 (Study 039) was terminated early due to lack of enrollment after 22 months of attempted enrollment. The aims of the development and the respective studies that are ultimately meant to support the sought indication are as follows-

- As adjunctive therapy in adults with refractory partial seizures (Studies AE/PT2, AE/ET1 and 021A),
- As adjunctive therapy in children and adults with LGS (Study 022),
- As adjunctive therapy in children with refractory partial seizures (Study 021P),
- As adjunctive therapy in adults and children with primary generalized tonic clonic (PGTC) seizures (Study 018), and
- As substitution mono-therapy or mono-therapy for partial seizures in adults and adolescents (Studies 016 and 038).

According to the sponsor, all studies initiated after 1995 were conducted in accordance with the principles of GCP. Since January 1997, all studies were in compliance with ICH guidelines on GCP (CPMP/ICH/135/95). Studies initiated prior to the effective date of GCP regulations were conducted in accordance with the relevant standards at the time.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Only those issues relevant to the clinical safety assessments are discussed. Overall, no significant unique preclinical issues that were identified generated concern in the clinical assessments. These are discussed below and references to these are made throughout the review.

3.1 CMC (and Product Microbiology, if Applicable)

Drug Formulations

During rufinamide clinical development, several oral formulations of rufinamide were evaluated in healthy subjects and in patients. These different formulations that were used throughout the clinical studies are presented in Table 3.1.A

Tablets strengths of 1mg and 10 mg were produced by _____ and were used in an initial safety and tolerability study (study A184). Tablet strengths 50, 100 and 200 mg were produced _____, referred to as the Clinical Service Form (CSF). These tablets were used in approximately half the clinical studies in healthy subjects and in three efficacy and safety studies in patients (See Table 3, Module 2, Section 7.1), at doses of up to 3200 mg per day in two equally divided administrations. Later, when higher tablet strength was needed (400 mg), the process _____ referred to as the Final Market Image (FMI). The FMI tablet had a different composition to the CSF tablet and is the formulation to be marketed. The FMI tablet is film coated _____ FMI tablet strengths of 100, 200 and 400 mg have been used in all the remaining clinical pharmacology studies (Sponsor's Table 3, Module 2, Section 7.1) and in 5 clinical and efficacy studies in patients with epilepsy.

b(4)

According to the sponsor, population modeling with data pooled across 7 Phase 2 and 3 studies (involving 1072 subjects), including trials with both FMI and CSF formulations, was used to examine the effect of dose on bioavailability and to compare the bioavailabilities of the 2 formulations.

An increased incidence of thyroid follicular adenomas was noted at dosages ≥ 60 mg/kg in the rat carcinogenicity study. This was accompanied by liver hypertrophy in males at ≥ 60 mg/kg and in females at 200 mg/kg. This effect, according to the sponsor, is species specific.

A raised incidence of benign and malignant liver tumors at 400 mg/kg in the mouse carcinogenicity study was noted. According to the sponsor, this was not unexpected since rufinamide is an enzyme inducer in rodents, like phenobarbital, and liver hypertrophy had already been noted. However, it is known that the mouse liver is sensitive to such enzyme-inducing agents.

There was also an increased incidence of benign bone tumors (osteomas) at 400 mg/kg in this carcinogenicity study. An additional investigative study in mice showed dose-related increases in concentrations of fluoride in the urine after per-oral administration of rufinamide for 14 days. Thus, the pathogenesis of this change was considered to involve the release of fluoride from rufinamide during the process of oxidative metabolism, which in turn activated a retrovirus present in the mice as part of their background pathology. This effect was also considered to be species specific by the sponsor.

Mutagenicity

According to the sponsor, bacterial reverse mutation assays, a mammalian cell point mutation assay and a chromosome aberration study were all negative in vitro. In vivo studies were performed in which three different end-points were assessed using bone marrow. Studies assessing nuclear anomalies and sister chromatid exchanges were both negative, as was a rat micronucleus study. Therefore, it was concluded that rufinamide showed no mutagenic, clastogenic or aneugenic potential.

Impairment of Fertility

According to the sponsor, there was no evidence of impairment of fertility in rats that were given oral doses of rufinamide up to 150 mg/kg (0.5 times the maximum recommended daily human dose on a mg/m² basis).

Pregnancy (Pregnancy Category C)

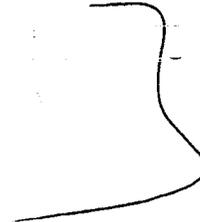
According to the sponsor rufinamide showed no evidence of teratogenicity at doses up to 300 mg/kg in rats (approximately the maximum recommended daily human dose on a mg/m² basis) and 700 mg/kg in rabbits (4 times the maximum recommended daily human dose on a mg/m² basis).

In the rat embryo-fetal development study at oral doses of 20, 100 and 300 mg/kg, effects on fetal weights and skeletal variations due to growth retardation were observed at the higher doses. These findings were accompanied by maternal toxicity. In the rabbit embryo-fetal development study at oral doses of 30, 200 and 700 mg/kg, similar findings were seen with increased incidences of skeletal variations accompanied by reductions in fetal weights and maternal toxicity at the higher doses.

In the fertility and reproductive toxicity study in rats at oral doses of 15, 50 and 150 mg/kg, reduced pup survival was observed at the higher doses, and increased post-implantation losses and stillbirths were observed at 150 mg/kg.

Peri- and post-natal development studies were performed at oral doses of 50, 150 and 500 mg/kg in mice and 15, 50 and 150 mg/kg in rats. In mice, there were no adverse effects on dams or F₁ pups at any dose. In rats, however, decreased F₁ pup survival during Days 0 to 4 of lactation was observed in the treatment groups, along with maternal toxicity in the form of reduced body weights. A follow-up cross-fostering study revealed that pup mortality was due to an in utero effect of rufinamide during late gestation. Another cross-fostering study suggested that the effects on fetuses in utero were secondary to maternal physiological changes induced by rufinamide toxicity.

There were no adequate and well-controlled studies in pregnant women. Based on these findings of embryo-fetal toxicity at doses associated with maternal toxicity, the proposed label classifies the drug as Pregnancy Category C with the following language- "Rufinamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus". In addition, the sponsor has made the following notation -



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For purposes of comprehensiveness, the following information on pregnancy is additionally presented (Ref: Sec 15, ISS).

The clinical protocols for the rufinamide clinical studies required that female participants of childbearing potential be using an acceptable method of contraception upon study entry and continue to use acceptable contraception throughout the course of the study. Oral contraceptives/hormonal contraceptive techniques were not considered acceptable methods of contraception. Study treatment was to be discontinued immediately if a woman became pregnant.

Thirteen pregnancies occurred during the clinical studies (Sponsor's Table 15.1-1, ISS). All pregnancies occurred in patients who were receiving rufinamide. Ten of the pregnancies occurred during open-label extensions, 1 occurred during the open-label, compassionate use study (Study 2301), and 2 occurred in patients who were receiving rufinamide during double-blind studies. The duration of rufinamide treatment in these 13 patients ranged from 3 days to 5.6 years. Six of the 13 pregnancies were known to have resulted in the birth of 6 healthy babies (normal progeny). One pregnancy was ended by a spontaneous abortion and 3 by elective abortions. According to the sponsor, no information was provided to the sponsor about the outcome of the remaining 3 pregnancies.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The summarized safety results in this NDA stemmed from all patients who received at least one dose of study treatment in the studies shown in Appendix Table 1.

The Integrated Summary of Safety (ISS) presented in this NDA included data from 20 studies in 1978 patients (adults and pediatrics combined- see Tables 7.2.1.1.A-C) with epilepsy who were exposed to Rufinamide. These studies included data from 8 controlled studies in patients with epilepsy (including one study—Study 021—which was summarized in 2 reports, 1 for the adult patients and 1 for the pediatric patients); 2 open-label studies in patients with epilepsy; and 2 controlled pharmacokinetic studies in patients with epilepsy. Eight of the studies, including the adult (021A) and pediatric (021P) parts of Study 021, had open-label extension phases in which long-term safety data were collected. Also included in this summary were safety results that were presented separately from the results in patients with epilepsy. This included data from the only study in a non-epilepsy indication (diabetic neuropathy), 22 biopharmaceutic / pharmacokinetic studies performed in healthy volunteers, and 2 studies (1 with an extension) performed in Japan for which only translated study reports were available.

The database lock date for the integrated safety data presented in this submission was February 1, 2005. There were 2 ongoing studies at that time: Study 2301, which was a compassionate-use trial for patients who wished to continue receiving rufinamide after another study was terminated, and Study E2080-A001-002, which was a definitive QT study in healthy volunteers. Data from 70 patients from Study 2301 were integrated in the ISS database. Data from 7 additional patients were not integrated. Two ongoing patients and 1 discontinued patient had no safety data from Study 2301 in-house as of the database lock date, and 4 patients had Case Report Forms (CRFs) undergoing querying. None of these patients died or had a serious adverse event as of the database lock date. Safety information for these patients was included in the 120-day update of the ISS. Study E2080-A001-002 was completed in May 2005 and was not integrated because the database for the study was not locked until June 2005. The Clinical Study Report (CSR) for Study E2080-A001-002 was included in this NDA and according to the sponsor, contained complete safety information for the study.

It should be noted that the clinical development in this drug program began as early as 1989.

Safety Information from Ongoing study (s) and from studies conducted in Japan was additionally presented. In addition, reference was made to the literature where 16 rufinamide articles were identified. These are discussed under section 8.6 (literature) and section 8.8 (other relevant materials) of this review.

Safety data that were summarized for the populations in safety assessments are shown and discussed in section 7.2.1

Reviewer Comments

The dates of trial beginning and ending for the referenced 1978 patients were not provided in the submission. Sponsor's Table 1.2-1 provided enrollment dates for all the studies listed. In a separate e-mail correspondence (Aug 25, 2006), this reviewer requested this information from the sponsor. The sponsor responded by referencing to the enrolment dates in Table 1.2-1.

4.2 Tables of Clinical Studies

The tabular listing of All Clinical Studies was presented in Module 5, section 5.2 of the submission and those that contributed to the integrated safety database that was presented in

Sponsor's Table 1.2-1 of the submission is attached in the appendix section of this review (Appendix Table 1).

4.3 Review Strategy

Approach and Strategy for Safety Review

This safety review addresses information that was submitted for review under NDA 021911 from the time of the filing date of November 17, 2005 through September 2006.

The safety analyses population (N=1978 unique rufinamide patients) were broken down into various subgroups by the sponsor and integrated. These subgroups were all double-blind studies, all studies combined, adult double-blind studies, adult double-blind with open-label extensions studies, mono-therapy double-blind studies (there were no open label mono-therapy studies), LGS double-blind study (s), LGS double-blind with open-label extension study (s), pediatric double-blind studies and pediatric double-blind with open label extension studies. These were further broadly identified into double-blind studies and double-blind studies with open-label extensions (if these were conducted) and by population (adult vs. pediatric). While the safety of the entire 1978 rufinamide patients was evaluated, emphasis was placed on those double-blind studies that would support the sought indication, viz., double-blind adjuvant partial seizure studies in adolescents (defined as ages 12 to < 16 years) and adults (defined as ages ≥ 16 years) and double-blind LGS study (S) in pediatrics (defined as ages > 4 years to < 16 years) and adults. Hence, some of the submitted tables that did not contain placebo treatment information (either all subgroups combined or open-label extensions) were not included in the appendix section of the review. The latter LGS indication, in essence, was supported by a single LGS double-blind study. Although the support for the sought indications could potentially originate only from a subset of the subgroups, because all subgroups contributed to the 1978 safety denominator, all subgroups were reviewed. In essence, data from the mono-therapy and pediatric studies did not contribute towards efficacy determinations.

5 . Re-formatting of the AE tables to support the sought indications in the intended populations was attempted during the review cycle. This required several interactions with the sponsor. This additionally required re-configuration of the number and demographics of patients that were adults, pediatrics and adolescents. 3

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The complexities in the regulatory drug development of rufinamide influenced the approach to the review. Several companies were involved in its development and the studies that contributed to the data submitted for review were conducted many years ago, starting as early as 1989, and many studies were performed outside the US. Based on the interactions with the sponsor during the review cycle when clarifications were sought, it was apparent that some of the discrepancies and lapses in information were either due to the complex changing of ownership and or the standards and conditions that existed at the time when the trials were conducted particularly those that were outside the US. Some of these lapses, such as the lack of standardization of lab values, availability of lab data (description of a dark urine without further characterization or lab tests- ? hematuria, myoglobinuria, bilirubinuria, etc.), the lack of information on the basis for a diagnosis (e.g., SAE of hyponatremia without lab values), were beyond the sponsor's remediable authority. Therefore, allowances for these lapses needed to be made and some of the

interpretations that were made were based on such experiences that additional information may not be available even to the sponsor from the remote centers. Of course, with the fixing of these lapses, there may have been more clarity to the interpretation of the results, but its absence did not influence the conclusion or the recommendation. These lapses were additionally those that could be addressed in the label.

Additional safety analyses and explorations were required in the assessments involving risk-benefits and the exhibited safety profile of rufinamide particularly for some AE such as Status epilepticus, CNS/Neuropsychiatric, Rash and hypersensitivity, SUDEP, hyperthermia, hyponatremia, etc. Both qualitative and quantitative comparisons to the approved drugs were performed by this reviewer. This was achieved via reviewing the labels for the approved agents and comparing these AEs to rufinamide. See 7.1.9.4.

4.4 Data Quality and Integrity

See 4.3 review strategy for comments on safety data quality and integrity.

4.5 Compliance with Good Clinical Practices

4.6 Financial Disclosures

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Description

Rufinamide) is a triazole derivative structurally unrelated to currently marketed antiepileptic drugs (AEDs). Rufinamide has the chemical name 1-[(2,6-difluorophenyl)methyl]-1*H*-1,2,3-triazole-4 carboxamide. It has an empirical formula of $C_{10}H_8F_2N_4O$ and a molecular weight of 238.2. The drug substance is a white, crystalline, odorless and slightly bitter tasting neutral powder. Rufinamide is practically insoluble in water, slightly soluble in tetrahydrofuran and in methanol, and very slightly soluble in ethanol and in acetonitrile. The drug is available for oral administration in film-coated tablets containing 100, 200, and 400 mg of rufinamide.

Mechanism of Action

The precise mechanism(s) by which rufinamide exerts its antiepileptic effect is unknown. Based on in vitro studies, it was noted that rufinamide limited the frequency of firing of sodium-dependent action potentials in rat neurons, an effect that could contribute to blocking the spread of seizure activity from an epileptogenic focus. The anti-epileptic effect of rufinamide was assessed in several animal models of generalized and partial seizures. These suggested that rufinamide exhibited broad-spectrum anti-convulsant properties.

Rufinamide is well absorbed after oral administration. However, the rate of absorption is relatively slow and the extent of absorption is decreased as dose is increased. The pharmacokinetics does not change with multiple dosing. There is moderate inter-subject variability. The extent of bioavailability of rufinamide is modestly affected by food when comparing exposure after single doses under fed and fasted conditions. However, there is no

effect of food upon repeat dosing. Rufinamide has low protein binding (approximately 34%) and its volume of distribution is in the order of total body water (50-80 L). Most elimination of rufinamide is via metabolism, with the primary metabolite resulting from enzymatic hydrolysis of the carboxamide moiety to form the carboxylic acid. This metabolic route is not cytochrome P450 dependent. The metabolite has no known pharmacological activity and is primarily renally excreted. The renal excretion of unchanged rufinamide accounts for less than 2% of the dose. Plasma half-life of rufinamide is approximately 6-10 hours. Half-life is unaffected by renal impairment and does not change notably with age. Rufinamide has minor drug-drug interactions with some other antiepileptic agents. Rufinamide may increase phenytoin levels by up to 21% but effects on other AEDs are minimal. Valproate co-administration may lead to elevation in rufinamide plasma levels, especially in children.

Single-dose studies: The onset of absorption of rufinamide was rapid, with a median time to reach peak concentrations of rufinamide varying between 4 and 6 hours both under fed and fasted conditions. In general, peak concentration (C_{max}) and plasma AUC of rufinamide increased less than proportionally with doses in both fasted and fed healthy subjects. This was probably related to dose-limited absorption due to the limited solubility of rufinamide.

A radiotracer study in three healthy male fed volunteers showed that, based on urinary excretion of radioactivity, the extent of absorption was at least 85% following oral administration of 600 mg rufinamide. The extent of absorption varies with the dose administered. INOVELON[®] tablets display decreasing bioavailability with increasing dose, both when administered as a single dose and on repeated dosing, in healthy subjects and in patients.

Food increased the extent of absorption of rufinamide in healthy volunteers by 34% and peak exposure (56%) after single doses. The time to reach peak concentration (T_{max}) was not significantly affected by food intake. Food had no other significant effect on the pharmacokinetics on rufinamide.

Multiple-dose studies: The disposition of rufinamide was linear and was not affected by multiple oral-dose administration in healthy volunteers or patients. Values of plasma AUC after single dosing (Day 0) and at steady state (Day 28) were comparable and plasma elimination half-lives were the same being slightly over 10 hours. The data confirmed the results of an independent study in healthy volunteers with single doses of 200 mg administered before and after weekly rising doses of up to 400 mg/day. In these two studies, the multiple oral-dose concentration profiles of rufinamide (1200 and 400 mg/day, respectively) were predictable from the pharmacokinetic profiles after single oral doses. Given a dosing frequency of every 12 hours, accumulation was as expected with the steady-state peak concentration approximately three times the peak concentration after a single dose.

As in single-dose studies, a less than dose proportional increase in steady-state rufinamide plasma levels was observed.

Population pharmacokinetics from clinical trials under steady state conditions, dosing b.i.d., showed that food did not appear to significantly affect the extent of absorption.

Distribution

34% of rufinamide (34%) was bound to human serum proteins, predominantly to albumin (27%). The fraction bound to α_1 -acid glycoprotein and to gamma globulins was less than 4% each

suggesting little risk of drug-drug interactions by displacement from binding sites during concomitant administration of other drugs. Rufinamide was evenly distributed between erythrocytes and plasma. The apparent volume of distribution of rufinamide is in the order of total body water but is dependent upon dose due to the non-linearity in exposure with increasing dose. Apparent volume of distribution varied with body size.

