

Very Common Adverse Events by Severity All Subgroups Combined

Sponsor's Table 6.2-7, ISS, displayed the events that occurred in 10% or more of the patients. Adverse events were judged by the investigators to be mild in 466 (23.6%) of the 1978 patients who received rufinamide; at least one adverse event was moderate in an additional 884 (44.7%) patients; and at least one severe adverse event occurred in 411 (20.8%) patients. The majority were mild or moderate in severity. The highest rate of severe events was for headache, which was severe in 2.7% of the patients.

Very Common Adverse Events by Dose All Subgroups Combined

The incidence of adverse events that occurred in 10.0% or more of the rufinamide-treated patients was presented by median dose in Sponsor's Table 6.2-8, ISS, for all treated patients with epilepsy. The rates of any adverse event and of each of the most frequently occurring adverse events generally increased as the median dose of rufinamide increased. According to the sponsor, the differences by dose was confounded by the duration of treatment, as patients who received higher median doses generally were treated at those doses for longer periods, as shown in Appendix Table 4 (Sponsor's Table 5.2-1, ISS). In addition, 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.

Reviewer Comments

Since the focus was on the clinically meaningful placebo-controlled data, for purposes of keeping the review concise, the AE data tables for the All Studies Combined were not included in the review. Likewise, those tables involving open-label data were also excluded.

Common AE Occurrence in Adult Double-blind Subgroup

Appendix Table 5 (Sponsor's Table 6.2-9, ISS) displays the incidence of adverse events by SOCs for all adults with partial seizures who received study drug in double-blind studies. At least one adverse event occurred in 80.6% of the rufinamide-treated patients and 81.4% of the placebo-treated patients. The rates of adverse events by most SOCs were similar in the two treatment groups. Eye disorders, musculoskeletal and connective tissue disorders, metabolism and nutrition disorders, and ear and labyrinth disorders occurred at higher rates in the rufinamide group compared to placebo.

Very Common Adverse Events by Preferred Term Adult Double-blind Subgroup

Appendix Table 5 (Sponsor's Table 6.2-10, ISS) displays the incidence of adverse events that occurred in 10.0% or more of the patients in either treatment group. The differences in the occurrence of headache and nausea were not remarkable in the 2 treatment groups. The percentages of patients with the remaining very common adverse events (dizziness, fatigue, and somnolence) were higher with rufinamide than placebo. While the overall incidence rates for common AE in the Adult double-blind subgroup were comparable between the two treatment groups (80.6 and 81.4 for rufinamide and placebo respectively), the very common AE rates by

preferred term for rufinamide were greater for dizziness (19.4% vs. 11.4%), fatigue (17.6% vs. 11.7%), and somnolence (10.4% vs. 7.2) compared to placebo.

Very Common Adverse Events by Severity Adult Double-blind Subgroup

Appendix Table 5 (Sponsor's Table 6.2-11, ISS) displays the events that occurred in 10% or more of the patients, by severity. Adverse events were judged by the investigators to be mild in 215 (29.9%) of the 720 patients who received rufinamide and in 110 (37.9%) of the 290 patients who received placebo. At least one adverse event was moderate in 274 (38.1%) and 96 (33.1%) rufinamide and placebo patients, respectively. At least one severe adverse event occurred in 91 (12.6%) rufinamide-treated patients and 30 (10.3%) placebo-treated patients. 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 this adult double-blind data. The majority were mild or moderate in severity. The highest rates of severe events were for headache, which was severe in 2.2% of rufinamide-treated patients and 2.4% of placebo-treated patients. The remaining very common adverse events were severe in 1.4% or fewer patients in either group.

Very Common Adverse Events by Dose Adult Double-blind Subgroup

The incidence of adverse events that occurred in 10.0% or more of the rufinamide-treated patients in this population is presented by median dose in Appendix Table 5 (Sponsor's Table 6.2-12, ISS). The rates of any adverse event and of each of the most frequently occurring adverse events were generally higher in the 2 highest dose groups (2400 - ≤ 3200). According to the sponsor, interpretation of the results for the lower median dose ranges was confounded by the inclusion of a relatively large number of patients 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. The results were similar for median dose and dose of maximum duration (Ref: Sponsor's Appendix I, Table 6.4.1-5). The dose-related trend was somewhat more pronounced when the results were analyzed by maximum dose (Ref: Sponsor's Appendix I, Table 6.4.1-7).