Metabolism

The metabolic processes involved in the biotransformation of the drug were evaluated in a radiotracer study performed in three fed healthy male volunteers (two extensive and one poor metabolizer of debrisoquine), each of whom received a single oral dose of 600 mg of [¹⁴C]-rufinamide administered as microcrystalline solid in capsules. Rufinamide was extensively metabolized with less than 2% of the dose being recovered unchanged in urine. The essential biotransformation pathway was hydrolysis of the carboxylamide group to the acid derivative CGP 47292 and mediated by carboxylesterase(s). A few minor additional metabolites were detected in urine, which appeared to be acyl-glucuronides of CGP 47292. Otherwise, no relevant metabolites were detected in urine and feces. There was no indication for involvement of oxidizing cytochrome P450 enzymes or glutathione in the biotransformation process.

Rufinamide demonstrated little or no significant capacity to act as a competitive or mechanism-based inhibitor of the following human P450 enzymes: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 or CYP4A9/11-12. Rufinamide showed weak carboxylesterase inhibition (10.1% inhibition at 100 µM), weak induction of CYP3A4, and no induction of CYP1A1/2 in human hepatocytes. Thus, rufinamide might induce metabolism of co-administered drugs mediated by CYP3A4.

Rufinamide was shown to be a substrate for human carboxylesterase using liver microsomes. Rufinamide did significantly inhibit metabolism of probe substrates for this enzyme and thus was not expected to have drug-drug interactions through this mechanism.

Elimination/Excretion

In a radiotracer study in three healthy volunteers, the parent compound (rufinamide) was the main radioactive component in plasma, representing about 80% of the total radioactivity, with the metabolite CGP 47292 constituting only about 15%. Renal excretion was the predominant route of elimination for drug related material, accounting for 84.7% of the dose. Of the metabolites identified in urine, at least 66% of the rufinamide dose was excreted as the acid metabolite CGP 47292, with 2% of the dose excreted as rufinamide. There was no indication of metabolism via glutathione conjugation.

The plasma elimination half-life was approximately 6-10 hours in healthy subjects and patients with epilepsy. When given twice daily at 12-hourly intervals, rufinamide accumulated to the extent predicted by its terminal half-life, indicating that the pharmacokinetics of rufinamide were time-independent (i.e. no autoinduction of metabolism).

Pharmacokinetic and Drug Interactions

In vitro studies with rufinamide indicated that it has a low propensity for drug-drug interactions. Rufinamide showed no significant inhibition of cytochrome P450 enzymes, very weak inhibition for carboxylesterase, and low protein binding. However, some *in vitro* and *in vivo* studies

indicated that rufinamide was a weak phenobarbital-type inducer of cytochrome P450 isoenzymes and was also an inducer of rat-specific UDP-GT.

According to the sponsor, since rufinamide does not induce its own metabolism, nor does it act as an inhibitor of carboxylesterase activity, it is not expected to have significant drug-drug interactions with other substrates for this enzyme. Drugs that may induce the activity of carboxylesterases may increase the clearance of rufinamide. Broad-spectrum inducers such as carbamazepine and phenobarbital may have minor effects on rufinamide metabolism via this mechanism. Drugs that are inhibitors of carboxylesterases may decrease metabolism of rufinamide.

Potential interactions between rufinamide and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on mean plasma concentrations were summarized in the review and included under PRECAUTIONS, Drug Interactions section of the proposed label.

Reviewer Comments

It is beyond the scope of this clinical safety review to comprehensively discuss the physico-chemical, PK and PD properties of rufinamide. The above discussions were meant to provide an overview of the drug's behavioral profile for a better understanding of the clinical safety data and under the assumption that the descriptions and characterizations discussed have been authenticated by other disciplines from the Agency. Reference is made to the Agency's CMC, PK and Pharm-tox reviews for validation of the employed methodologies, the results and their significance with respect to the claims in the label and for further comments.

5.2 Pharmacodynamics

Refer to Agency PK reviewer comments.

5.3 Exposure-Response Relationships

Refer to Agency PK reviewer comments. See 7.2.1.

6 INTEGRATED REVIEW OF EFFICACY

Per Dr. Herschkowitz.

6.1 Indication

Since the indication and the intended population are critical in safety assessments, they are included in this safety review.

Proposed Indication

INOVELON[®] (rufinamide) is indicated as:

3. *Adjunctive treatment of partial-onset seizures with and without secondary generalization in adults and adolescents 12 years of age and older.*
4. *Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults.*

Reviewer Comment

The presented safety data and analyses do not match the sought indication. Specifically, the AE data that matches age groups >12 to < 16 years and ≥ 16 years for the adjunct partial seizure indication or age groups that match > 4 to < 16 and ≥ 16 years for the LGS indication were not provided.

Following a discussion with the Agency Team Leader, in a TCON with the sponsor (on Aug 30, 2006), this issue was discussed and information was requested. In a second TCON with the sponsor on Sep 5, 2006, following an e-mail response, the need for such data broken down by ages was reiterated. During this Sep 5 2006 TCON, the sponsor indicated that data from only 4 adolescents with partial seizures were included for the sought indication. In an e-mail on Sep 5 2006, this information on the age breakdowns were provided. The following is the breakdown of patients based on ages for each of the sought indications-

Adjunctive Partial Epilepsy indication in adolescents and adults (Total N = 720 rufinamide and 290 placebo for the double-blind adult subgroup): Adolescents (ages 12 to < 16 yrs) = 4 rufinamide and 0 placebo, Adults (≥ 16 years) = 716 rufinamide and 290 placebo.

Pediatric and Adult LGS indication (Total N = 74 rufinamide and 64 placebo for the LGS double blind subgroup): Pediatric (< 12 age) = 31 rufinamide and 33 placebo, Adolescents (12 - <16 yrs) = 18 rufinamide and 10 placebo, Adults (≥ 16 years) = 25 rufinamide and 21 placebo.

6.1.1 Methods

Per Dr. Herschkowitz.

6.1.2 General Discussion of Endpoints

Per Dr. Herschkowitz.

6.1.3 Study Design

Per Dr. Herschkowitz.

6.1.4 Efficacy Findings

Per Dr. Herschkowitz.

6.1.5 Clinical Microbiology

Per Dr. Herschkowitz.

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6.1.6 Efficacy Conclusions

Per Dr. Herschkowitz.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety information presented in the NDA was from the sponsor conducted clinical trials and formed the primary source of the clinical data upon which safety assessments were made. The focus of the safety analyses was on the integrated data stemming primarily from the studies involving the 1978 unique rufinamide patients. The approach to the review is discussed in section 4.3 (review strategy). The study type, design and other protocol methodology are discussed in section 7.2.1.1.

Safety Parameters Evaluated

The safety variables that were evaluated were: Adverse events; Clinical laboratory tests (blood chemistry, hematology, and urinalysis); tests of Thyroid function were performed in some protocols; Vital sign measurements and body weight; ECGs; Physical examinations/Neurological examinations.

The schedule of safety assessments for each of the safety studies was presented in the individual CSRs (Module 5). An overview of the safety parameters evaluated in each of the clinical trials in epilepsy is presented in Table 7.1.A.

SAFETY TABLE 7.1.A OVERVIEW OF EVALUATED SAFETY PARAMETERS				
Referenced Study	AE	Vitals & Weight	Laboratory ^A	ECG
AE/ET1 & AE/ET1E	X	X	X ^B	X
AE/PT1	X	X	X ^B	X
AE/PT2	X	X	X ^B	X
AE/PT3	X	X	X ^B	X
016 & 016E	X	X	X ^B	X
018 & 018E	X	X	X ^B	X
021A & 021AE	X	X	X ^B	X
021P & 021PE	X	X	X ^B	X
022 & 022E	X	X	X ^B	X
027 & 027E	X	X	X ^B	X
038 & 038E	X	X	X ^C	X
039 & 039E	X	X	X	X
0101	X	X	X	X
2301	X	X	X	X
Ref: Modified from Sponsor's Table 3.3-1, ISS, p. 52				
Note:				
A = Included Standard hematology, Blood Chemistry and UA				
B = Included Thyroid Function Tests				
C = Included Thyroid Function Tests at Baseline Only				

Safety Analyses, Statistical Methods, and Criteria

Analysis Population

The relevant safety population for analyses is discussed under 7.2.1.1.

Analysis of Extent of Exposure

The methods involving the extent of exposure to study drug was analyzed in three ways-

1. the median daily dose of rufinamide that a patient received during his or her entire duration of exposure to the drug;
2. the daily dose that the patient received for the longest period of time (called daily dose of maximum duration); and
3. the maximum daily dose that the patient received. The daily dose was calculated from doses taken during the Maintenance Period in studies that included both Titration and Maintenance Periods, i.e., Studies 016, 021A and 021P, 022, and 038. These data were summarized using descriptive statistics (mean, median, standard deviation, range).

Duration of exposure to rufinamide was summarized by median daily dose, maximum daily dose, and daily dose of maximum duration. The distribution of patients was shown for the following intervals: 0 to <1 month, 1 to <3 months, 3 to <6 months, 6 to <12 months, 12 to <24 months, 24 to <36 months, 36 to <48 months, and ≥ 48 months. The distribution was shown for doses in mg/kg/day (<10, 10 to <20, 20 to <30, 30 to ≤ 45 , >45 mg/kg/day) or in mg/day (<400, 400 to <1600, 1600 to <2400, 2400 to ≤ 3200 , >3200 mg/day). For the population of all treated patients with epilepsy, distributions of duration by median daily dose were also generated for subgroups of patients categorized by their weight at baseline (<18.0, 18.0 to 29.0, 29.1 to 50.0, 50.1 to 70.0, ≥ 70.1 kg).

Analyses of Safety Parameters

Adverse events

In the rufinamide studies, an adverse event was defined as any undesirable sign, symptom, laboratory abnormality, or medical condition occurring after study treatment, even if the event was not considered to be treatment-related. Information was recorded on the adverse event CRF about all adverse events, whether volunteered by the patient, discovered by investigator, or detected through physical examination, laboratory test, or other means.

In all epilepsy trials, events that are to be expected due to the trial indication (such as seizures in patients with epilepsy) were not be treated as adverse events or serious adverse events, unless the event represented a significant worsening of the symptom (e.g., new seizure type, clinically significant increase in seizure severity, status epilepticus or hospitalization, etc.).

Coding dictionary

The investigators were instructed to record adverse events using standard medical terminology. For the CSRs, the specific terms that the investigators recorded were coded to Low Level Terms and to Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA), Version 6.0. Coding to Version 6.0 was done either as part of the original CSR or as an addendum to the original CSR. To maintain consistency in terminology for this safety summary, all investigator terms from all studies were recoded using MedDRA, Version 7.1. Transition to

the MedDRA coding affects only the Preferred Terms; all other variables such as verbatim term, severity, relationship, and action taken regarding the study drug were not changed. The MedDRA dictionary was accessed through the ClinPlus® Coding, Version 2.00 v 8a. The coding was performed in two stages, i.e., auto encoding followed by manual encoding as necessary. In auto-encoding, each verbatim term that has matched to the Low Level Term of the dictionary was automatically assigned a Preferred Term and System Organ Class (SOC). The terms that were not recognized during the auto-encoding were manually coded. An output of these terms was manually coded to the Low Level Term that was the closest match to the medical concept in the reporter's verbatim term, and updated accordingly.

Populations for analysis and pooling of data

Adverse events data were pooled using the analysis populations defined above.

Presentation of adverse event data

Tables within the text that displayed the overall incidence of patients with at least one adverse event and adverse events by MedDRA SOC showed the results for every adverse event reported. Additional tables were focused on very common adverse events, defined as any adverse event that occurred in 10.0% or more of the patients within a treatment group. The very common adverse events were summarized by Preferred Term, by severity, and by dose of rufinamide. All of these presentations were based on adverse events regardless of causality.

The relation between the occurrence of adverse events and the dose of rufinamide was evaluated for 1) the median dose of rufinamide that a patient received during his or her entire duration of exposure to the drug, excluding exposure during titration; 2) the dose that the patient received for the longest period of time (called daily dose of maximum duration); and 3) the maximum daily dose that the patient received. Most of the double-blind studies evaluated stable doses of rufinamide, so the median dose, dose of maximum duration, and maximum dose were generally the same for patients in those studies. Adjustments of dose were allowed during open-label extensions.

Serious adverse events were summarized by showing the number and percent of patients who experienced at least one event and each specific event. The total number of events per treatment group, and the number of events leading to discontinuation, was also noted for each analysis population. The number of events was based on the serious adverse event reports received by the sponsor. Some of these included multiple events that occurred concurrently in a single patient. Such concurrent events were counted as a single serious adverse event only when determining the total number of events. For example, if a patient had nausea and vomiting that occurred concurrently and was reported on one serious adverse event form, this was counted as one event when determining the total number of serious events. In tabulations showing numbers of patients with individual events, the nausea and vomiting in this patient are each counted as occurring in one patient.

Reviewer Comments on presentation of Non-fatal SAE and Discontinuations

During the review, it was noted that the patient narratives for non-fatal serious AEs and AEs that led to discontinuation were included only in the respective individual study reports and not in the respective sections, thereby rendering the review process arduous. On Aug 21, 2006, in a TCON with the sponsor, this issue was discussed and the sponsor indicated submitting these narratives

separately and tabulating the events with provision for easy navigation as presented for the fatal events. These were subsequently submitted on Aug 25, 2006.

Laboratory tests

Clinical laboratory data were summarized using descriptive statistics for values obtained at baseline and at the last post-baseline visit, and for the difference between those two evaluations. Two distinct definitions of baseline were used: 1) in analyses of populations from well-controlled studies, the baseline measure of a parameter was the last reported value prior to initiation of randomized study treatment; 2) in analyses of the remaining populations, where the interest was in change since initiation of rufinamide, the baseline measure was the last reported value for a parameter prior to initiation of treatment with rufinamide. The last post-baseline value was defined as the last reported value within the Double-blind Phase for the analyses of data from controlled studies. For the remaining populations, the last post-baseline value was defined as the last reported value after initiation of rufinamide treatment. Individual patients with changes in laboratory parameters of potential clinical significance were identified in two ways. First, shift tables were generated to show the number of patients with values for each parameter that were below, within, or above the normal range at baseline and below, within, or above the normal range at the last post-baseline evaluation. Second, the numbers and percentages of patients who had changes in any laboratory parameter that met predefined criteria for clinically notable values were calculated.

Normal ranges and clinically notable criteria used in the analyses of individual studies, and reported in the individual CSRs, varied. They were not always modified appropriately depending on the patients' ages, and the clinically notable criteria were not in accordance with current standards. Therefore, for consistency and accuracy, a single set of age-adjusted normal ranges and clinically notable criteria was used for this ISS. The age-adjusted normal ranges, those that were recommended by the Mayo Medical Laboratories Test Catalog, were shown in Appendix I, Table 8.1.0 of the submission.

Not every study required that all of these laboratory parameters be measured. In addition, data were included in the laboratory analyses only for those patients who had both baseline values and at least 1 post-baseline value. The numbers of patients who were included in each analysis were shown in the in-text tables. The standard definitions/criteria of clinically notable values of lower limit and upper limit for hepatobiliary, renal (BUN and Cr), hematology, general chemistry and thyroid functions used in the ISS analyses that were presented in Table 3.4-1, ISS, p. 55 has been included in this review for reference (Appendix Table 2).

Reviewer Comments on Labs

Note that for some of the clinically notable lab safety parameters (e.g., BUN), the sponsor has used international units rather than conventional units. Also, the chosen ranges of lower or upper limits for some of the parameters are too liberal. See Appendix Table 2. The disposition of patients with clinically notable values (changes from baseline), were not specified. How these patients with clinically notable changes were managed or followed was not provided and the outcome was unknown. *It is recommended that this information be requested from the sponsor.*

Vital signs and Body Weight

Vital signs and weight were evaluated two ways *viz.*, summary statistics and incidences based on identifying clinically notable changes.

Summary statistics (means, medians, standard deviations, ranges) were calculated (but not integrated- see comments below) at baseline and at the last post-baseline evaluation, and for the difference between those two evaluations. Two distinct definitions of baseline were used: 1) in analyses of populations from well-controlled studies, the baseline measure of a parameter was the last reported value prior to initiation of randomized study treatment; 2) in analyses of the remaining populations, where the interest was in change since initiation of rufinamide, the baseline measure was the last reported value for a parameter prior to initiation of treatment with rufinamide. The last post-baseline value was defined as the last reported value within the Double-blind Phase for the analyses of data from controlled studies. For the remaining populations, the last post-baseline value was defined as the last reported value after initiation of rufinamide treatment.

The incidence of patients with clinically notable changes was determined, using the definitions of clinically notable changes that was presented in Table 3.4-2, ISS, p. 56, for pulse rate, SBP, DBP and Weight has been included in this review for reference (Appendix Table 3). Patients were included in the evaluation of clinically notable changes only if they had both a baseline value and at least 1 post-baseline value for vital signs and weight.

Reviewer Comments on Vital Signs

The specified set criteria for clinically notable changes in vital signs were- "*Clinically notable means that a value must have met both the criterion value and satisfied the magnitude of change relative to baseline*". (Ref: See note in Table 3.4-2, ISS, p. 56- included in review as APPENDIX TABLE 2). The magnitude of change for DBP that was considered significant was ≥ 15 mmHg. Such dual criterion that requires a value change **and** a magnitude change is not clinically meaningful. Because a change in magnitude will not be considered notable unless it also falls outside the set values, there will be an under representation of the true effects of the drug. Secondly, a change that may not meet the specified magnitude may still have clinical significance depending on the underlying vasomotor compensatory mechanisms and CVS state of the subject. As an example, a change in either SBP or DBP lesser than the specified magnitude when the baseline BP is low may lead to potential problems. Further, the chosen magnitude of change for DBP of ≥ 15 mmHg is liberal. A change of ≥ 10 mmHg DBP is more relevant.

Information on the mean changes and shifts in vital signs were not integrated. However, the referenced Tables 9.1.1-0 to 9.1.1-10 in the Appendix section of the submission included statistical results (Median, Mean, SD, Min and Max) for vital signs and weight for each subset of the analyzed populations. These results did not raise specific concerns in any of the population subsets including the diabetic neuropathy and healthy volunteer subgroups. These are discussed in the findings section.

ECG

The ECGs recorded in the clinical studies did not undergo centralized review. Instead, each center provided each patient's ECG with an automatic readout, confirmed by the principal investigator. Each ECG that was recorded was given an overall interpretation of normal or abnormal. The results were summarized in shift tables comparing the interpretations at baseline

and at the final post-baseline evaluation. In addition, potential effects of rufinamide on cardiac related parameters were examined by a review of ECG- and cardiovascular-related adverse events, serious adverse events, and discontinuations due to adverse events.

Reviewer Comments on ECG

The ECG, QT and related CVS safety data has been reviewed by the DNDP safety team (Dr. Lisa Jones). To avoid redundancy, reference is made to that review. In any event, the value of the reported ECG data is limited since there was no centralized read and only an automated on-site read was executed. Further, the on-site read was qualitative and whether the on-site principal investigator (s) was qualified to interpret ECGs is unknown. Based on these aspects, the value of the collected ECG data is limited. Please refer to the safety review of Dr. Jones for additional details and comments.

Physical and Neurological Examinations

According to the sponsor, no summaries or tabulations for these findings were neither integrated nor submitted for the ISS (3.4.3.5, ISS, p. 56).

Reviewer Comments on Clinical Exam

Interpretation via correlation of abnormalities that occur in some of the safety parameters with clinical findings is critical and required. In the absence of such information, meaningful interpretation of safety findings may be curtailed.

The safety findings are discussed below.

7.1.1 Deaths

ALL RUFINAMIDE DEATHS

All deaths that occurred in the studies in which rufinamide was administered are discussed below.

Fatal AE (Deaths and Sudden Deaths)

Twenty-eight patients (23 who received rufinamide and 5 who received placebo) of the 1978 exposed patients died in this drug development program (Sponsor's Table 7.1-1). Eighteen rufinamide patients died either during the clinical studies or within 30 days after receiving the last dose of study drug and 5 rufinamide patients died > 30 days after receiving the last dose of rufinamide. Seven patients (2 who received rufinamide and 5 who received placebo) died during double-blind studies, and 21 patients died while taking rufinamide either during open-label studies or open-label extension studies. According to the sponsor, for all treated patients with epilepsy, the rate of deaths was 0.71 per 100 patient-years of exposure to rufinamide. The rates were 0.69 per 100 patient-years of exposure to rufinamide and 2.67 per 100 patient-years of exposure to placebo for all patients with epilepsy who received study drug in double-blind studies.

According to the sponsor, one death was suspected by the investigators of being related to study drug: cardiac arrest in Patient 0001-03008 (Study AE/ET1) who received placebo (Sponsor's Table 7.1-1, ISS).

Table 7.1.1.A (Sponsor's Table 7.1-1, ISS) identifies each of the patients who died following rufinamide treatment and provides information about the cause of death, dose and duration of therapy, and this reviewer's assessment of relationship to treatment. Table 7.1.1.B, Table 7.1.1.C, and Table 7.1.1.D provide other details on the deaths. Table 7.1.1.B provides an overview of all deaths with salient features in a clinically meaningful way, Table 7.1.1.C provides an overview of the death rates by study population in the rufinamide program and Table 7.1.1.D provides SUDEP death rates for some of the approved anti-epileptics and the background SUDEP rate.

*Appears This Way
On Original*

**SAFETY TABLE 7.1.1.A
RUFINAMIDE DEATHS PATIENT LISTING**

#	Patient ID	Age/Sex	Last Dose (mg/day)	Duration of Therapy (days)	Autopsy	Reviewer Comments
DEATHS DURING STUDY PERIOD OR < 30 DAYS AFTER LAST DOSE						
1	0003-06419 (DB)	26/M	1600	69	Yes	Brain edema and herniation, and hyperthermia (cannot rule out associated malignant hyperthermia)
2	0074-06307 (DB)	40/M	3200	18	No	Fall that led to head injury and death could have been due to dizziness. Cause of dizziness not known.
3	0011-06232 (Open Ext)	47/F	1600	612	Unknown [#]	Severe head trauma with ICH led to death. Cause of head trauma/ICH not known
4	1257-05122 (Open Ext)	20/F	3200	1039	Yes	<u>Un-witnessed sudden death.</u> Autopsy details not provided. Autopsy reported as consistent due to presumed seizure
5	1282-05025 (Open Ext)	59/F	3600	919	No	<u>Un-witnessed sudden death.</u> Cause unknown
6	0001-06005 (Open Ext)	64/M	1600	Not provided	Unknown [#]	Unrelated death due to prostate cancer 3 years after last dose
7	0001-09009 (Open Ext)	34/F	1200	406	Yes	<u>Un-witnessed sudden death.</u> Autopsy reported as death consistent due to seizure
8	0002-02056 (Open Ext)	33/F	400	193	Yes	<u>Witnessed sudden death.</u> Autopsy reported as asphyxia as cause of death due to witnessed seizure
9	0002-07029 (Open Ext)	48/F	400	504	Unknown [#]	Unrelated. Death likely due to adenocarcinoma of stomach
10	0008-01159 (Open Ext)	24/M	1400	173	Unknown [#]	No other details to determine any relation
11	3054-02071* (Open Ext)	4/F	1600	389	No	<u>Un-witnessed sudden death.</u> Malignant hyperthermia requiring hospitalization 6 months prior to death
12	0002-04803 (Open Ext)	15/F	1000	139	No	Unrelated. Death likely due to underlying complex medical problems
13	0006-04411 (Open Ext)	6/F	1000	743	No	<u>Un-witnessed sudden death</u> presumed due to seizure due to tongue biting
14	1255-00557 (Open)	19/F	4000	608	Yes	<u>Un-witnessed sudden death.</u> Autopsy reported as death consistent due to seizure
15	0051-00001 (Open)	36/F	2400	301	Yes	Aspiration pneumonia as cause of death due to witnessed seizure
16	0052-00008 (Open)	69/M	800	358	No	Death due to spontaneous ICH and complications
17	0052-00011 (Open)	65/M	1200	119	Unknown [#]	<u>Sudden death</u> following witnessed seizure
18	0052-00016	33/M	800	96	Yes	<u>Un-witnessed sudden death</u> with

	(Open)					blood in subject's mouth. Autopsy inconclusive. Death presumed due to seizure
DEATHS > 30 DAYS AFTER LAST DOSE						
1	1747-02021 (Open Ext)	15/M	400	385	No	Unrelated. Death likely due to post operative aspiration pneumonia
2	1141-00087 (Open)	41/M	200	1126	Unknown [#]	Unrelated. Death likely due to vomiting and aspiration
3	1146-00069 (Open)	43/M	1600	417	Yes	Un-witnessed death. Body found decomposed 87 days after last dose. Autopsy reported as death consistent due to seizure
4	0051-00006 (Open)	74/M	800	646	Unknown [#]	Death 60 days after last dose due to terminal metastatic lung cancer
5	0507-00003 (Open)	61/F	3200	273	No	Death due to complications from small cell carcinoma of bronchus
Ref: Sponsor's Table 7.1-1, ISS, pp 146-147; CRF and summaries.						
Note:						
DB= Double-blind studies; Open Ext= Open-label extensions of double-blind studies; Open= Open-label studies;						
*=Case 3054-02071 was not identified as a case of Sudden Death by the Sponsor. Hatched Patient ID = Two cases of Sudden death (1282-05025 and 3054-02071) – Cause not known or determinable; #Unknown= Not specified if autopsy was conducted or not- most likely not conducted						

SAFETY TABLE 7.1.1.B OVERVIEW OF DEATHS	
All Deaths (all treatments) (N)	28
During Placebo treatment (N)	5
During Rufinamide treatment (N)	23
Deaths during study or < 30 days after last dose of Rufinamide (N)	18
Deaths > 30 days after last dose of Rufinamide (N)	5
Sudden Death - during study or < 30 days after last dose of Rufinamide (N)	Sponsor = 8*, FDA = 9*
Sudden Death - > 30 days after last dose of Rufinamide (N)	0
Deaths Attributable to other underlying causes (N)	12
Deaths indeterminable if it was sudden or not (N)	2
Rufinamide Treatment Gender (N)	Male = 11, Female = 12
Rufinamide Treatment Age (N)	> 18 = 20, < 18 = 3
Deaths in DB Studies	2 R, 5 P
Deaths in OL and or OL Extension of DB Studies	21 R, 0 P
Deaths in Mono-therapy DB Studies	0
Deaths in LGS DB Studies	0
Deaths in Diabetic Neuropathy or Healthy Volunteer Subset	0
Sudden Deaths in DB Studies	0
Autopsy (N)	Yes= 8, No= 8, Unknown [#] =7
Autopsy (N) in Sudden Death Cases (N=9)	Yes =5, No= 3, Unknown [#] =1
Sudden Death with Autopsy Findings Suggestive of Seizure as cause of Sudden death- Definite SUDEP***	5
Sudden Death following witnessed seizure or signs suggestive of seizure and no Autopsy- Probable SUDEP***	2 (0006-04411, 0052-00011)
Sudden Death without witnessed seizures or signs of seizure and no Autopsy – Probable SUDEP***	2** (3054-02071, 1282-05025)
Ref: See Table Above; Sponsor's Table 7.1-1, ISS, pp 146-147	
Note:	
DB= Double-blind; OL= Open-label; R = Rufinamide; P= Placebo; *=Case 3054-02071 was not identified as a case of Sudden Death by the Sponsor and therefore sponsor's calculations are based on the 8 cases. Comments are based on the 9 sudden deaths; #Unknown= Not specified if autopsy was conducted or not- most likely not conducted; **= Two cases of Sudden death (1282-05025, 3054-02071) in whom there was no autopsy and sudden death could not be attributed to	

witnessed seizure or signs of seizures or other causes. ***= see SUDEP discussion in text.

SAFETY TABLE 7.1.1.C OVERVIEW OF DEATH RATES BY STUDY POPULATION SUBGROUPS						
	Rufinamide (R)			Placebo (P)		
	Deaths N (%)	Estimated Exposure ^B	Death Rate ^A	Deaths N (%)	Estimated Exposure	Death Rate ^A
All Patients (R=1978)	18 (0.9)	2552.96	0.71	--	--	--
Sudden Death All patients (R=1978)	8* (0.4)	2552.96	0.31*	--	--	--
	9* (0.45)	2552.96	0.35*	--	--	--
All DB studies (R=1240, P=635)	2 (0.2)	291.51	0.69	4 (0.6)	149.60	2.67
Sudden Death All DB (R=1240, P=635)	0	--	0	4	--	2.67
Adult DB (R=720, P=290)	2 (0.3)	187.49	1.07	3 (1.0)	74.17	4.04
Adult DB + OL (R=931)	10 (1.1)	1190.94	0.84	--	--	--
DB Mono therapy	0	--	--	0	--	--
LGS DB	0	--	--	0	--	--
LGS DB + OL (R=135)	1 (0.7)	166.60	0.60	--	--	--
Pediatric DB (R=212, P=197)	0	50.32	0	1 (0.5)	46.54	2.15
Pediatric DB + OL (R=391)	3 (0.8)	489.46	0.61	--	--	--
Diabetic Neuropathy Studies	0	0	0	0	0	0
Healthy Volunteers Studies	0	0	0	0	0	0

Ref: ISS, pp 147-148

Note:
A= Per 100 patient-years; B= Patient-years; R= Rufinamide; P= Placebo; DB= Double-blind; OL= Open-label;
*=Case 3054-02071 was not identified as a case of Sudden Death by the Sponsor and therefore sponsor's rates are based on the 8 cases. The rates based on the 9 sudden deaths were calculated by this reviewer.

SAFETY TABLE 7.1.1.D RATES OF SUDDEN UNEXPLAINED DEATHS IN EPILEPSY (SUDEP) - COMPARISON				
Name (Approval Date ^D)	Exposed (N)	Patient-years ^A	SUDEP (N)	SUDEP Rate ^B
Rufinamide	1978	2552.96	8 (Sponsor)	0.0031*
	1978	2552.96	9 (Reviewer)	0.0035*
Lamictal (Lamotrigine) (1994)	4700	5747	20	0.0035
Topamax (Topiramate) (1996)	Not provided	2796	10	0.0035
Neurontin (Gabapentin) (1993)	2203	2103	8	0.0038
Gabitril (Tiagabine) (1997)	2531	3831	10	0.0026
Zonegran (Zonisamide) (2000)	991	Not provided	9	0.0077 (7.7/1000)
SUDEP Background Rate ^C	0.0005 For General Population with Epilepsy 0.005 For Patients with Refractory Epilepsy			

Ref: 2006 PDR; pp 1452, 2441, 2500, 998, 1090; Table 7.1.1.C

Note:
A= Exposure Rate, B= Incidence Per Patient Year (also called Incidence Density); C= Source- 2006, PDR, Lamictal, p. 1452; D= Source: <http://cdernet.cder.fda.gov/>- Drugs at FDA; Lyrica (pregabalin) was approved for epilepsy in 2005 (earlier approval for neuropathy) but information on SUDEP is not mentioned. Hence this was not included in this table.
*=Case 3054-02071 was not identified as a case of Sudden Death by the Sponsor and therefore sponsor's rates are based on the 8 cases. The rates based on the 9 sudden deaths were calculated by this reviewer.

In 12 cases, the deaths were attributable to other underlying causes. In two cases (0008-01159 and 1146-00069), it was not possible to determine if these deaths were sudden or not. In one case no information was provided and in the second case, no meaningful deductions were

possible because the body was found decomposed 87 days after the last dose and the autopsy was reported to be consistent with seizure.

The focus therefore, was on those 9 sudden death cases (witnessed or un-witnessed that occurred < 30 days after the last dose of rufinamide- highlighted under reviewer comments in Table 7.1.1.A) in whom no other obvious underlying cause was found (see SUDEP discussion and definition below). Brief narratives for these 9 sudden deaths followed by reviewer comments (see comments in Table also) are provided below.

Another case of death (patient who died due to brain herniation and edema) is also discussed due to its complexity.

1. Patient 1257/5122: Sudden Death

This 20-year-old Caucasian female patient entered double-blind study 021 with a diagnosis of inadequately controlled partial seizures. The patient's medical history included viral encephalitis (encephalopathy) at age 11. The patient was randomly assigned to receive placebo during the Double-blind Phase of study 021 and completed 91 days of treatment. The patient then entered the Extension Phase and began receiving open-label rufinamide on 18-Jan-99. Concomitant non-AED medications during the Extension Phase included folic acid and Depo-Provera.; concomitant AED therapy included lamotrigine, tiagabine, lorazepam, and topiramate. An ECG obtained on 20-Aug-01 was normal. On _____ of the Extension Phase), while receiving 3200 mg of rufinamide daily, 750 mg of lamotrigine daily, and 150 mg of topiramate daily, the patient died suddenly. No other information regarding the death was available. In the opinion of the autopsy medical examiner, the death was due to the patient's epileptic seizure disorder. The investigator assessed this event as not related to study medication.

b(6)

Reviewer Comments:

Un-witnessed Sudden Death with autopsy – findings that meets the criteria (see discussion below of SUDEP) of Definite SUDEP.

2. Patient Number 1282/5025: Sudden Death

This 59-year-old Caucasian female patient entered double-blind study 021 with a diagnosis of inadequately controlled partial seizures. The patient's medical history included benign breast lumpectomy. Active medical conditions upon enrollment in the double-blind study were allergy and sinus problems, dizziness, and headaches. The patient was randomly assigned to receive placebo during the Double-blind Phase of study 021 and completed 91 days of treatment. She then entered the Extension Phase and began receiving open-label rufinamide on 10-Mar-98. Concomitant non-AED medications during the Extension Phase included aspirin, Ben-Gay, ofloxacin, Acular, Maxitrol, and artificial tears; concomitant AED therapy included phenytoin, lamotrigine, and topiramate. An ECG performed on 02-Feb-00 was normal. On _____ of the Extension Phase), while receiving 3600 mg of rufinamide and 800 mg topiramate daily, the patient died. The patient's brother last saw her alive on _____. He went to the patient's home on _____ and had to break in to gain entry. The patient was found expired on the floor lying face down with her fists clenched and her feet in an abnormal position. There was no evidence of trauma or blood found at the scene. An autopsy was not performed. The death certificate indicated the cause of death as hypoxia/anoxia probably secondary to seizure. The investigator assessed this event as not related to study medication.

b(6)

Reviewer Comments:

Un-witnessed Sudden Death, no witnessed seizures or signs of seizure and no autopsy- Probable SUDEP (see discussion on SUDEP below).

3. Patient Number 0001/9009: Sudden Death

This 34-year-old female patient entered the double-blind phase of the study AE/ET1 with a diagnosis of inadequately controlled partial seizures (severe epilepsy of undefined etiology, with very frequent generalized and temporal epileptic seizures since the age of 12). No medical history was recorded at study entry, and the only active medical condition other than epilepsy present at enrollment was fatigue since 1972. The patient was randomly assigned to receive placebo during the Double-blind Phase of study AE/ET1. She then entered the Extension Phase and began receiving open-label rufinamide treatment on 05-Jul-94. The only concomitant medication recorded during the Extension Phase was concomitant AED therapy (carbamazepine and valproate throughout the Extension Phase). On _____ of rufinamide therapy), while receiving 1200 mg/day, the patient was found dead in her bed at 9:26 AM having last taken rufinamide on 25-Feb-95. An autopsy was performed and macroscopic findings included mild brain congestion and a finding consistent with mild temporal lobe atrophy. Mild congestion of the lungs was also visible. On the basis of the autopsy, the potential cause of death was an epileptic seizure. In the investigator's opinion, the event was not suspected to be related to study medication.

b(6)

Reviewer Comments:

Un-witnessed Sudden Death with autopsy – findings that meets the criteria (see discussion below of SUDEP) of Definite SUDEP.

4. Patient Number 0002/2056: Sudden Death

This 33-year-old female patient entered the double-blind phase of the study AE/ET1 with a diagnosis of inadequately controlled partial seizures. Medical history recorded at study entry included adenoidectomy (1969), tonsillectomy (1969), and uterine dilation and curettage (1985). Active medical conditions present upon enrollment were asthma (since 1960), muscle spasms (since 1990), and head injury (since 1981). The patient was randomly assigned to receive rufinamide during the Double-blind Phase of study AE/ET1. She then entered the Extension Phase and began receiving open-label rufinamide treatment on 08-Feb-94. Non-AED concomitant medications recorded during the Extension Phase included Anusol, cyclobenzaprine, imipramine, paracetamol; concomitant AED therapy included carbamazepine throughout the Extension Phase. Or _____ of rufinamide therapy), the patient experienced a seizure and died. The autopsy indicated the cause of death was asphyxia. At Visit 51 on 17-May-94, the decision was made to taper and discontinue study drug over the subsequent 6 to 8 weeks due to lack of benefit. The dose of rufinamide was reduced from 1600 mg/day to 1200 mg/day on 18-May-94 and then to 600 mg/day on 31-May-94. In the investigator's opinion, the event was not suspected to be related to study medication.

b(6)

Reviewer Comments:

Sudden Death following witnessed seizure with autopsy that meets the criteria (see discussion below of SUDEP) of Definite SUDEP.