Occurrence of Common AE > 2% and > Placebo in Adult Double-blind Subgroup

Appendix Table 5 (Sponsor's Table 6.2-13, ISS) displays all adverse events that occurred in more than 2.0% of the rufinamide-treated patients with an incidence that was higher in the rufinamide group than in the placebo group.

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Reviewer Comments

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Common AE Occurrence in Adult Double-blind with Open-label Extension Subgroup

Sponsor's Table 6.2-14, ISS, displayed the incidence of adverse events by SOCs for adults with partial seizures who received rufinamide during a Double-blind Phase, an Extension Phase, or both phases in any study. At least one adverse event occurred in 86.5% of the patients. The

rates of adverse events by most SOC's were higher than during double-blind treatment only, reflecting the longer duration of exposure (1190.94 patient-years).

Very Common AE Occurrence by Preferred Term in Adult Double-blind with Open-label Extension Subgroup

Sponsor's Table 6.2-15, ISS, displayed the incidence of adverse events that occurred in 10.0% or more of the adults with partial seizures 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 (33.9%), dizziness (26.4%), and fatigue (20.6%).

Very Common AE Occurrence by Severity in Adult Double-blind with Open-label Extension Subgroup

Sponsor's Table 6.2-16; ISS displayed the events that occurred in 10% or more of the patients. The majority were mild or moderate in severity. The highest rate of severe events was for headache, which was severe in 3.4% of the patients. Adverse events were judged by the investigators to be mild in 209 (22.4%) of the 932 patients who received rufinamide; at least one adverse event was moderate in 405 (43.5%) patients; and at least one severe adverse event occurred in 192 (20.6%) patients.

Very Common AE Occurrence by Dose in Adult Double-blind with Open-label Extension Subgroup

The incidence of adverse events that occurred in 10.0% or more of the rufinamide-treated patients was presented by median dose in Sponsor's Table 6.2-17, ISS. The rates of any adverse event and of each of the most frequently occurring adverse events generally increased as the median dose of rufinamide increased. According to the sponsor, the differences by dose was confounded by the duration of treatment, because patients who received higher median doses generally were treated at those doses for longer periods, as shown in Appendix Table 4 (Sponsor's Table 5.4-1, ISS). In addition, interpretation of the results for the lower median dose ranges is confounded by the inclusion of 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. The results were similar for median dose and dose of maximum duration (Ref: Sponsor's Appendix I, Table 6.5.1-5). The dose-related trend was somewhat more pronounced when the results were analyzed by maximum dose (Ref: Sponsor's Appendix I, Table 6.5.1-7).

Reviewer Comments

Since the focus was on the placebo-controlled data, for purposes of keeping the review concise, the AE data tables involving open-label data (as for the All Studies Combined) were not included in the review.

Common AE Occurrence in Double-blind Mono-therapy Substitution Subgroup

Sponsor's Table 6.2-18, ISS, displayed the incidence of adverse events by SOC's for all patients in the double-blind mono-therapy substitution studies. At least one adverse event occurred in 64.9% of the rufinamide-treated patients and 70.1% of the placebo-treated patients. The rates of

adverse events by most SOCs were similar in the two treatment groups. General disorders, psychiatric disorders, infections and infestations, and metabolism and nutrition disorders occurred at higher rates in the rufinamide group, whereas musculoskeletal and connective tissue disorders and injury, poisoning, and procedural complications occurred at higher rates in the placebo group.

Very Common AE Occurrence by Preferred Term in Double-blind Mono-therapy Substitution Subgroup

Sponsor's Table 6.2-19, ISS, displayed the incidence of adverse events that occurred in 10.0% or more of the patients in either treatment group. Three events occurred at that rate. Nausea and headache occurred in comparable percentages of patients in the 2 groups, whereas somnolence occurred in a higher percentage of patients in the placebo group than the rufinamide group.