5. Patient Number 3054/2071: Sudden Death (This case was not identified as case of sudden death by sponsor)

This 4-year-old black female patient was enrolled in the open-label extension trial of rufinamide Protocol 022 for patients with inadequately controlled seizures associated with Lennox-Gastaut syndrome. Medical history included bronchospasm NOS (1995), feeding disorder NOS (1995), gastroesophageal reflux disease (1995), hypotonia (1995), otitis media NOS (1995), aspiration (1996), dysphagia (1996), zinc deficiency (1996), bronchoscopy (1997), pneumonia respiratory syncytial viral (1997), gingival hyperplasia (1999) and upper respiratory tract infection NOS (1999). Active medical conditions included developmental delay NOS (since 1995), encephalopathy (since 1995), fundoplication (since 1995), cerebral palsy (since 1997) and pulmonary congestion (since 1998). The patient was randomly assigned to receive rufinamide during the Double-blind Phase of study 022. She then entered the Extension Phase and began receiving open-label rufinamide treatment on 29-Sep-99. Concomitant AEDs included clonazepam, phenobarbital and topiramate. Concomitant non-AEDs included bactrim, cefotaxime, cefuroxime axetil, chloral hydrate, chlorpromazine hydrochloride, clonazepam, electrolyte solutions, erythromycin, glycopyrronium bromide, guaifenesin, ibuprofen, lorazepam, paracetamol, pediasure, pip/tazo, salbutamol and triamcinolone acetonide. On _____ while receiving 1000 mg/day of rufinamide, the patient developed symptoms of pneumonia, and she was admitted to the hospital. She was treated with albuterol and Zosyn. Her condition improved, and she recovered completely on 26-Oct-99. The investigator assessed this adverse event as not related to rufinamide. b(6)

On _____ she was admitted to the hospital for a fever of 107 degrees F. The condition improved, and she recovered completely on 30-Nov-99. The investigator assessed this adverse event as not related to rufinamide. b(6)

On 01-Feb-00, the patient developed a fever. Blood culture and chest x-ray showed no evidence of microbial growth, pneumonia or a cardiopulmonary process. Urine culture also showed no growth. On 06-Feb-00 an airway fluoroscopy revealed a fairly long segment tracheomalacia involving the cervical trachea and the proximal thoracic trachea, symmetrical motion of the diaphragmatic leaflets, peribronchial thickening consistent with chronic lung disease, and mucus within the pyriform sinuses versus a small aryepiglottic cyst.

On _____ the patient was brought to the emergency room with an uncontrollable fever. She was also very agitated and inconsolable. She was treated with IV fluids, lorazepam, chlorpromazine, a cooling blanket and cefotaxime. The fever was controlled and she was admitted to the hospital with a diagnosis of malignant hyperthermia and dehydration. The investigator assessed this adverse event as not related to rufinamide. She was started on Robinul and chest physical therapy. Albuterol was continued. On 07-Feb-00, an EEG showed some new tonic seizure activity. A video EEG showed that all of her agitation was not seizure activity. During her admission she was restarted on clonazepam and continued on rufinamide 1000 mg/day, topiramate and phenobarbital. She was also started on trimethoprim/sulfamethoxazole. Her high fever was considered neurogenic and not associated with infection. She recovered completely and was discharged on _____. b(6)

On _____ of rufinamide), while receiving 1600 mg/day of rufinamide, she was found expired in bed. The patient had been chronically ill due to long-standing static encephalopathy secondary to Otoharz's [sic] syndrome. No autopsy was performed. The cause of death was presumed to be related to her seizure disorder. The investigator assessed this adverse event as not related to rufinamide.

b(6)

Reviewer Comments:

Un-witnessed Sudden Death, no witnessed seizure or signs of seizure and no autopsy- Probable SUDEP (see discussion on SUDEP below).

While the cause of death in this patient was not due to fever, this 4 year old female, while receiving rufinamide (started Sep 1999), experienced several episodes of high fever (Oct 99, Nov 99, _____), that was not associated with status or seizures or an infective focus (workup during _____ hospitalization between the 1st and 17th, was negative for an infective source). A diagnosis of malignant hyperthermia (neurogenic origin per sponsor) was made. She recovered fully and was discharged from the hospital after a stay of 17 days in _____. No details or criteria that led to the diagnosis of malignant hyperthermia were provided. See malignant hyperthermia below.

b(6)

6. Patient Number 0006/4411: Sudden Death

This 6-year-old Caucasian female patient entered double-blind study 021P with a diagnosis of inadequately controlled partial seizures. She had suffered epilepsy from the age of 5 months (seizures with loss of consciousness). The patient's medical history included dementia NOS (1995). Active medical conditions upon enrollment in the double-blind study were food allergy (since 1993) and drug intolerance NOS (since 1993). The patient was randomly assigned to receive rufinamide during the Double-blind Phase of study 021P. She completed 91 days of double-blind treatment. The patient then entered the Extension Phase and began receiving open-label treatment on 22-Sep-98. The dose was titrated to 1000 mg/day by 29-Sep-98 and remained at that level until the patient's death. Concomitant AEDs during the Extension Phase included benzobarbital and valproate.

On 23-May-00, the patient experienced a seizure with a brief loss of consciousness. She was given diazepam. On 04-Jul-00, following a visit home, the patient was dysphoric, excited, and aggressive; she was poorly controlled by pedagogic correction. On _____ of total exposure to rufinamide in the Double-blind and Extension Phases), at 2:00 AM, the patient was found dead. Examination revealed her tongue was bitten. It was hypothesized that the death had been caused by status epilepticus during the patient's sleep complicated by acute cardiovascular failure. The patient's parents refused performance of an autopsy. A death certificate issued on _____ reported the reason for the patient's death as cerebral edema and "unclear cerebral impairment." The investigator assessed this adverse event (death during a seizure) as not related to study medication.

b(6)

Follow-up information received on 28-Sep-00 indicated that the assumption of the complication of acute cardiovascular failure was based on clinical findings, but could not be confirmed because an autopsy was not performed. The patient had no history of cardiovascular disease. It was not clear if status epilepticus had actually occurred or whether the status epilepticus was associated with the cerebral edema and "unclear" cerebral impairment reported on the death

certificate. "Unclear cerebral impairment" was used to describe the cause of death because there were insufficient data to define the disease state more precisely.

Reviewer Comments: Status epilepticus not confirmed although there was tongue biting. Un-witnessed Sudden Death with signs of seizure (tongue biting) and no autopsy- Probable SUDEP (see discussion on SUDEP below).

7. Patient Number 1255/0557: Sudden death

This 19-year-old Caucasian female patient entered double-blind study 016 with a diagnosis of inadequately controlled partial seizures. The patient's medical history included ear infection NOS (1979), foreign body aspiration (1979), urinary tract infection NOS (1980), amputation NOS (1983) and thermal burn (1998). Active medical conditions upon enrollment in the double-blind study were drug hypersensitivity (since 1980), contusion (since 1982), headache NOS (since 1992), and dysmenorrhea (since 1995). The patient was randomly assigned to receive rufinamide 300 mg/day during the Double-blind Phase of study 016. She met one of the study exit criteria (prolongation or clinically significant worsening of generalized seizure duration or frequency deemed by the investigator to require intervention) after 28 days of treatment. The patient then entered the Extension Phase and began receiving open-label treatment on 17-Sep-98. Concomitant medications during the Extension Phase included lamotrigine, topiramate, lorazepam, naproxen sodium, and anesthetics and analgesics related to having wisdom teeth extracted. On the morning of _____ of the Extension Phase), while receiving 4000 mg of rufinamide daily, the patient was found dead in her dormitory bed. An autopsy revealed findings consistent with seizure disorder. The death was deemed a result of natural causes. No alcohol or illicit drugs were found in the patient's system. The investigator assessed this adverse event as not related to study medication.

b(6)

Reviewer Comments:

Un-witnessed Sudden Death with autopsy - findings that meets the criteria (see discussion below of SUDEP) of Definite SUDEP.

8. Patient Number 052/0011: Sudden Death

This 65-year-old Caucasian male patient entered open-label study 0101 with a diagnosis of symptomatic secondarily generalized seizures. The patient provided no medical history at study entry. Active medical conditions present upon enrollment were depression, hypercholesterolemia, hypertension, hypothyroidism, and hyperhomocystinemia (all since 10-Dec-98). The patient began receiving open-label rufinamide treatment on 26-Jun-99. His weight at study entry was 84 kg. Concomitant non-AED medications during the study period included acetylsalicylate calcium and dipyridamole (the patient was taking these drugs at study entry, with cerebrovascular accident given as the indication, although cerebrovascular accident was not recorded in the medical history) and amiloride, diltiazem, levothyroxine, paroxetine, and simvastatin; concomitant AED therapy included carbamazepine (started on 30-Sep-99). On 11-Aug-99 (Day 47 of rufinamide therapy), while receiving 1200 mg/day of rufinamide, the patient experienced moderate sleep apnea syndrome. Study treatment was continued unchanged. On _____ while receiving rufinamide and carbamazepine therapy, the patient died in bed following an epileptic seizure. Prior to the event, the patient had experienced persisting epileptic seizures and ongoing nocturnal apneas. In the investigator's opinion, the events of sleep apnea syndrome and death were not suspected to be related to study medication.

b(6)

Reviewer Comments:

Sudden Death following witnessed seizure with no autopsy that meets the criteria (see discussion below of SUDEP) of Probable SUDEP.

9. Patient Number 052/0016: Sudden Death

This 33-year-old Caucasian male patient entered open-label study 0101 with a diagnosis of seizures NOS. The patient reported no medical history at study entry, and no active medical conditions other than epilepsy were present upon enrollment. The patient began receiving open-label rufinamide treatment on 24-Jul-99. The only concomitant medication recorded during the study period was AED therapy with carbamazepine (started on 17-Aug-99). ~~of rufinamide therapy~~ of rufinamide therapy), while receiving rufinamide 800 mg/day and carbamazepine (dose unavailable), the patient was found dead in bed. An autopsy provided no information. The investigator felt it was possible that the event may have been the result of an epileptic seizure, since blood was found in the patient's mouth (suggesting he may have suffocated). In the investigator's opinion, the death was not suspected to be related to study treatment.

b(6)

Reviewer Comments:

Un-witnessed Sudden Death with signs of seizure (blood in mouth) and with autopsy that meets the criteria (see discussion below of SUDEP) of Definite SUDEP.

Reviewer Comments:

General Understanding of SUDEP

Prior to discussing the death results, it is perhaps prudent to acknowledge that sudden death is linked to epilepsy. This occurrence of sudden unexpected deaths in epilepsy (SUDEP) is a complex issue that is beyond the scope of this review to discuss comprehensively.

In 2001, in a FDA authored article titled "Mortality in Antiepileptic Drug Development" (Neurology, 2001;56:514-519), Racoosin et al, pooled data from NDAs submitted to the FDA to examine the incidence and causes of mortality in patients with epilepsy participating in clinical trials of AEDs and to examine the incidence of and risk factors for SUDEP. According to this article, in 1993, Burroughs-Wellcome convened a panel of experts and the salient diagnostic criteria for SUDEP were formulated. These were- 1) The victim had epilepsy, defined as recurrent unprovoked seizures, 2) The victim died unexpectedly while in a reasonable state of health, 3) If observed, the death occurred within minutes, 4) The death occurred during normal activities and benign circumstances, thus excluding accidental deaths (ACC) such as drownings, motor vehicle accidents (where the patient was the driver), and falls with immediate death due to trauma, 5) An obvious medical cause of death was not found. An autopsy was necessary to establish a definite SUDEP; if an autopsy was not performed and an obvious medical cause of death was also not established, the case was considered a probable SUDEP, and 6) The death did not occur in the setting of status epilepticus. In addition, a death occurring during or after a seizure was considered SUDEP, but a death in the setting of status epilepticus was not considered to be a SUDEP. The presence of substantial aspiration of gastric contents on autopsy as an obvious medical cause of death was not considered a SUDEP.

In essence, sudden expected, non-traumatic, non-drowning death in an individual with epilepsy, witnessed or un-witnessed, in which postmortem examination did not reveal an anatomical or toxicological cause of death (although several autopsy reports have shown some findings in the brain, lungs, heart and liver in patients with SUDEP) can be considered SUDEP. A definite SUDEP was when all cases met all the criteria with sufficient descriptions of the circumstances of the death and the post mortem did not reveal an obvious cause for death. A probable SUDEP was one that met all the criteria described for the definite SUDEP but without an autopsy.

References for SUDEP

- a) 'Mortality in antiepileptic drug development programs'; Judith A. Racoosin, MD, MPH; et al; *Neurology* 2001;56:514-519
- b) 'Sudden Unexpected Death in Epilepsy'; Shahin Nouri, Et al; <http://www.emedicine.com/neuro/topic659.htm>
- c) http://www.e-epilepsy.org.uk/pages/articles/show_article.cfm?id=108

Based on the understanding of sudden deaths in epilepsy and SUDEP, the rufinamide death cases were examined. 8 deaths were considered sudden deaths by the sponsor. However, following a thorough review of the cases, in the opinion of this reviewer, an additional sudden death case was identified (patient 3054-02071). In 5 of the 9 sudden death cases the cause of death was reported in the autopsy as being most consistent due to seizures (details were lacking). In two cases, although an autopsy was not performed, the most likely causes for the sudden death were seizure related- in one a witnessed seizure preceded death (patient 0052-00011) and in a second case, while no seizures were witnessed, there were tongue bite marks suggesting that the patient had a seizure (patient 006-04411). Therefore, 5 of the 9 sudden death cases met the definite SUDEP criteria because of sudden death and autopsy findings. 2 (patient 0006-04411 and patient 0052-0008) of the remaining 4 sudden death cases met the probable SUDEP criteria of the sudden death (no autopsy and the death occurred following a witnessed seizure in one and with signs of a seizure [tongue biting] in the other). The remaining 2 (patients 3054-02071 and 1282-05025) sudden death cases without an autopsy (or associated seizures or evidences of a seizure) and with no other identifiable causes, also met a probable SUDEP criteria based on the circumstances surrounding the deaths. In essence, 5 sudden deaths met the definite SUDEP criteria and 4 sudden deaths met the probable SUDEP criteria. All rufinamide deaths could be considered SUDEP.

In the context of the concerns of QT shortening and its associated risk of causing sudden cardiac death (stated to be similar and equal to that of QT prolongation) induced by rufinamide (see Safety QT review by Dr. Jones and PK review on special cardiac QT studies), the importance of causes of the sudden death cases described above and their potential attribution to QT shortening become important and relevant particularly when rufinamide is the first antiepileptic where such trait has been unfolded and documented. However, although different chemically, but with a similar mechanism of action on the sodium dependent channels like rufinamide, the several approved agents that have not been tested formally for QT shortening have hitherto not caused worrisome fatal arrhythmias despite the possibility that such pro-arrhythmic potential may exist. Further, while it is plausible that all the 9 sudden deaths (5 definite SUDEP and 4 probable SUDEP) described above may be due to a rufinamide fatal cardiac arrhythmia, the additional critical analyses on death rates as presented in Tables 7.1.1.D does not raise concerns even if such an association between rufinamide and QT is known to exist. Table 7.1.1.D provides comparisons of death rates of rufinamide with those of the approved comparable agents and the

overall SUDEP rates. As shown, the rufinamide SUDEP rate if any is similar to those drugs in the market and well within the background SUDEP rate.

Case (patient 0003-06419) that eventually resulted in death (not sudden) that occurred during rufinamide treatment is discussed below because of its complexity and unusual course of events. Within the complex course the following events were noteworthy although no logical explanation could be deduced. These features were- a) the hemorrhagic pancreatitis, b) the hyperthermia (temperatures as high as 106.16 ° F and 107.24 ° F), tachypnea, tachycardia and stupor c) the rapid downhill course leading to coma and d) the autopsy findings of brain edema and herniation.

Patient number 0003/06419: Death- Brain Edema and Herniation

This 26-year-old male patient entered the study with a diagnosis of partial seizures. The patient's significant medical history included CT-confirmed hydrocephalus, excision of right temporal cystic lesion for the treatment of therapy resistant seizures in 1989, meningeal adhesions in areas of convex and right temporal lobe, and a syndrome of intracranial hypertension. The intracranial hypertension was diagnosed by echoencephalography at 8 years of age following an influenza infection. Symptoms of the intracranial hypertension were intermittent headaches, nausea and vomiting. The patient was treated with biannual 3-week courses of acetazolamide (Diacarb) and potassium/magnesium aspartate (Panangin) for the previous 5 years as prophylactic treatment of the intracranial hypertension.

The patient began rufinamide treatment on 16-Feb-1999. On _____, approximately _____ after entry into the Double-blind Phase, the patient had five episodes of serial complex partial seizures. The rufinamide dose at the time of this adverse event was 3200 mg/day. Concomitant medications were carbamazepine 1200 mg/day and clonazepam 12 mg/day. The patient was treated with diazepam 10 mg p.o. and 10 mg i.m. and hospitalized. Laboratory assessments (hemoglobin and WBC count with differential) were within normal limits. The patient had three more episodes of serial complex partial seizures and was treated with diazepam 100 mg i.v. and hexobarbital 1000 mg i.m. On the following day he received 80 mg of diazepam i.v. in addition to daily carbamazepine and clonazepam as detailed above. The investigator considered the patient to have completely recovered from the seizure exacerbation on 23-Apr-1999. In the investigator's opinion this adverse event was not suspected to be study-drug related but related to the patient's underlying disease. On the evening of _____, while still hospitalized, the patient experienced abdominal pain, hyperthermia (38.5°C), peritoneal signs, and a single episode of vomiting. At the time of the abdominal symptoms, the WBC was 10.5 x 10⁹/L (differential: 79% segmented neutrophils, 4% band cells, 10% lymphocytes and 7% monocytes) and the erythrocyte sedimentation rate (ESR) was 6 mm/h. Amylase and lipase levels were not reported. The patient underwent emergency diagnostic laparotomy with a resultant diagnosis of acute hemorrhagic pancreatitis, peritonitis and intestinal paresis. Abdominal drainage was performed and the patient was transferred to the Intensive Care Unit (ICU). He was treated with cefazolin 2g q.i.d. i.v., gentamycin 240 mg i.m., and enzyme inhibitors for treatment of suspected peritonitis. Rufinamide was discontinued. Laboratory assessments on the following day showed a WBC of 14.6 x 10⁹/L (differential: 55% segmented neutrophils, 39% band cells, 9% lymphocytes and 7% monocytes) and an ESR of 36 mm/h. Hemoglobin, hematocrit, AST/ALT, bilirubin and platelets were within normal limits. An EEG showed no epileptic activity. On 25-Apr-1999, the patient became stuporous and was diagnosed with cerebral edema based on clinical examination findings. On 26-Apr-1999, the patient developed a temperature of 41.8°C (= 107.24° F), tachycardia, tachypnea and a decreased level

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of consciousness; a lumbar puncture was performed which demonstrated increased intracranial pressure. Cerebral spinal fluid (CSF) analysis of protein, glucose, RBCs and WBCs was within normal limits. Laboratory analyses showed a WBC count of $7.8 \times 10^9/L$ (differential: 53% segmented neutrophils, 32% bands cells, 9% lymphocytes and 6% monocytes), an ESR of 46 mm/h, sodium of 149.8 mmol/l and creatinine of 170.8 umol/l. The remainder of the measured laboratory results was within normal limits (hemoglobin, hematocrit, AST/ALT, glucose, potassium and amylase). The patient's stupor, hyperthermia ($41.2^\circ C = 106.16^\circ F$), tachycardia and tachypnea persisted and the patient was intubated and mechanically ventilated. Laboratory results showed a WBC count of $10.6 \times 10^9/L$ (differential: 45% segmented neutrophils, 33% band cells, 18% lymphocytes and 4% monocytes) and a platelet count of $72 \times 10^9/L$. On _____ the patient died. No additional clinical seizure activity had been reported and treatment with 60 mg diazepam i.v., carbamazepine 1200 mg/day and clonazepam 12 mg/day (administered rectally) had continued. The investigator assessed the cause of death to be due to cerebral edema with subsequent cerebral herniation. An autopsy confirmed the diagnosis of cerebral edema (cerebral mass 1700 g) and herniation. Additional findings at autopsy were: pulmonary edema, dystelectases in posterobasal parts of lungs, dynamic intestinal ileus with focal intramural hemorrhages in the small intestine and venous congestion in all visceral organs. In the investigator's opinion these adverse events were not suspected to be study-drug related.

b(6)

Reviewer Comments

There were several unusual adverse events that this patient experienced before dying- hyperthermia, hemorrhagic pancreatitis and the autopsy findings of cerebral edema and herniation. This patient (0003-06419) following full recovery from a series (5) of seizures, developed fever, abdominal pain and vomiting. A diagnostic laparotomy revealed hemorrhagic pancreatitis, peritonitis and intestinal paresis (no details as to how one arrived at such diagnoses). The WBC count was noted to be $14.6 \times 10^9/L$ (55% N, 39% bands, 9% L and 7% M) with normal LFTs and other CBC parameters (amylase and lipase not reported). Over the next 48 hours, the patient became stuporous with rising temperatures ($106.16^\circ F$ and $107.24^\circ F$) and a clinical diagnosis of cerebral edema was made (no details as to how one arrived at such a diagnosis). Repeat WBC continued to show a shift to the left (with bands) and the patient's clinical condition continued to deteriorate with continued fever and requiring intubation with mechanical ventilation. Subsequently the patient died and autopsy showed cerebral edema and herniation. In this case, the peritonitis, although on antibiotic therapy, probably continued to contribute to the fever, the resilient high fever coupled with unexplained cerebral edema and herniation could not be solely attributable to the underlying "peritonitis" or seizures. Of note, the patient was on a carbonic anhydrase inhibitor, and it is known that patients are at greater risk of developing a heat related disorder with the concomitant administration of anticonvulsants and carbonic anhydrase inhibitors (see 2006 PDR, Topamax [p. 2441]).

In conjunction with the case 3054-02071 (described above under sudden death)- the 4 year old female patient, who, while receiving rufinamide (started Sep 1999), experienced several episodes of "fever" (Oct 99, Nov 99, Feb 00) that was not associated with seizures or an infective focus (workup during _____ hospitalization between the 1st and 17th, was negative for an infective source), the occurrence of hyperthermia with rufinamide administration is a concern that requires further consideration. In this patient (3054-02071), a diagnosis of malignant hyperthermia (of neurogenic origin) was made. She recovered fully and was discharged from the hospital after a stay of 17 days in _____

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The cluster of pyrexia cases (see below) noted in LGS patients (Common AE section and Appendix Table 5 [Sponsor's Tables 6.2-23, 6.2-24]) or in the pediatric subgroup (Common AE section and Appendix Table 5 [Sponsor's Tables 6.2-34, 6.2-35, 6.2-36]) coupled with the two cases described above, made this association between rufinamide and malignant hyperthermia (or pyrexia) plausible. The details of the pyrexia were not available since these events were considered neither severe nor the patients discontinued (confirmed by the sponsor in a TCON during the review cycle [as mentioned above]).

While the full picture of the clinical syndrome of malignant hyperthermia was not provided (either did not occur or was not described adequately), other considerations that further favor such plausibility of an association between rufinamide and hyperthermia are— a) hyperthermia with oligohidrosis (no indication that rufinamide patients experienced oligohidrosis) is reported in the warning section of the labels of other anticonvulsants that have a similar mechanism of action as rufinamide on the sodium channels (Zonegran and Topamax), b) in malignant hyperthermia, a genetically heterogeneous disorder, disease-causing mutations have been identified in the genes encoding the α -subunit of the voltage gated sodium channels in addition to the ryanodine receptor (that interacts with L-type calcium channel) (ref: Neurology in Clinical Practice, Bradley et al, 4th edition, Chapter 70, p. 1856 [ISBN 0-7506-7469-5) and c) predisposition for hyperthermia in patients simultaneously receiving drugs such as carbonic anhydrase inhibitors or anticholinergics (as noted in case 0003-06419 who was receiving acetazolamide and as noted in the Topamax label).

It is recommended that the label precaution section incorporate the association between rufinamide and hyperthermia (pyrexia).

The sudden deaths (SUDEP) in this drug program are not reflected in the proposed label. Further, the label does not include a warning section. It is recommended that rufinamide associated SUDEP be included in the Warning section of the label.

7.1.2 Other Serious Adverse Events

TREATMENT EMERGENT NON-FATAL SERIOUS ADVERSE EVENTS

Listings of key information for individual patients with serious adverse events was presented in Sponsor's Appendix I, Tables 7.3.1-0 and 7.3.1-1 (all treated patients with epilepsy), 7.3.1-2 and 7.3.1-3 (adults with partial seizures), 7.3.1-4 (mono-therapy studies), 7.3.1-5 and 7.3.1-6 (LGS study), and 7.3.2-7 and 7.3.2-8 (pediatric patients).

Reviewer's Comment

On Jun 22, 2006, the sponsor submitted a 95 page safety amendment that primarily involved updated and corrected information on SAEs for following subgroups- Adult Double-blind Open-label extension population, LGS Double-blind Open-label extension population, and Pediatric Double-blind Open-label extension population. This resulted in changes in the respective tables (7.2-2, 7.2-5, 7.2-9, and 7.2-13 in the ISS submitted under the NDA). The non-fatal SAE update involved 13 new cases and 4 deletions.

The following was the listing of the 13 patients who experienced a non-fatal SAE who were included into the new tables submitted in Jun 2006 that were not included previously in the original submission:

Protocol 0021E (adult stratum): ZAF/0077/6601: Convulsion; USA/1257/5112: Appendicitis; USA/1272/5054: Convulsion; USA/1272/5125: Skin laceration; USA/1283/5103: Urosepsis; USA/1284/5033: Hyponatremia; USA/1280/5144: Umbilical hernia (this was a second SAE for this patient).

Protocol 0021E (pediatric stratum): USA/1266/3066: Status epilepticus; USA/1274/3157: Clostridium colitis; USA/1274/3159: Gastroenteritis; Pharyngitis; USA/1279/3023: Convulsion; ARG/0001/04610: Acute dehydration; drug intoxication; hyperthermia; hypotension; nystagmus; pallor; vomiting

Protocol 0022E: D/0005/2519: Convulsion (this was a second SAE for this patient)

In addition, four adverse events in four patients were categorized as SAEs due to data entry in the original report for Study 0018E and Study 0021E (adult stratum). The four adverse events incorrectly included as SAEs in these reports are as follows:

Protocol 0018E: USA/1881/0117: weight decreased;

Protocol 0021E (adult stratum): USA/1272/5015: ear pain; USA/1273/5150: dizziness; USA/1280/5141: osteoporosis.

The inadvertent omission of the 13 patients that should have been included and the inclusion of the four SAEs that should not have been included affected Section 7.2.2, Section 7.2.4, Section 7.2.7, and Section 7.2.9 of the ISS. The corrected text and accompanying corrected in-text tables were provided, and the corrected post-text tables were attached.

Overview of All Non-Fatal SAE

Table 7.1.2.A provides an overview of all the non-fatal SAEs by subgroups of the study analysis population. *The incidence of non-fatal SAE (any by SOC term) experienced was greater across all the subgroups for those patients who received rufinamide compared to those who received placebo (hatched areas in Table 7.1.2.A).*

SAFETY TABLE 7.1.2.A				
OVERVIEW OF TREATMENT EMERGENT ANY NON-FATAL SAE ALL STUDY SUBGROUPS				
STUDY ANALYSIS POPULATION	Rufinamide (R)		Placebo (P)	
	N (Patient)	%	N (Patient)	%
All Double-blind				
Exposed	1240	100	635	100
Any AE (Patient N)	78	6.3	25	3.9
All Study Subgroups Combined*				
Exposed	1978	100	--	--
Any AE (Patient N)	268	13.5	--	--
Adult Double-blind				
Exposed	720	100	290	100
Any AE (Patient N)	51	7.1	10	3.4
Adult Double-blind with Open-label*				
Exposed	932	100	--	--
Any AE (Patient N)	124	13.3	--	--
Mono-therapy Double-blind				
Exposed	208	100	67	100
Any AE (Patient N)	7	3.4	0	0
LGS Double-blind				

Exposed	74	100	64	100
Any AE (Patient N)	3	4.1	2	3.1
LGS Double-blind with Open-label*				
Exposed	135	100	--	--
Any AE (Patient N)	22	16.3		
Pediatric Double-blind				
Exposed	212	100	197	100
Any AE (Patient N)	16	7.5	11	5.6
Pediatric Double-blind with Open-label*				
Exposed	391	100	--	--
Any AE (Patient N)	66	16.9	--	--
Ref: Tables 7.2-1, 7.2-2, 7.2-4, 7.2-5, 7.2-7, 7.2-8, 7.2-9, 7.2-12, 7.2-13, ISS, pp 151-165; *Information presented were extracted from the Safety Addendum, Jun 2006, pp 1-97				
Note:				
Hatched areas = greater incidence with rufinamide compared to placebo.				

Treatment Emergent Non-fatal SAE in All Double-blind Subgroup

Appendix Table 6 (Sponsor's Table 7.2-1, ISS), displays the non-fatal serious adverse events that occurred in more than one patient per treatment group. There were a total of 98 serious adverse event reports for 78 (6.3%) rufinamide-treated patients and a total of 28 serious adverse event reports for 25 (3.9%) placebo-treated patients. The estimated exposure in this population was 291.51 patient-years for rufinamide and 149.60 patient-years for placebo. The rates of serious adverse events were therefore 26.76 and 16.71 per 100 patient-years, respectively (Ref: Sponsor's Appendix I, Table 7.3.2-1). No serious adverse events occurred at an incidence greater than 0.6%. The most frequently reported serious events in both treatment groups were related to epilepsy: convulsion (0.6% of patients in both treatment groups), grand mal convulsion (0.4% in the rufinamide group versus 0.6% in the placebo group), partial seizures with secondary generalization (0.3% versus 0%), status epilepticus (0.3% versus 0%), complex partial seizures (0.2% versus 0%), epilepsy (0.1% versus 0%), and petit mal epilepsy (0% versus 0.2%).

Twenty-three serious adverse event reports in the rufinamide group and 7 serious adverse event reports in the placebo group led to discontinuation of treatment.

Treatment Emergent Non-fatal SAE in All Subgroups Combined

Sponsor's Table 7.2-2, Amendment to ISS, displayed the non-fatal serious adverse events that occurred in more than one patient who received rufinamide in any of the studies in patients with epilepsy. There were a total of 343 serious adverse event reports for 268 (13.5%) patients. The estimated exposure to rufinamide in this population was 2552.96 patient-years. The rate of serious adverse events was therefore 10.50 per 100 patient-years (Ref: Sponsor's Appendix I, Table 7.3.2-1).

No serious adverse events occurred at an incidence greater than 2.4%. The most frequently reported serious events with rufinamide were related to epilepsy: convulsion (47 patients), status epilepticus (20 patients), grand mal convulsion (11 patients), partial seizures with secondary generalization (8 patients), complex partial seizures (4 patients), epilepsy (4 patients), and partial seizures (1 patient). The most frequently occurring non-epilepsy related serious adverse events with rufinamide were pneumonia (15 patients) and vomiting (12 patients).

Fifty-three serious adverse event reports led to discontinuation of treatment.

Appendix Table 6 (Sponsor's Table 7.2-3, ISS) displays the distribution of serious adverse events that occurred in more than 5 patients, by median dose in mg/day. (The cut-off of 5 was chosen because the dose information was grouped into 5 categories.) There was no apparent dose-response relationship, for the incidence of either any serious adverse event or individual events except convulsion. However, there was no apparent dose-response relationship for status epilepticus, grand mal convulsion, or partial seizures with secondary generalization.

Treatment Emergent Non-fatal SAE in Adult Double-blind Subgroup

Appendix Table 6 (Sponsor's Table 7.2-4, ISS) displays the non-fatal serious adverse events that occurred in more than one patient per treatment group. There were a total of 56 serious adverse event reports for 51 (7.1%) rufinamide-treated patients and a total of 11 serious adverse event reports for 10 (3.4%) placebo-treated patients. The estimated exposure in this population was 187.49 patient-years for rufinamide and 74.17 patient-years for placebo. The rates of serious adverse events were therefore 27.20 and 13.48 per 100 patient-years, respectively (Ref: Sponsor's Appendix I, Table 7.3.2-2). No serious adverse events occurred at an incidence greater than 1.0%. The most frequently reported serious events in both treatment groups were related to epilepsy: partial seizures with secondary generalization (0.6% in the rufinamide group versus 0% in the placebo group), convulsion (0.4% versus 1.0%), grand mal convulsion (0.3% in each group), and complex partial seizures (0.3% versus 0%). The most common serious event not related to epilepsy was diplopia (0.8% in the rufinamide group versus 0% in the placebo group).

Sixteen serious adverse event reports in the rufinamide group and 4 serious adverse event reports in the placebo group led to discontinuation of treatment.

Treatment Emergent Non-fatal SAE in Adult Double-blind with Open-label Extension Subgroup

Sponsor's Table 7.2-5, Jun 2006 Addendum, ISS, displayed the non-fatal serious adverse events that occurred in more than 1 adult patient with partial seizures who received rufinamide. There were a total of 159 serious adverse event reports for 124 (13.3%) patients. The estimated exposure to rufinamide in this population was 1190.94 patient-years. The rate of serious adverse events was therefore 10.41 per 100 patient-years (Ref: Sponsor's Appendix I, Table 7.3.2-2).

No serious adverse events occurred at an incidence greater than 1.4%. The most frequently reported serious events with rufinamide were related to epilepsy: convulsion (13 patients), partial seizures with secondary generalization (8 patients), grand mal convulsion (6 patients), status epilepticus (5 patients), complex partial seizures (3 patients), epilepsy (2 patients), and partial seizures (1 patient). The most frequently occurring non-epilepsy related serious adverse events with rufinamide were diplopia (8 patients) and ataxia (8 patients).

Sponsor's Table 7.2-6, ISS, displayed the distribution of serious adverse events that occurred in more than 5 patients, by median dose in mg/day. There was no apparent dose-response relationship, for the incidence of either any serious adverse event or individual events.

Twenty-five serious adverse event reports led to discontinuation of treatment.

Treatment Emergent Non-fatal SAE in Double-blind Mono-therapy Subgroup

As shown in Appendix Table 6 (Sponsor's Table 7.2-7, ISS), no placebo-treated patient in this population experienced a serious adverse event. There were a total of 7 serious adverse event reports for 7 (3.4%) rufinamide-treated patients. The estimated exposure in this population was 27.80 patient-years for rufinamide and 2.89 patient-years for placebo. The rates of serious adverse events were therefore 25.18 and 0 per 100 patient-years, respectively (Ref: Sponsor's Appendix I, Table 7.3.2-3). No serious adverse events occurred at an incidence greater than 1.0%. The most frequently reported serious events were convulsion and status epilepticus, which each occurred in 2 patients. Two of the patients with serious adverse events (convulsion and epilepsy) received median doses of <400 mg/day, whereas the remaining 5 patients with serious adverse events received median doses of 2400 to 3200 mg/day (Ref: Sponsor's Appendix I, Table 7.3.7-3). The dose of maximum duration (Ref: Sponsor's Appendix I, Table 7.3.7-2) and maximum daily dose (Sponsor's Appendix I, Table 7.3.7-4) were the same as the median dose for these 7 patients.

No patient discontinued treatment because of a serious adverse event.

Treatment Emergent Non-fatal SAE in LGS Double-blind Subgroup

Appendix Table 6 (Sponsor's Table 7.2-8, ISS) displays all of the non-fatal serious adverse events that occurred in the Double-blind Phase of the LGS study. There were a total of 5 serious adverse event reports for 3 (4.1%) rufinamide-treated patients and a total of 2 serious adverse event reports for 2 (3.1%) placebo-treated patients. The estimated exposure in this population was 16.04 patient-years for rufinamide and 14.19 patient-years for placebo. The rates of serious adverse events were therefore 18.71 and 14.10 per 100 patient-years, respectively (Ref: Sponsor's Appendix I, Table 7.3.2-4). Serious adverse events led to discontinuation of treatment in 1 patient, who was in the rufinamide group and had serious adverse events of vomiting, fatigue, and rash.