Very Common AE Occurrence by Severity in Double-blind Mono-therapy Substitution Subgroup

Sponsor's Table 6.2-20, ISS, displayed the events that occurred in 10% or more of the patients, by severity. Adverse events were judged by the investigators to be mild in 75 (36.1%) of the 208 patients who received rufinamide and in 26 (38.8%) of the 67 patients who received placebo. At least one adverse event was moderate in an additional 49 (23.6%) and 21 (31.3%) patients, respectively. At least one severe adverse event occurred in 11 (5.3%) rufinamide-treated patients and 0 placebo-treated patients. The majority were mild or moderate in severity.

Very Common AE Occurrence by Dose in Double-blind Mono-therapy Substitution Subgroup

The incidence of the very common adverse events in this population was presented by median dose in Sponsor's Table 6.2-21, ISS. There were essentially 2 median dose groups for this population, and the overall rate of adverse events was similar for the 2 groups. Nausea occurred at a higher rate in the higher dose group.

Reviewer Comments

This double-blind mono-therapy population differed from the other populations presented in this summary because of the designs of the studies pooled (Studies 016, 038, and 039; see Appendix Table 1 [Sponsor's Table 1.2-1, ISS]). First, Study 016 was designed to compare 2 doses of rufinamide and did not include a placebo group. Thus, the number of placebo-treated patients in this population was smaller than the number of rufinamide-treated patients. Second, 70 of the rufinamide-treated patients (all from Study 016) received very low doses (300 mg/day) per the study protocol. These factors made interpretations of the results difficult. For these reasons and because the focus was on the placebo-controlled adjunctive therapy data (the sought indication), for purposes of keeping the review concise, the AE data tables involving mono-therapy data were (as for the All Studies Combined and open-label extensions) not included in the review.

Common AE Occurrence in LGS Double-blind Subgroup (Single study)

The incidence of adverse events by SOCs is presented for the study in LGS in Appendix Table 5 (Sponsor's Table 6.2-22, ISS). The incidences of any adverse events and of adverse events by most SOCs were similar in the two treatment groups.

Very Common AE Occurrence by Preferred Term in LGS Double-blind Subgroup

The incidence of adverse events that occurred in 10.0% or more of the patients in either treatment group is presented for the study in LGS in Appendix Table 5 (Sponsor's Table 6.2-23, ISS). In this population, the patients in the two treatment groups had similar durations of exposure to study drug (median of 2.8 months in both groups). Four events occurred in 10% or more of the patients in either group. Somnolence and vomiting were more frequent with rufinamide (somnolence 24.3% vs. 12.5% and vomiting 21.6% vs. 6.3%) than placebo and pyrexia and diarrhea were more frequent with placebo than rufinamide.

Very Common AE Occurrence by Severity Term in LGS Double-blind Subgroup

Appendix Table 5 (Sponsor's Table 6.2-24, ISS) displays the events that occurred in 10% or more of the patients, by severity. Adverse events were judged by the investigators to be mild in 17 (23.0%) of the 74 patients who received rufinamide and in 31 (48.4%) of the 64 patients who received placebo. At least one adverse event was moderate in an additional 33 (44.6%) and 15 (23.4%) rufinamide and placebo patients, respectively. At least one severe adverse event occurred in 10 (13.5%) rufinamide-treated patients and 6 (9.4%) placebo-treated patients. The majority were mild or moderate in severity. The highest rate of severe events was for somnolence, which was severe in 4.1% of rufinamide-treated patients and 0% of placebo-treated patients. The more frequent events of somnolence and vomiting in patients in the LGS double-blind study (s) were also greater in severity compared to placebo.

Very Common AE Occurrence by Dose in LGS 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 6.2-25, ISS) for the double-blind study in LGS. Doses in this study were administered based on each patient's body weight, so the results are shown for median doses in mg/kg/day. It was difficult to draw firm conclusions about dose response from these data because, the study was designed to have patients attain a maintenance dose of approximately 45 mg/kg/day, and most of the patients had median doses near that target and the sample sizes were small.

For comparison, the results based on median doses in mg/day (the actual doses received) are shown in Appendix Table 5 (Sponsor's Table 6.2-26, ISS). The results were generally similar when the incidence of adverse events was analyzed by the dose of maximum duration (Ref: Sponsor's Appendix I, Table 6.7.1-8) and by the maximum daily dose (Ref: Sponsor's Appendix I, Table 6.7.1-10). The dose-related trend for somnolence was somewhat more pronounced when the results were analyzed by maximum dose.