Treatment Emergent Non-fatal SAE in LGS Double-blind with Open-label Extension Subgroup

Sponsor's Table 7.2-9, Addendum Jun 2006, ISS, displayed all of the non-fatal serious adverse events experienced during either the Double-blind or Extension Phase of the LGS study by patients who received rufinamide. There were a total of 32 serious adverse event reports for 22 (16.3%) patients. The estimated exposure to rufinamide in this population was 166.60 patient-years. The rate of serious adverse events was therefore 13.21 per 100 patient-years (Sponsor's Appendix I, Table 7.3.2-4). The most frequently reported serious adverse events were pneumonia (6 patients) and vomiting (5 patients). Serious epilepsy-related events were status epilepticus (2 patients), convulsion (2 patients), and grand mal convulsion (1 patient). Sponsor's Tables 7.2-10 and 7.2-11, ISS, displayed the distribution of serious adverse events that occurred in more than one patient, by median dose in mg/kg/day and in mg/day, respectively. The small number of events, and the fact that patients with the longest durations of treatment usually received higher doses, limited the ability to draw conclusions from these data.

Seven serious adverse event reports led to discontinuation of treatment in 5 patients, 1 in the Double-blind Phase and 4 in the Extension Phase.

Treatment Emergent Non-fatal SAE in Pediatric Double-blind Subgroup

Appendix Table 6 (Sponsor's Table 7.2-12, ISS) displays the non-fatal serious adverse events that occurred in more than one patient per treatment group in the double-blind studies in

pediatric patients. There were a total of 17 serious adverse event reports for 16 (7.5%) rufinamide-treated patients and a total of 11 serious adverse event reports for 11 (5.6%) placebo-treated patients. The estimated exposure in this population was 50.32 patient-years for rufinamide and 46.54 patient-years for placebo. The rates of serious adverse events were therefore 31.80 and 23.63 per 100 patient-years, respectively (Sponsor's Appendix I, Table 7.3.2-5). Serious epilepsy-related events were convulsion (2 patients), status epilepticus (2 patients), and grand mal convulsion (1 patient) in the rufinamide group, and grand mal convulsion (2 patients) and petit mal epilepsy (1 patient) in the placebo group. Seven serious adverse event reports led to discontinuation of treatment in the rufinamide group and 2 serious adverse event reports led to discontinuation of treatment in the placebo group.

Treatment Emergent Non-fatal SAE in Pediatric Double-blind with Open-label Extension Subgroup

Sponsor's Table 7.2-13, Addendum Jun 2006, ISS, displayed the non-fatal serious adverse events that occurred in more than one patient who received rufinamide in the combined double-blind and open-label phases of the studies in pediatric patients. There were a total of 88 serious adverse event reports for 66 (16.9%) patients. The estimated exposure to rufinamide in this population was 489.46 patient-years. The rate of serious adverse events was therefore 13.48 per 100 patient-years (Sponsor's Appendix I, Table 7.3.2-5). No serious adverse event occurred at an incidence greater than 3.3%. The most frequently reported serious events with rufinamide were related to epilepsy: convulsion (13 patients), status epilepticus (9 patients), grand mal convulsion (2 patients), and complex partial seizures (1 patient). The most frequently reported non-epilepsy related events were pneumonia (8 patients) and vomiting (7 patients). Sponsor's Table 7.2-14 displayed the distribution of serious adverse events that occurred in more than one patient, by median dose in mg/kg/day. There was no apparent dose-response relationship, but the small number of patients who experienced specific events limited the ability to draw conclusions from these analyses. The results were similar when the occurrence of serious adverse events was examined by dose taken for the maximum duration (Ref: Sponsor's Appendix I, Table 7.3.11-5) or by maximum daily dose (Ref: Sponsor's Appendix I, Table 7.3.11-7). Results by dose in mg/day were summarized in Sponsor's Appendix I, Tables 7.3.11-2, 7.3.11-3, and 7.3.11-4.

Nineteen serious adverse event reports led to discontinuation of treatment.

Non-fatal SAE in the Diabetic Neuropathy Subgroup

One (1.7%) of 60 rufinamide-treated patients and no placebo-treated patient had 3 serious adverse events (angina unstable, coronary artery occlusion, and dyspnea). The rate of serious adverse events was 22.7 per 100 patient-years of exposure to rufinamide. (Ref: Sponsor's Appendix I, Tables 7.3.1-9, 7.3.2-6 and 7.3.12-1.)

Non-fatal SAE in the Healthy Volunteer Subgroup

No healthy volunteer experienced a serious adverse event.

7.1.3 Dropouts and Other Significant Adverse Events

Discontinuations due to AE

Discontinuations due to treatment induced cognitive and psychiatric disorders are discussed under Other Significant AE (7.1.3.3)

Listings of key information for individual patients who discontinued due to adverse events was presented in Sponsor's Appendix I, Tables 7.5.1-0 and 7.5.1-1 (all treated patients with epilepsy), 7.5.1-2 and 7.5.1-3 (adults with partial seizures), 7.5.1-4 (mono-therapy studies), 7.5.1-5 and 7.5.1-6 (LGS study), and 7.5.1-7 and 7.5.1-8 (pediatric patients).

Table 7.1.3.A provides an overview of the incidence of treatment emergent discontinuations due to any AE that occurred in each of the subgroups that the population was categorized for safety analysis.

SAFETY TABLE 7.1.3.A OVERVIEW OF TREATMENT EMERGENT DISCONTINUATIONS DUE TO ANY AE ALL STUDY SUBGROUPS				
STUDY ANALYSIS POPULATION	Rufinamide (R)		Placebo (P)	
	N (Patient)	%	N (Patient)	%
All Double-blind				
Exposed	1240	100	635	100
Any AE →DC (Patient N)	100	8.1	27	4.3
All Study Subgroups Combined				
Exposed	1978	100	--	--
Any AE →DC (Patient N)	259	13.1	--	--
Adult Double-blind				
Exposed	720	100	290	100
Any AE →DC (Patient N)	74	10.3	18	6.2
Adult Double-blind with Open-label				
Exposed	932	100	--	--
Any AE →DC (Patient N)	138	14.8	--	--
Mono-therapy Double-blind				
Exposed	208	100	67	100
Any AE →DC (Patient N)	7	3.4	2	3.0
LGS Double-blind				
Exposed	74	100	64	100
Any AE →DC (Patient N)	6	8.1	0	0
LGS Double-blind with Open-label				
Exposed	135	100	--	--
Any AE →DC (Patient N)	18	13.3	--	--
Pediatric Double-blind				
Exposed	212	100	197	100
Any AE →DC (Patient N)	15	7.1	4	2.0
Pediatric Double-blind with Open-label				
Exposed	391	100	--	--
Any AE →DC (Patient N)	49	12.5	--	--
Ref: Tables 7.4-1, 7.4-3, 7.4-5, 7.4-7, 7.4-9, 7.4-10, 7.4-11, 7.4-14, 7.4-18, ISS, pp 181-204;				
Note:				
Hatched areas = greater incidence with rufinamide compared to placebo.				

Reviewer Comments

It is clear from Table 7.1.3.A that the discontinuation rates for all those subgroups that could be compared with placebo, including the populations for the two sought indications, showed a greater incidence of discontinuations when treated with rufinamide than with placebo.

AEs → DC All Double-blind Subgroup

In the population of all patients with epilepsy who received study drug in double-blind studies, 100 (8.1%) of 1240 rufinamide-treated patients and 27 (4.3%) of 635 placebo-treated patients discontinued treatment due to adverse events. Appendix Table 8 (Sponsor's Table 7.4-1, ISS) displays the adverse events that led to the discontinuation of more than 1 patient in either treatment group. No adverse event was cited as a reason for discontinuation of more than 1.8% of the patients. The events most frequently leading to discontinuation with rufinamide were dizziness (22 patients), fatigue (20 patients), headache (14 patients), nausea (13 patients), and diplopia (12 patients). Rash was the cause of discontinuation for 6 (0.5%) rufinamide-treated patients and 1 (0.2%) placebo-treated patient. The occurrence of rash/ hypersensitivity is discussed in detail under other significant AE.

Appendix Table 8 (Sponsor's Table 7.4-2, ISS) displays the distribution of adverse events leading to discontinuation which occurred in 5 or more patients in the rufinamide group, by median dose in mg/day. The cut-off of 5 was chosen by the sponsor because the dose information was grouped into 5 categories. There were no apparent dose-response relationships. The results were similar when the occurrence of adverse events leading to discontinuation was examined by dose taken for the maximum duration (Ref: Sponsor's Appendix I, Table 7.5.2-2) or by maximum daily dose taken (Ref: Sponsor's Appendix I, Table 7.5.2-4). Kaplan-Meier curves of the time to onset of the first adverse event leading to discontinuation in the 2 treatment groups were also presented. *In both groups (rufinamide and placebo), a majority of patients who discontinued in the all double-blind combined subgroup did so as a result of adverse events within the first 10 days of treatment.*

AEs → DC All Study Subgroups Combined

In the population of all treated patients with epilepsy, 259 (13.1%) of 1978 patients treated with rufinamide discontinued study drug due to adverse events. Sponsor's Table 7.4-3, ISS displayed the adverse events that led to discontinuation of rufinamide in more than one patient. No adverse event was cited as the reason for discontinuation of more than 1.9% of the patients. The events most often leading to discontinuation of rufinamide were fatigue (38 patients), headache (32 patients), nausea (31 patients), and dizziness (31 patients).

Sponsor's Table 7.4-4, ISS, displayed the distribution of adverse events leading to discontinuation which occurred in more than 5 patients, by median dose in mg/day. As noted previously, the cut-off of 5 was chosen by the sponsor because the dose information was grouped into 5 categories. There were no apparent dose-response relationships. The results were similar when the occurrence of adverse events leading to discontinuation was examined by dose taken for the maximum duration (Ref: Sponsor's Appendix I, Table 7.5.3-2) or by maximum daily dose taken (Ref: Sponsor's Appendix I, Table 7.5.3-4).

AEs → DC Adult Double-blind Subgroup

In the population of adults with partial seizures who received study drug in double-blind studies, 74 (10.3%) of 720 rufinamide-treated patients and 18 (6.2%) of 290 placebo-treated patients discontinued treatment due to adverse events. Appendix Table 8 (Sponsor's Table 7.4-5, ISS) displays the adverse events leading to the discontinuation of more than one patient in either treatment group. No adverse event was cited as a reason for discontinuation of more than 2.6%

of the patients. The events most frequently leading to discontinuation of rufinamide were dizziness (19 patients), fatigue (17 patients), headache (13 patients), and diplopia (11 patients).

Appendix Table 8 (Sponsor's Table 7.4-6, ISS) displays the distribution of adverse events leading to discontinuation which occurred in 5 or more patients in the rufinamide group, by median dose in mg/day. As noted previously the cut-off of 5 was chosen by the sponsor because the dose information was grouped into 5 categories. *Dizziness, headache, and diplopia led to discontinuation of higher percentages of patients with median doses of 2400 to 3200 mg/day, relative to patients with lower median doses.* There were no other apparent dose relationships.

The results were similar when the occurrence of adverse events leading to discontinuation was examined by dose taken for the maximum duration (Ref: Sponsor's Appendix I, Table 7.5.4-2) or by maximum daily dose taken (Ref: Sponsor's Appendix I, Table 7.5.4-4). Kaplan-Meier curves of the time to onset of the first adverse event leading to discontinuation in the 2 treatment groups were provided. *According to the sponsor, in both groups (rufinamide and placebo), a majority of patients who discontinued in the adult double-blind subgroup (as in the all double-blind combined subgroup) did so as a result of adverse events within the first 10 days of treatment.*

AEs → DC Adult Double-blind with Open-label Extension Subgroup

In the population of all adults with partial seizures who received rufinamide, 138 (14.8%) of 932 patients discontinued study drug due to adverse events. Sponsor's Table 7.4-7, ISS, displayed the adverse events that led to discontinuation of rufinamide in more than one patient. No adverse event was cited as the reason for discontinuation of more than 2.6% of the patients. The events most often leading to discontinuation of rufinamide were fatigue (24 patients), dizziness (21 patients), and headache (20 patients).

Sponsor's Table 7.4-8, ISS, displayed the distribution of adverse events leading to discontinuation which occurred in more than 5 patients, by median dose in mg/day. As noted previously the cut-off of 5 was chosen by the sponsor because the dose information was grouped into 5 categories. The percentage of patients with dizziness increased as the median dose increased. Otherwise, there were no apparent dose-response relationships. The results were similar when the occurrence of adverse events leading to discontinuation was examined by dose taken for the maximum duration (Ref: Sponsor's Appendix I, Table 7.5.5-2) or by maximum daily dose taken (Appendix I, Table 7.5.5-4).

AEs → DC Mono-therapy Double-blind Subgroup

In the population of patients who received study drug in double-blind mono-therapy substitution studies, 7 (3.4%) of 208 rufinamide-treated patients and 2 (3.0%) of 67 placebo-treated patients discontinued treatment due to adverse events. Appendix Table 8 (Sponsor's Table 7.4-9, ISS) displays all of the adverse events leading to discontinuation. No adverse event was cited as a reason for discontinuation of more than 1.5% of the patients in either group. The events most frequently leading to discontinuation of rufinamide were anxiety (3 patients), nausea (2 patients), paresthesia (2 patients), and rash (2 patients). The occurrence of rash is discussed in detail in the other significant AE Section (Rash/hypersensitivity). No event led to the discontinuation of more than one placebo-treated patient.

The 7 patients in the rufinamide group who discontinued because of adverse events each received the same median dose (Ref: Sponsor's Appendix I, Table 7.5.6-3), maximum dose (Ref: Sponsor's Appendix I, Table 7.5.6-4), and dose of maximum duration (Ref: Sponsor's Appendix I, Table 7.5.6-2). One patient, who discontinued because of nausea, dizziness, headache, received 400 to less than 1600 mg/day. The remaining 6 patients were among the 125 patients in this population who had median doses, maximum doses, and doses of maximum duration within the range of 2400 to 3200 mg/day.

AEs → DC LGS Double-blind Subgroup

Six (8.1%) of 74 rufinamide-treated patients and no placebo-treated patients discontinued study drug during the double-blind study in LGS due to adverse events, as shown in Appendix Table 8 (Sponsor's Table 7.4-10, ISS). The events leading to discontinuation of more than one patient were vomiting (3 patients), somnolence (2 patients), and rash (2 patients). No patient had laboratory abnormalities as a primary reason for discontinuation. Rash is discussed separately under Other Significant AE.

Of the 6 patients in this LGS double-blind population with adverse events leading to discontinuation, one (who discontinued due to rash) received a median dose of <10 mg/kg/day, one (who discontinued due to somnolence) received a median dose of 10 to <20 mg/kg/day, and one (who discontinued due to pneumonia) received a median dose of more than 45 mg/kg/day (Ref: Sponsor's Appendix I, Table 7.5.7-6). The remaining three patients (who discontinued due to a combination of the remaining events shown in Appendix Table 8 [sponsor's table 7.4-10]) received median doses of 30 to 45 mg/kg/day. The results were similar by the dose of maximum duration (Ref: Sponsor's Appendix I, Table 7.5.7-5) and by maximum daily dose (Ref: Sponsor's Appendix I, Table 7.5.7-7). The results are summarized by dose in mg/day in Sponsor's Appendix I, Tables 7.5.7-2, 7.5.7-3, and 7.5.7-4. Three of the 6 patients discontinued due to adverse events that began between Day 2 and Day 17 of treatment. The remaining 3 patients discontinued due to adverse events that began on Day 34 (anorexia, somnolence, and vomiting), Day 36 (somnolence), and Day 59 (pneumonia).

AEs → DC LGS Double-blind with Open-label Extension Subgroup

Sponsor's Table 7.4-11, ISS, displayed the events that led to discontinuation of treatment in the combined double-blind and open-label phases of the LGS study. The events most frequently leading to discontinuation of rufinamide were rash (5 patients) and vomiting (4 patients).

Sponsor's Tables 7.4-12 and 7.4-13 displayed the distribution of adverse events that led to discontinuation of rufinamide in more than one patient, by median dose in mg/kg/day and in mg/day, respectively. The results were similar when analyzed by the dose taken for the maximum duration (Ref: Sponsor's Appendix I, Tables 7.5.8-2 and 7.5.8-5) or by the maximum daily dose taken (Ref: Sponsor's Appendix I, Tables 7.5.8-4 and 7.5.8-7). *There was no apparent dose-response relationship, but the small number of events limited the ability to draw conclusions from these data.*

AEs → DC Pediatric Double-blind Subgroup

In the double-blind studies in pediatric patients, 15 (7.1%) of 212 rufinamide-treated patients and 4 (2.0%) of 197 placebo-treated patients discontinued treatment due to adverse events. Appendix Table 8 (Sponsor's Table 7.4-14, ISS) displays the adverse events leading to the

discontinuation of more than 1 patient in either treatment group. No adverse event was cited as a reason for discontinuation of more than 1.4% of the patients. The events most frequently leading to discontinuation of rufinamide were fatigue, convulsion, and rash (3 patients each). Rash is discussed separately under Other Significant AE.

Appendix Table 8 (Sponsor's Tables 7.4-15 and 7.4-16, ISS) display the distribution of adverse events that led to discontinuation in more than one rufinamide-treated patient, by median dose in mg/kg/day and in mg/day, respectively. There was no apparent dose-response relationship, but the small number of events limits the ability to draw conclusions from these data.

The results were similar when analyzed by the dose taken for the maximum duration (Ref: Sponsor's Appendix I, Tables 7.5.9-2 and 7.5.9-5) or by the maximum daily dose taken (Ref: Sponsor's Appendix I, Tables 7.5.9-4 and 7.5.9-7). Kaplan-Meier curves of the time to onset of the first adverse event leading to discontinuation in the 2 treatment groups were presented. *In both groups, a majority of patients who discontinued did so as a result of adverse events with early onset (within the first week of treatment).*

AEs → DC Pediatric Double-blind with Open-label Extension Subgroup

Sponsor's Table 7.4-17, ISS, displayed the adverse events leading to the discontinuation of more than one patient who received rufinamide in the combined double-blind and open-label phases of the studies in pediatric patients. No adverse event was cited as a reason for discontinuation of more than 2.0% of the patients. The events most frequently leading to discontinuation of rufinamide were rash (8 patients) and convulsion (7 patients). Sponsor's Tables 7.4-18 and 7.4-19, ISS, displayed the distribution of adverse events that led to discontinuation in more than one rufinamide-treated patient, by median dose in mg/kg/day and in mg/day, respectively. There were no apparent dose-response relationships, but the small number of patients who experienced specific events limits the ability to draw conclusions from these data. The results were similar when the occurrence of adverse events leading to discontinuation was examined by dose taken for the maximum duration (Ref: Sponsor's Appendix I, Tables 7.5.10-2 and 7.5.10-5) or by maximum daily dose (Ref: Sponsor's Appendix I, Tables 7.5.10-4 and 7.5.10-7).

AEs → DC Diabetic neuropathy Subgroup

Six (10.0%) of 60 rufinamide-treated patients and 4 (6.3%) of 63 placebo-treated patient discontinued study drugs due to adverse events (Ref: Sponsor's Appendix I, Tables 7.5.1-9 and 7.5.11-1).

AEs → DC Healthy Volunteer Subgroup

Five (1.5%) of 326 rufinamide-treated subjects discontinued due to adverse events. All 5 subjects discontinued for multiple events. The most commonly cited reasons for discontinuation were headache (3 subjects) and dizziness (2 subjects). The remaining events led to discontinuation of only one subject each (Ref: Sponsor's Appendix I, Tables 7.5.1-10 and 7.5.12-1). Data from Study E2080-A001-002 (definitive QT study) were not integrated with data from the other studies in healthy volunteers because the study report had not been completed at the time of database lock for this ISS. Information about discontinuations from Study E2080-A001-002 because of adverse events was presented in the CSR in Module 5.

7.1.3.1 Overall profile of dropouts

There were reasons for drop outs besides related to adverse events such as those due to protocol violations, noncompliance, consent withdrawal, etc. The dropouts due to AE are also discussed in sections 7.1.2, 7.1.3 and 7.1.3.3.

Disposition and Overall Profile of Dropouts

The disposition of the subjects included in the analysis population described under safety analysis population can be discussed under two broad categories.

All patients with epilepsy (double-blind studies with open-label extensions)

The disposition of all patients with epilepsy who received study treatment in the rufinamide clinical studies is summarized in Table 7.1.3.1.A. Similar percentages of patients in the rufinamide group (80.4%) and the placebo group (86.1%) completed double-blind treatment. The most common reasons for premature discontinuation were adverse events (8.1% with rufinamide and 4.3% with placebo) and unsatisfactory therapeutic effect (6.5% and 4.3%, respectively). Other reasons (as shown in Table 7.1.3.1.A) for premature discontinuation occurred in similar percents of patients in the two treatment groups.

According to the sponsor, patients participating in the open-label extensions could continue receiving rufinamide indefinitely. When the sponsor discontinued development of rufinamide, 30.1% of the patients were still receiving drug and returned to the study sites for termination visits (defined in sponsor's Table 2.1-1, ISS, as "number completed"). The most common reason for premature discontinuation of the remaining patients in the open-label extensions was unsatisfactory therapeutic effect (41.6%). However, it is important to note that the maximum duration of exposure to rufinamide in these studies was long, ranging from 3 to 8.5 years.

Patients with epilepsy by study category (double-blind studies)

The disposition of all patients with epilepsy by study category is summarized in Table 7.1.3.1.A for double-blind studies. Among the patients who received rufinamide, 74.4% to 92.8% completed the studies, as did 81.4% to 92.2% of the patients who received placebo. The most common reasons for premature discontinuation of rufinamide were unsatisfactory therapeutic effect (0% to 9.9%) and adverse events (3.4% to 10.3%). They were also the most common reasons for premature discontinuation of placebo (0% to 7.6%) and (0% to 6.2%). Other reasons (as shown in Table 7.1.3.1.A) for premature discontinuation occurred in similar percents of patients in the 2 treatment groups within each study category.

Criteria	ALL DOUBLE-BLIND + OPEN-LABEL			DOUBLE-BLIND SUBGROUPS							
	Double-Blind		Extension	Adult		Monotherapy		LGS		Pediatric	
	R	P	R	R	P	R	P	R	P	R	P
	N	N	N	N	N	N	N	N	N	N	N
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Number Treated	1240	635	1382 [#]	720	290	208	67	74	64	212	197
	100	100	100 [#]	100	100	100	100	100	100	100	100
Number Completed	997	547	416 [#]	536	236	193	58	64	59	183	180
	80.4	86.1	30.1 [#]	74.4	81.4	92.8	86.6	86.5	92.2	86.3	91.4
Number Discontinued	241	88	945	182	54	15	9	10	5	29	17

		19.4	13.9	68.4	25.3	18.6	7.2	13.4	13.5	7.8	13.7	8.6
Reason For Discontinuation	Unsatisfactory Therapeutic Effect	80	27	575	71	22	0	0	3	1	5	4
	Adverse Experience	6.5	4.3	41.6	9.9	7.6	0	0	4.1	1.6	2.4	2.0
	Consent Withdrawal	100	27	134	74	18	7	2	6	0	15	4
	Administrative problem	8.1	4.3	9.7	10.3	6.2	3.4	3.0	8.1	0	7.1	2.0
	Lost to Follow-up	17	10	79	11	5	2	3	1	1	2	2
	Does Not Meet Protocol Criteria	1.4	1.6	5.7	1.5	1.7	1.0	4.5	1.4	1.6	0.9	1.0
	Death	13	5	71	7	1	3	1	0	1	3	2
	Abnormal Lab Value	1.0	0.8	5.1	1.0	0.3	1.4	1.5	0	1.6	1.4	1.0
	Other	4	3	21	0	1	1	0	0	0	1	0
	No Information on Disposition	0.3	0.5	1.5	0	0.3	0.5	0	0	0	0.5	0
		12	11	14	6	4	1	3	0	2	3	4
		1.0	1.7	1.0	0.8	1.4	0.5	4.5	0	3.1	1.4	2.0
		2	3	13	2	2	0	0	0	0	0	1
		0.2	0.5	0.9	0.3	0.7	0	0	0	0	0	0.5
		4	0	3	2	0	1	0	0	0	0	0
		0.3	0	0.2	0.3	0	0.5	0	0	0	0	0
		9	2	35	9	1	0	0	0	0	0	0
	0.7	0.3	2.5	1.3	0.3	0	0	0	0	0	0	
	2	0	21	2	0	0	0	0	0	0	0	
	0.2	0	1.5	0.3	0	0	0	0	0	0	0	

Ref: Sponsor's Tables 2.1-1 and 2.1-2, pp 44-45, ISS, Section 2

Note:
= In the open-label extensions, "completed" patients were those who were still participating in the study when Sponsor ended product development and who returned to the study site for a termination visit.
R= Rufinamide; P= Placebo; LGS= Lennox-Gastaut syndrome;

For the diabetic neuropathy subgroup, in Study 0201, 53 (88.3%) of 60 rufinamide-treated patients and 56 (88.9%) of 63 placebo-treated patients completed the study. The most common reason for discontinuation in both groups was adverse events, which led to premature withdrawal of 6 (10.0%) and 4 (6.3%) patients, respectively. The details were presented in Appendix I, Table 2.1-7 of the submission.

For the healthy volunteer subgroup, three hundred seven (94.2%) of 326 rufinamide-treated subjects completed the studies. The most common reasons for discontinuation were adverse events (5 subjects; 1.5%), withdrawal of consent (4 subjects; 1.2%), and request of the investigator or sponsor (4 subjects; 1.2%). Of the 90 placebo-treated subjects, 89 (98.9%) completed the studies and 1 (1.1%) discontinued because of request of the investigator or sponsor. The details were presented in Appendix I, Table 2.1-8 of the submission.

7.1.3.2 Adverse events associated with dropouts

See 7.1.3 above on treatment emergent premature discontinuations due to adverse event.

7.1.3.3 Other significant adverse events

Under this subset analyses, the sponsor provided results on certain conditions of interest that are known to occur typically with antiepileptics. Discussions on each of these will follow.

Skin Rash & Hypersensitivity Reactions

According to the sponsor, the occurrence of skin reactions in patients who received rufinamide was of interest because- rashes are a frequent occurrence with other AEDs, children are more

prone to develop rashes than are adults, and rashes can be part of a more severe dermatologic or systemic disorder.

All MedDRA Preferred Terms that refer to rash were identified. Appendix Table 7 (Sponsor's Table 7.3-1, ISS) displays the incidence of these events individually, and pooled together into an overall category of rash, for all patients with epilepsy who received study drug in double-blind studies. Results were presented in Sponsor's Appendix I, Table 7.4.1-2 for pediatric patients and in Appendix I, Table 7.4.1-3 for adults with partial seizures. Table... shows these results by population and study type. In concurrence with the sponsor, choice of the double-blind subgroup population for analyses was appropriate because it provides the largest number of patients in whom clinically meaningful comparisons were possible since they received rufinamide and placebo.

Table 7.1.3.3.A provides an overview of all rashes that occurred in the pediatric and adult double-blind subgroups.

SAFETY TABLE 7.1.3.3.A OVERVIEW OF RASH						
SOC	All Double-blind		Pediatrics Double-blind		Adult Double-blind	
	Rufinamide N = 1240	Placebo N = 635	Rufinamide N = 212	Placebo N = 197	Rufinamide N = 720	Placebo N = 290
Skin/Subcutaneous n (%)	122 (9.8)	52 (8.2)	25 (11.8)	8 (4.1)	73 (10.1)	30 (10.3)
All Rash n (%)	38 (3.1)	21 (3.3)	11 (5.2)	4 (2.0)	21 (2.9)	11 (3.8)
Ref: Sponsor's Appendix I, Table 7.4.1-1 for All Double-blind combined; Appendix I, Table 7.4.1-2 for pediatric patients; Appendix I, Table 7.4.1-3 for adults with partial seizures; Sponsor's Table 7.3-1, ISS. Note: Hatched areas indicate significance (see comments in the review section) in the pediatric population.						

Rash occurred in similar percentages of rufinamide-treated patients (3.1%) and placebo-treated patients (3.3%) in the all double-blind combined subgroup, even when the incidence was not corrected for duration of exposure. Rash was a serious adverse event in 3 (0.2%) and 1 (0.2%) patients, who received rufinamide and placebo respectively. Rash led to discontinuation of treatment in 10 (0.8%) and 1 (0.2%) patients, who received rufinamide and placebo respectively. The incidence of rash in the pediatric double-blind subgroup showed the greatest differences between rufinamide and placebo (11 [5.2%] vs. 4 [2.0%] respectively).

To examine the potential for significant events of rash, the adverse events that occurred in all treated patients with epilepsy were reviewed by the sponsor. None of the 1978 patients experienced erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Rash (defined as any of the terms shown in the Appendix Table 7 [Sponsor's Table 7.3-1, ISS]) was a serious adverse event in 5 (0.3%) patients and led to the discontinuation of treatment in 24 (1.2%) patients.

Sponsor's Figures 7.3-1 to 7.3-4, ISS, displayed Kaplan-Meier curves of the time to first occurrence of rash for all double-blind studies combined, adult double-blind subgroup, LGS double-blind subgroup, and the pediatric double-blind subgroup. In the all double-blind subgroup and in adult double-blind subgroup, the curves showed that the onset of rash was similar in both treatment groups, and that the onset of rash was distributed over the course of treatment. There was no sudden increase in onset early or late in treatment. However, in the LGS and pediatric populations, rash tended to occur during the first 2 weeks of treatment.

Three patients had a serious adverse event coded as hypersensitivity and 4 patients (1 of those 3, plus 3 more) discontinued due to hypersensitivity. A total of 5 patients (2 with serious adverse events coded as hypersensitivity and 3 others with serious adverse events coded as pyrexia or rash) suffered an antiepileptic drug hypersensitivity syndrome (fever, rash, and any evidence of internal organ involvement). In all cases, the reaction appeared during the first 4 weeks of treatment. All patients were children. None of them had mucosal involvement or blistering of the skin. All patients quickly recovered after discontinuation of rufinamide. A full description of the patient narratives was included in the CSRs (Module 5). These five patients were-

Patient 0005-02670 (Study 022): SAE- Rash, Allergic Reaction, Fatigue + Discontinuation

About 2 weeks after start of rufinamide therapy, the patient, 12-year old male experienced a rash, (fever was not mentioned as an adverse event) and elevated LFTs (moderate increase in SGPT, from 69 U/L at baseline to 127 U/L, and in SGOT, from 56 U/L at baseline to 147 U/L). Concomitant AEDs were lamotrigine, valproate, and ethosuximide. Lamotrigine had been started about 8 weeks before the baseline visit. Both rufinamide and lamotrigine were discontinued and the patient recovered completely within 4 days of this event.

Patient 1260-03117 (Study 021P): SAE- Hypersensitivity (Allergic reaction) + Discontinuation

This 8-year-old female, 12 days after the start of rufinamide, experienced facial edema, dermatitis (rash), lethargy, and decreased appetite. The patient was ill-appearing with fever, facial swelling, abdominal discomfort, bilateral otitis, and enlarged left preauricular cervical lymph nodes. Cefuroxime axetil had been started 6 days before the onset of the rash for otitis media. Liver enzymes and eosinophils were within normal limits performed 3 days after the onset of the rash. The patient was discontinued from the study. Within 15 days of the onset of the adverse events, the patient completely recovered.

Patient 0005-04408 (Study 021PE): SAE- Hypersensitivity

This 12-year-old female received placebo during the double-blind phase of Study 021P and then entered the open-label Extension Phase. Laboratory tests obtained at that time revealed all values within the normal ranges. On Day 29 of rufinamide treatment, she developed a fever, throat hyperemia, and general weakness, diagnosed as a cold. She was treated with metamizole and acetylsalicylic acid/paracetamol/caffeine. Three days later, she developed a punctate confluent rash that disappeared. The fever recurred on Day 39, and throat hyperemia was again observed. The patient received co-trimoxazol. Three days later, she had darkened urine (note-hematuria was not confirmed), facial edema, and confluent spotted rash. Treatment consisted of ampicillin and taverlyl. The patient was hospitalized on Day 43 in a stuporous state (regarded as life-threatening), suffering from high temperature, intoxication, severe facial edema, edema of neck, tongue and facies, abundant papular rash, and urticaria. Acute respiratory viral infection, toxic allergic rash, and hepatitis were diagnosed. Rufinamide treatment was stopped on Day 60 due to adverse events. Laboratory tests performed on Day 59 revealed values of 82.08 mmol/L for total bilirubin (normal range, 0-42.75 mmol/L), 49.59 mmol/L for direct/conjugated bilirubin (normal range, 0-5.10 mmol/L), 1335 U/L for LDH (normal range, 0-500 U/L), 1345 U/L for SGOT (normal range, 0-100 U/L), and 2165 U/L for SGPT (normal range, 0-110 U/L). The patient was discharged in satisfactory condition on Day 71. No follow-up laboratory data were recorded. The investigator considered the hypersensitivity event not related to study medication but considered it possible that an interaction between anti-epileptic medication and co-

medication in the presence of a viral infection could have contributed to the onset of the event. See also Section 8.1.2.3, Clinically Notable Values.

Patient 1266-03109 (Study 021PE): SAE- Rash, Pyrexia (fever)

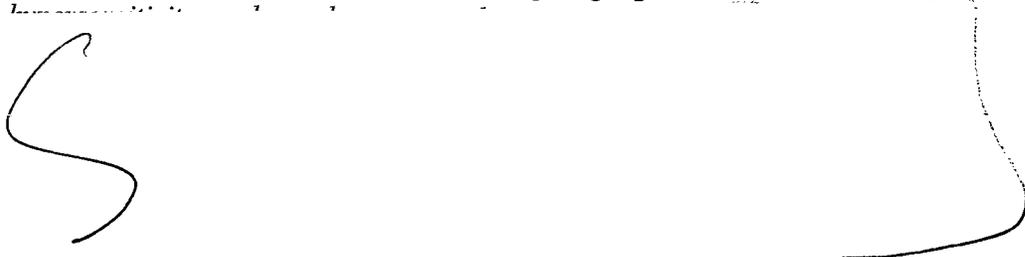
This 8-year-old black male developed fever and a rash on day 11 of rufinamide treatment. No laboratory data were reported prior to these events. A laboratory test performed 3 days later revealed a normal value for eosinophils; slightly low values for WBCs ($2.90 \times 10^9/L$; normal range, $3-15 \times 10^9/L$) and neutrophils (28.37%; normal range, 30-90%); an elevated value for monocytes (20.44%; normal range, 0-20%); and elevated values for LDH (614 U/L; normal range, 0-500 U/L), SGOT (278 U/L; normal range, 0-100 U/L), and SGPT (322 U/L (normal range, 0-110 U/L). Rufinamide was discontinued, and the events resolved by 3 days after their occurrence. A follow-up laboratory test 10 days later revealed a tendency to normalization for LDH (380 U/L; normal range, 0-500 U/L), SGOT (49 U/L; normal range, 0-100 U/L), and SGPT (102 U/L (normal range, 0-110 U/L).

Patient 0008-04216 (Study 021PE): SAE- Allergic Rash, Hematuria

This 7-year-old Caucasian male patient presented with skin erythema on day 12 after the start of rufinamide treatment, which was followed the next day by fever of $39^\circ C$, and then on day 15 by morbilliform exanthema on his face and body, bilateral conjunctival discoloration, and hematuria. The only laboratory values reported for this patient were from samples obtained approximately 2 weeks before the onset of these adverse events. He had normal values for eosinophils (2.0%; normal range, 0-10%) and WBCs ($6.1 \times 10^9/L$; normal range, $3-15 \times 10^9/L$) at that time. According to the sponsor, the patient was seen by the investigator approximately 10 days later and his condition was improving, but he still exhibited some erythema.

Reviewer Comments

The concerns based on cases of hypersensitivity reactions described under other significant adverse events are captured in the proposed label under the precautions section as hypersensitivity reactions with the following language -



b(4)

The question is whether the concern of hypersensitivity reaction depicted in the precautions section of the proposed label needs further emphasis by inclusion in a new warning section. Like wise, the skin rash needs to be included in the label.

The issue of inclusion of skin rash in the label and in the appropriate section and the inclusion of hypersensitivity reactions in the appropriate section (s) of the label, in essence, is one that is not

unique to rufinamide. Several approved anticonvulsants are known to cause both. In order to address this issue further, the labels of some of the approved anticonvulsants specifically related to the information on skin/dermatology rash and hypersensitivity reactions were reviewed. These are summarized in Table 7.1.3.3.B which provides an overview related to skin/dermatology and hypersensitivity reactions.