Occurrence of Common AE > 2% and > Placebo in LGS Double-blind Subgroup

Appendix Table 5 (Sponsor's Table 6.2-27, ISS) displays all adverse events that occurred in more than 2.0% of the rufinamide-treated patients with an incidence that was higher in the rufinamide group than in the placebo group.

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Reviewer Comments

Common AE Occurrence in LGS Double-blind with Open-label Extension Subgroup

Sponsor's Table 6.2-28, ISS, displayed the incidence of adverse events by SOCs for patients who received rufinamide in the Double-blind Phase, the Extension Phase, or both phases of the study in LGS. As anticipated, the incidences of any adverse events and of adverse events by most SOCs were higher than in the Double-blind Phase alone possibly because the median duration of exposure to rufinamide was 14.3 months (166.60 patient-years) for the combined phases, compared with 2.8 months (16.04 patient-years) for the double-blind Phase.

Very Common AE Occurrence by Preferred Term in LGS Double-blind with Open-label Extension Subgroup

Sponsor's Table 6.2-29, ISS, displayed the incidence of adverse events that occurred in 10.0% or more of the patients who received rufinamide in the Double-blind Phase, the Extension Phase, or both phases of the study in LGS. The median duration of exposure to rufinamide in this group (14.3 months) was much longer than in the Double-blind Phase only (2.8 months). The 3 most frequently reported events were the same as during the Double-blind Phase, i.e., vomiting, pyrexia, and somnolence. More events occurred in at least 10% of the patients during the longer exposure to the drug, as might be expected.

Very Common AE Occurrence by Severity in LGS Double-blind with Open-label Extension Subgroup

Sponsor's Table 6.2-30, ISS, displayed the events that occurred in 10% or more of the patients, by severity. Adverse events were judged by the investigators to be mild in 23 (17.0%) of the 135 patients who received rufinamide; at least one adverse event was moderate, in an additional 61 (45.2%) patients; and at least one severe adverse event occurred in 40 (29.6%) patients. The majority were mild or moderate. The highest rates of severe events were for vomiting and constipation, which were each severe in 3.0% of the patients.

Very Common AE Occurrence by Dose in LGS Double-blind with Open-label Extension Subgroup

The incidence of adverse events that occurred in 10.0% or more of the rufinamide-treated patients was presented by median dose in Sponsor's Table 6.2-31, ISS, for the Double-blind and Extension Phases of the study in LGS. Comparison of the 2 highest median dose groups, which included the majority of the population, showed a dose response for the incidences of nearly all of the very common adverse events. These results were probably confounded by the longer duration of exposure of the patients in this population.

The results were similar when the incidence of adverse events was analyzed by the dose of maximum duration (Ref: Sponsor's Appendix I, Table 6.8.1-5) and by the maximum daily dose (Ref: Sponsor's Appendix I, Table 6.8.1-7). For comparison, the results based on median doses in mg/day (the actual doses received) were presented in Sponsor's Table 6.2-32, ISS. The results were similar when the incidence of adverse events was analyzed by the dose of maximum

duration (Ref: Sponsor's Appendix I, Table 6.8.1-8) and by the maximum daily dose (Sponsor's Appendix I, Table 6.8.1-10).

Reviewer Comments

Since the focus was on the placebo-controlled data, for purposes of keeping the review concise, the AE data tables involving open-label data were (as for the All Studies Combined) not included in the review.

Common AE Occurrence in Pediatrics Double-blind Subgroup

The incidence of adverse events by SOCs is presented in Appendix Table 5 (Sponsor's Table 6.2-33, ISS) for the double-blind studies in pediatric patients. The incidences of any adverse events and of adverse events by most SOCs were generally greater for the patients exposed to rufinamide than those exposed to placebo (83.5% vs. 74.6%). In particular, the incidences of nervous system disorders, gastrointestinal disorders, eye disorders, and general disorders and administration site conditions were higher in the rufinamide group.

Very Common AE Occurrence by Preferred Term in Pediatrics Double-blind Subgroup

The incidence of adverse events that occurred in 10.0% or more of the patients in either treatment group is presented in Appendix Table 5 (Sponsor's Table 6.2-34, ISS) for the double-blind studies in pediatric patients. Except for upper respiratory tract infection (placebo > rufinamide), somnolence (17.0% vs. 8.1%), vomiting (16.5% vs. 7.1%), headache (16.0% vs. 8.1%) and pyrexia (difference not remarkable) occurred at a greater frequency with rufinamide.