SAFETY TABLE 7.1.3.3.B OVERVIEW OF SKIN & HYPERSENSITIVITY REACTIONS OF SOME APPROVED ANTIEPILEPTICS					
	Trade Name (Chemical)	AE	LABEL SECTION		Comments/Findings
			Warning	Precautions	
1	Carbotrol, Tegretol (Carbamazepine)	Skin / Rash	x	--	Fatal SJ Reaction, Toxic Epi. Necrolysis (Lyell's syndrome)
		Hypersensitivity	--	--	Not mentioned
2	Tripletal (Oxcarbazepine)	Skin / Rash	x	--	S J Reaction, Toxic Epi. Necrolysis (Lyell's syndrome)
		Hypersensitivity	x	--	Multi-organ hypersensitivity under precautions
3	Gabitril (Tiagabine)	Skin / Rash	--	x	4 cases (one SJ)
		Hypersensitivity	--	--	None mentioned
4	Zonegran (Zonisamide)	Skin / Rash	x	--	Sulfa like drug; 7 skin related SJ deaths in the Japan (postmarket)
		Hypersensitivity	--	--	Not mentioned
5	Lamictal (Lamotrigine)	Skin / Rash	x	x	Black Box Warning
		Hypersensitivity	x	--	
6	Lyrica (Pregabalin)	Skin / Rash	--	x	Based on preclinical findings
		Hypersensitivity	--	--	Not mentioned
7	Keppra (Levetiracetam)	--	--	--	Not mentioned
8	Depacon (Valproate)	--	--	--	Not mentioned
9	Topamax (Topiramate)	--	--	--	Not mentioned
10	Neurontin (Gabapentin)	--	--	--	Not mentioned
Ref: 2006 PDR, pp 412, 998, 1089, 1449, 2279, 2281, 2438, 2499, 2525, 3307, 3175					
Note: Hatched areas = Both skin and hypersensitivity reactions were noted in the label.					

It should be noted that rufinamide, like two other agents Tripletal and Lamictal (shown as hatched areas in Table 7.1.3.3.B) *caused both skin rash and hypersensitivity reaction.*

Based on the nature of the skin rash noted with rufinamide, specifically with the absence of severe reactions such as Stevens Johnson, toxic epidermal necrosis, mucosal lesions, etc, the inclusion of concerns based on the observed skin reactions under the precautions section seems appropriate at this time. *This label amendment is recommended.*

The addition of a warning section to the label and the inclusion of hypersensitivity under this new warning section is recommended. The greater incidence of rash and serious adverse events of rash and or hypersensitivity reactions in the pediatric population should also be included in the label.

Cognitive Adverse Events & Discontinuations

To examine the occurrence of cognitive adverse events, all Preferred Terms that refer to such events were identified. Appendix Table 7 (Sponsor's Table 7.3-2, ISS) displays the incidence of these events individually, and pooled together into an overall category of cognitive disorder, for all patients with epilepsy who received study drug in double-blind studies. In concurrence with the sponsor, choice of the double-blind subgroup population for analyses was appropriate because it provides the largest number of patients in whom clinically meaningful comparisons were possible since they received rufinamide and placebo. Appendix Table 7 (Sponsor's Table 7.3-3, ISS) displays the incidence of cognitive disorder leading to discontinuation from the study.

Based on the pooled Preferred Terms, cognitive disorder occurred in 16.6% of the rufinamide-treated patients and 13.9% of the placebo-treated patients in the all double-blind subgroup population (N= 1240 for rufinamide and N= 635 for placebo). Only one of the adverse events shown in Appendix Table 7 (Sponsors' table 7.3-2, ISS) was a serious adverse event: aphasia in 1 (0.1%) rufinamide-treated patient (Patient 0002-08019 who had a seizure and a prolonged post-ictal phase characterized by hemiparesis and aphasia).

Cognitive disorder led to discontinuation of treatment in 19 (1.5%) rufinamide-treated patients and 4 (0.6%) placebo-treated patients, as shown in Appendix Table 7 (Sponsor's Table 7.3-3, ISS) in the all double-blind subgroup. The most frequently cited reason for discontinuation was somnolence (8 rufinamide-treated patients and 2 placebo-treated patients) followed by disturbance in attention, sedation and others.

Serious cognitive adverse events that occurred in all 1978 treated patients with epilepsy occurred in 5 (0.3%) patients and led to the discontinuation of treatment in 36 (1.8%) patients.

Psychiatric Adverse Events & Discontinuations

Appendix Table 7 (Sponsor's Table 7.3-4, ISS) displays the incidence of psychiatric events (within the MedDRA SOC) for all patients with epilepsy who received study drug in double-blind studies. In concurrence with the sponsor, choice of the double-blind subgroup population for analyses was appropriate because it provides the largest number of patients in whom clinically meaningful comparisons were possible since they received rufinamide and placebo. Appendix Table 7 (Sponsor's Table 7.3-6, ISS) displays the incidence of psychiatric disorder leading to discontinuation from the study and Appendix Table 7 (Sponsor's Table 7.3-5, ISS) displays the incidence of psychiatric disorder as serious AE.

The incidences of any psychiatric disorder (14.0% rufinamide vs. 13.9% placebo) and of specific psychiatric adverse events were similar for the two treatment groups. The most frequently reported event in both groups was insomnia, which occurred in 3.0% of the rufinamide-treated patients and 2.5% of the placebo-treated patients. The next most frequently reported events were anxiety (2.7%) in the rufinamide group (vs. 1.4% placebo) and irritability (1.6%) in the placebo group (vs. 1.2% rufinamide).

Psychiatric disorders were serious adverse events in fewer than 1% of the patients in both treatment groups, as shown in Appendix Table 7 (Sponsor's Table 7.3-5, ISS). The only events that were serious in more than 1 patient per group were psychotic disorder (3 patients) and apathy (2 patients), which were serious events in the rufinamide group only.

Psychiatric disorders led to the discontinuation of treatment in 1.5% of the rufinamide-treated patients and 1.6% of the placebo-treated patients, as shown in Appendix Table 7 (Sponsor's

Table 7.3-6, ISS). The events most commonly leading to discontinuation of rufinamide treatment were anxiety and irritability (4 patients each).

Suicide and Suicide Attempt

No patient who died in any of the rufinamide clinical studies committed suicide (see Table 7.1.1.A). Three patients in the clinical studies had adverse event that was coded to the Preferred Term of suicide attempt.

In the double-blind, adjunctive therapy studies in adults with partial seizures, this event occurred in 1 (0.1%) of the 720 patients in the rufinamide group and 1 (0.3%) of the 290 patients in the placebo group (Ref: Sponsor's Appendix I, Table 6.4.1-2). One additional adult with partial seizures had an adverse event of suicide attempt during the Extension Phase of a double-blind study (Ref: Sponsor's Appendix I, Table 6.5.1-2). Therefore, the overall rate of suicide attempt among the 1978 patients who received at least 1 dose of rufinamide was 0.1% (2 patients) (Ref: Sponsor's Appendix I, Table 6.3.1-2).

Brief narratives for these patients who received rufinamide are provided below.

Patient 0004-03048 (Study AE/ET1): SAE- Suicide Attempt + Discontinuation

Patient was a 38-year-old female with partial seizures whose medical history included a suicide attempt approximately 10 years before she entered the study, although this information had not been provided to the investigator when the patient enrolled in the study. She was randomly assigned to receive rufinamide 800 mg/day and began treatment on 16-Jul-93. Concomitant medications included phenytoin and clonazepam. On Day _____ of treatment, the patient attempted to commit suicide by ingesting 5 g of phenytoin. She was hospitalized and treated, and subsequently referred to a psychiatric hospital. Rufinamide treatment was discontinued at the time of the event. The investigator considered the suicide attempt to be unrelated to study medication.

b(6)

Patient 0003-01614 (Study AE/ET1E): SAE- Suicide Attempt + Discontinuation, SAE- Osteoarthritis

Patient was a 37-year-old male who received rufinamide during the double-blind portion of Study AE/ET1 and entered the open-label extension on 07-Jul-94. On _____ of rufinamide therapy), while receiving 1200 mg/day of rufinamide, the patient was hospitalized following a suicide attempt (not involving rufinamide). Although not reported at study entry, the patient had a history of depression but not suicide attempt. The patient was assessed as recovered with sequelae on the day of admission, but remained hospitalized to undergo psychiatric follow-up. Study drug was discontinued as a result of the suicide attempt, with the last dose given on _____ (the day of admission). In the investigator's opinion, the suicide attempt was not suspected to be related to study medication.

b(6)

Two additional rufinamide-treated patients had adverse events that coded to the Preferred Term of overdose, but neither overdose was connected with a suicide attempt.

Patient 1284-05045 (Study 021A) experienced SAE- Depression aggravated (Suicide attempt) and discontinued. This patient was treated with placebo.

Reviewer Comments on CNS/Neuropsychiatric AE

The incidences of CNS AEs under the common AE and very common AE (section 7.1.5), coupled with those discussed in the Other significant AE (section 7.1.3.3 under the CNS and psychiatric), are similar and comparable to those reflected in the labels of the some of the approved antiepileptics. This review of AE under CNS/Neuropsychiatric AEs for some of the approved agents (names listed in Table 7.1.3.3.B and Table 7.1.3.3.C]) from the labels indicated the following- a) the CNS/Neuropsychiatric AEs were either listed under the precaution or warning section of the label, b) *the rates of incidences listed under the preferred terms either under common AE, discontinuations, or SAEs when indicated appeared to be generally comparable to rufinamide. These suggested that both qualitatively and quantitatively, the CNS/Neuropsychiatric AE profile of rufinamide was no better or no worse than those of some of the approved agents.*

It is recommended that under a new warning section in the label (see hypersensitivity reaction comments) — neuropsychiatric AEs be included.

b(4)

Status Epilepticus/Convulsions

Appendix Table 7 (Sponsor's Table 7.3-7, ISS) displays the incidence of selected epilepsy-related events for all patients with epilepsy who received study drug in double-blind studies. In concurrence with the sponsor, choice of the double-blind subgroup population for analyses was appropriate because it provides the largest number of patients in whom clinically meaningful comparisons were possible since they received rufinamide and placebo.

The incidences of convulsion as an adverse event, a serious adverse event, and an adverse event leading to discontinuation were similar in the two treatment groups. The incidences of grand mal convulsion as an adverse event, a serious adverse event, and an adverse event leading to discontinuation were lower in the rufinamide group than in the placebo group. Status epilepticus occurred only in the rufinamide group and in 0.9% of the patients.

The interpretation and significance of these results on epilepsy-related events (Appendix Table 7 [Sponsor's Table 7.3-7, ISS]) were difficult because the placebo rates were generally equal or greater than rufinamide rates for convulsions and grand mal in contrast to status rates.

While it can be argued that the lower rates with rufinamide compared to placebo for the categories of convulsion and grand mal convulsion may reflect drug benefit, the rates of 0.9% and 0% for rufinamide and placebo respectively, for the category of status, however questions this benefit. Because standard definitions were not implemented (as acknowledged by the sponsor- see below for language in proposed label) and in order to further assess the higher incidence of status, the comparative status epilepticus rates for the approved antiepileptics were sought. These are shown in Table 7.1.3.3.C. No firm conclusions can be drawn other than that rufinamide's profile with respect to status epilepticus, generally can be considered no better or worse than the others. *It is recommended that additional information from the sponsor should be sought- such as those with previous history of status, to assess the possibility if there was a particular subgroup of patients in whom such exacerbations occurred, etc.*

Although it is premature to negotiate label language at this time, it is worth noting that the following language was included in the proposed label under the precaution section-

SAFETY TABLE 7.1.3.3.C OVERVIEW OF STATUS EPILEPTICUS OF SOME APPROVED ANTIEPILEPTICS						
	Trade Name (Chemical)	LABEL SECTION		Controlled		All Studies
		Warning	Precautions	Drug	Placebo	
1	Rufinamide	--	Proposed	N=1240 11 (0.9%)	635 0 (0)	NP
2	Gabitril (Tiagabine)	x	--	N=494 4 (0.8%)	N=275 2 (0.7%)	N=NP (5%)
3	Zonegran (Zonisamide)	--	x	N= NP (1.1%)	N=NP (0%)	N=NP (1%)
4	Lamictal (Lamotrigine)	--	x	NP	NP	7/2343 (0.29%)
5	Neurontin (Gabapentin)	x	--	N=543 3 (0.6%)	N=378 2 (0.5%)	31/2074 (1.5%)
6	Trileptal (Oxcarbazepine)	Not mentioned				
7	Lyrica (Pregabalin)	Not mentioned				
8	Keppra (Levetiracetam)	Not mentioned				
9	Depacon (Valproate)	Not mentioned				
10	Topamax (Topiramate)	Not mentioned				
11	Carbotrol, Tegretol (Carbamazepine)	Not mentioned				

Ref: 2006 PDR, pp 999, 1090, 1452, 2500; Sponsor's Table 7.3-7, ISS
Note: NP=Not Provided

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

Information pertinent to sections 7.4.2.1 - 7.4.2.5 under 7.4.2 (explorations for predictive factors) is also discussed in here.

Overview of Any Common AE Occurrence All Studies

The overall incidences of treatment emergent any common AEs for all the subgroup populations that were analyzed are presented in Table 7.1.5.A. *Except for the pediatric double-blind subgroup, the incidence of common AE between the rufinamide and placebo treated subjects were comparable. The rates for the pediatric double-blind subgroup are shown as hatched areas in Table 7.1.5.A.*

SAFETY TABLE 7.1.5.A

OVERVIEW OF TREATMENT EMERGENT ANY COMMON AE ALL STUDY SUBGROUPS				
STUDY ANALYSIS POPULATION	Rufinamide (R)		Placebo (P)	
	N (Patient)	%	N (Patient)	%
All Double-blind				
Exposed	1240	100	635	100
Any AE (Patient N)	975	78.6	497	78.3
All Study Subgroups Combined				
Exposed	1978	100	--	--
Any AE (Patient N)	1761	89.0	--	--
Adult Double-blind				
Exposed	720	100	290	100
Any AE (Patient N)	580	80.6	236	81.4
Adult Double-blind with Open-label				
Exposed	932	100	--	--
Any AE (Patient N)	806	86.5	--	--
Mono-therapy Double-blind				
Exposed	208	100	67	100
Any AE (Patient N)	135	64.9	47	70.1
LGS Double-blind				
Exposed	74	100	64	100
Any AE (Patient N)	60	81.1	52	81.3
LGS Double-blind with Open-label				
Exposed	135	100	--	--
Any AE (Patient N)	124	91.9		
Pediatric Double-blind				
Exposed	212	100	197	100
Any AE (Patient N)	177	83.5	147	74.6
Pediatric Double-blind with Open-label				
Exposed	391	100	--	--
Any AE (Patient N)	357	91.3	--	--
Ref: Tables 6.2-1, 6.2-5, 6.2-9, 6.2-13, 6.2-14, 6.2-18, 6.2-22, 6.2-27, 6.2-28, 6.2-33, 6.2-37 ISS, pp 88-122				
Note:				
Hatched areas = greater incidence with rufinamide compared to placebo.				

Common AE Occurrence in All Double-blind Subgroup

The incidence of common treatment emergent AE by SOC is presented in Appendix Table 5 (Sponsor's Table 6.2-1, ISS). At least one adverse event occurred in 78.6% of the rufinamide-treated patients and 78.3% of the placebo-treated patients. *The rates of common adverse events by most SOCs were similar in the two treatment groups, except that nervous system disorders, general disorders and administration site conditions, and eye disorders occurred at higher rates in the rufinamide group.*

Very common adverse events by Preferred Term in All Double-blind Subgroup

Appendix Table 5 (Sponsor's Table 6.2-2, ISS) displays the incidence of very common adverse events, i.e., those that occurred in 10.0% or more of the patients in either treatment group, by Preferred Term. While the overall incidence rates for common AE in All Double-blind subgroup were comparable between the two treatment groups (78.6 and 78.3 for rufinamide and placebo respectively), the very common AE rates by preferred term for rufinamide were greater compared to placebo. The most frequently reported events in both groups were headache (22.9%

vs. 18.8%), dizziness (15.5% vs. 9.4%), fatigue (13.6% vs. 9.0), somnolence (11.8% vs. 9.1%), and nausea (11.4% vs. 7.6%).

Very Common Adverse Events by Severity in All Double-blind Subgroup

As shown in Appendix Table 5 (Sponsor's Table 6.2-3, ISS), adverse events were judged by the investigators to be mild in 394 (31.8%) of the 1240 patients who received rufinamide and in 240 (37.8%) of the 635 patients who received placebo. At least one adverse event was considered moderate in an additional 448 (36.1%) and 199 (31.3%) rufinamide and placebo patients, respectively. At least one severe adverse event occurred in 133 (10.7%) rufinamide-treated patients and 58 (9.1%) placebo-treated patients.

The table additionally displays the events that occurred in 10% or more of the patients, by severity. The majority were mild or moderate in severity. The overall rates by severity for the most common events of headache, dizziness, fatigue, somnolence and nausea in patients who received rufinamide was greater than those who received placebo in the All double-blind combined data. The highest rates of severe events were for headache, which was severe in 1.6% of rufinamide-treated patients and 1.9% of placebo-treated patients. The remaining very common adverse events were severe in 1% or fewer patients in either group.

Very Common Adverse Events by Dose in All Double-blind Subgroup

The incidence of adverse events that occurred in 10.0% or more of the patients is presented by median dose in Appendix Table 5 (Sponsor's Table 6.2-4, ISS) for all patients with epilepsy who received study drug during double-blind studies. According to the sponsor, interpretation of the results for the lower median dose ranges was confounded by the inclusion of children and a relatively large number of adults who were enrolled in studies (primarily Studies AE/ET1 and AE/PT2) that evaluated lower doses and that used the older Clinical Service Form of rufinamide tablets, which is known to have lower bioavailability than the newer Final Market Image formulation. Such patients had less exposure to rufinamide than did patients who received higher doses and/or the newer formulation, making it difficult to draw conclusions about dose relationships based solely on the amount of drug taken. The results were generally similar when adverse events were analyzed by the dose of maximum duration (Ref: Sponsor's Appendix I, Table 6.2.1-5) and by maximum dose (Ref: Sponsor's Appendix I, Table 6.2.1-7). There was an apparent dose-response relationship between the doses administered and the occurrence of dizziness, somnolence, and nausea in the All double-blind combined data.

Common AE Occurrence in All Subgroups Combined

Sponsor's Table 6.2-5, ISS, displayed the incidence of adverse events by SOCs for all patients with epilepsy who received rufinamide. At least 1 adverse event occurred in 89.0% of the patients. The rates of adverse events by most SOCs were higher than during double-blind treatment only, reflecting the longer duration of exposure (2552.96 patient-years).

Very Common Adverse Events by Preferred Term All Subgroups Combined

Sponsor's Table 6.2-6, ISS, displayed the incidence of adverse events that occurred in 10.0% or more of the patients with epilepsy who received rufinamide during a Double-blind Phase, an Extension Phase, or both phases in any study. The most frequently reported adverse events were headache (29.5%), dizziness (22.5%), and fatigue (17.7%).