Very Common AE Occurrence by Severity in Pediatrics Double-blind Subgroup

Appendix Table 5 (Sponsor's Table 6.2-35, ISS) displays the events that occurred in 10% or more of the patients, by severity. All adverse events were judged by the investigators to be mild in 65 (30.7%) of the 212 patients who received rufinamide and in 82 (41.6%) of the 197 patients who received placebo. At least one adverse event was moderate in an additional 93 (43.9%) and 52 (26.4%) rufinamide and placebo patients, respectively. At least one severe adverse event occurred in 19 (9.0%) rufinamide-treated patients and 13 (6.6%) placebo-treated patients. The majority were mild or moderate in severity. The highest rates of severe events were for vomiting, which was severe in 1.4% of rufinamide-treated patients and 0% of placebo-treated patients. The remaining very common adverse events were severe in fewer than 1% of the patients. The more frequent events of somnolence, vomiting and headache in patients in the pediatric double-blind studies were also greater in severity compared to placebo.

Very Common AE Occurrence by Dose in Pediatrics 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 6.2-36, ISS) for the double-blind studies in pediatric patients. There was no apparent dose-response relationship based on the submitted results. Discernable differences in AE by dose that were clinically meaningful were not seen.

Common AE Occurrence in Pediatrics Double-blind with Open-label Extension Subgroup

Sponsor's Table 6.2-37, ISS, displayed the incidence of adverse events by SOCs for patients who received rufinamide in the Double-blind Phase, the Extension Phase, or both phases of the studies in pediatric patients. The incidences of any adverse events and of adverse events by most SOCs were higher than in the Double-blind Phase only, reflecting the longer exposure to rufinamide (489.46 patient-years).

Very Common AE by Preferred Term in Pediatrics Double-blind with Open-label Extension Subgroup

Sponsor's Table 6.2-38, ISS, displayed the incidence of adverse events that occurred in 10.0% or more of the patients who received rufinamide in the Double-blind Phase, the Extension Phase, or both phases of the studies in pediatric patients. The 5 most frequently reported events were the same as during the Double-blind Phase. More events occurred in at least 10% of the patients during the longer exposure to the drug, as might be expected.

Very Common AE by Severity in Pediatrics Double-blind with Open-label Extension Subgroup

Sponsor's Table 6.2-39, ISS, displayed the events that occurred in 10% or more of the patients, by severity. All adverse events were judged by the investigators to be mild in 91 (23.3%) of the 391 patients who received rufinamide; at least one adverse event was moderate in an additional 180 (46.0%) patients; and at least one severe adverse event occurred in 86 (22.0%) patients. The majority were mild or moderate. The highest rate of severe events was for vomiting, which was severe in 2.3% of the patients. Severe events occurred in 1% or fewer of the patients for the remaining very common events.

Very Common AE by Dose in Pediatrics Double-blind with Open-label Extension Subgroup

The incidence of adverse events that occurred in 10.0% or more of the rufinamide-treated patients was presented by median dose in Sponsor's Table 6.2-40, ISS, for the Double-blind and Extension Phases of the double-blind studies in pediatric patients. There was no apparent dose-response relationship.

Reviewer Comments

Since the focus was on the placebo-controlled data, for purposes of keeping the review concise, the AE data tables involving open-label data (and All Studies Combined) were not included in the review.

Common AE in the Diabetic Neuropathy Subgroup

According to the Sponsor, the incidence of adverse events was comparable in rufinamide-treated patients (60.0%; 36/60) and placebo-treated patients (60.3%; 38/63) in the diabetic neuropathy study. The most frequently reported adverse events were nausea (23.3% with rufinamide versus 11.1% with placebo), headache (16.7% versus 11.1%), fatigue (15.0% versus 4.8%), and dizziness (11.7% versus 3.2%). All adverse events were judged by the investigators to be mild in 22 (36.7%) of the 60 patients who received rufinamide and in 16 (25.4%) of the 63 patients who received placebo in the diabetic neuropathy study. At least one adverse event was moderate, and none were severe, in an additional 9 (15.0%) and 16 (25.4%) patients, respectively. At least one severe adverse event occurred in 5 (8.3%) rufinamide-treated patients and 6 (9.5%) placebo-treated patients. Adverse events for this population were summarized in

Sponsor's Appendix I, Tables 6.11.1-1 (by SOC), 6.11.1-2 (by Preferred Term), 6.11.1-3 (by SOC and Preferred Term), and 6.11.1-4 (by severity).

Common AE in the Healthy Volunteer Subgroup

According to the Sponsor, ninety-six (29.4%) of the 326 rufinamide-treated subjects and 18 (20.0%) of the 90 placebo-treated subjects experienced at least one adverse event. Adverse events occurred most commonly within the SOCs of nervous system disorders (20.6% and 15.6%, respectively) and general disorders and administration site conditions (9.5% and 10.0%, respectively). The only adverse event that occurred in 10% or more of the subjects was headache (15.6% and 8.9%, respectively). Four (1.2%) rufinamide-treated subjects experienced severe adverse events (headache, fatigue, somnolence, accommodation disorder, depression, apathy, palpitations), as did 3 (3.3%) placebo-treated subjects (fatigue, somnolence, disturbance in attention). Adverse events for this population were summarized in Sponsor's Appendix I, Tables 6.12.1-1 (by SOC), 6.12.1-2 (by Preferred Term), 6.12.1-3 (by SOC and Preferred Term), and 6.12.1-4 (by severity).

Occurrence of Adverse Events in Subpopulations of Patients

Adverse Events by Age

Analyses of adverse events were performed for the following age subgroups: <12 years, 12 to 16 years, 17 to 64 years, ≥65 years. Some of the analysis populations had small numbers of patients (or no patients) in the youngest and oldest categories, limiting the ability to draw conclusions about possible age-related effects.

AE by Age in All Double-blind Subgroup

The incidence of adverse events reported by 10% or more of all treated patients with epilepsy (double-blind studies) was presented by age group in Sponsor's Table 6.3-1, ISS. In general, the results within each age group were similar to those for all treated patients, i.e., rates of the very common adverse events were higher with rufinamide than with placebo. There were few discernible age-related patterns. Headache, dizziness, and nausea occurred at lowest rates in the youngest group, and at comparable rates in the three older groups. This was true in both the rufinamide and placebo groups for headache and nausea, but not dizziness. Somnolence occurred at the highest rate in the youngest group of rufinamide-treated patients; rates were comparable by age in placebo-treated patients. Small sample sizes restricted interpretation in the lower age groups.

AE by Age in All Studies Combined

The incidence of adverse events reported by 10% or more of all treated patients with epilepsy was presented by age group in Sponsor's Table 6.3-2, ISS. Younger patients had lower rates of headache and dizziness, and higher rates of somnolence, vomiting, and upper respiratory tract infection, relative to older patients.

AE by Age in Adult Double-blind Subgroup

The incidence of adverse events reported by 10% or more of the patients in rufinamide and placebo treatment group was presented by age group in Sponsor's Table 6.3-3, ISS. No patient in

this population was <12 years old. Because more than 98% of the patients were between the ages of 17 and 64 years, the results for that subgroup were similar to the results for all patients in this population. Headache and nausea occurred in similar percentages of patients in the rufinamide and placebo groups, whereas dizziness, fatigue, and somnolence occurred in higher percentages of rufinamide-treated than placebo-treated patients.

AE by Age in Adult Double-blind with Open-label Extension Subgroup

The incidence of adverse events reported by 10% or more of the patients in this population was presented by age group in Sponsor's Table 6.3-4, ISS. Sample sizes for the 12-16 and > 65 years were small (N=9 and N=5) respectively.

AE by Age in LGS Double-blind Subgroup

The incidence of adverse events reported by 10% or more of the patients with LGS (double-blind studies) was presented by age group in Sponsor's Table 6.3-5, ISS. No patient in this population was ≥65 years old. The rates of any adverse event and of pyrexia were highest in the youngest age group, for both rufinamide- and placebo-treated patients. Somnolence occurred at lower rates in the youngest age group than in the 2 older age groups. Vomiting occurred in higher percentages of rufinamide-treated patients than placebo-treated patients in all age groups. Diarrhea occurred at similar rates in the rufinamide and placebo groups for patients who were <12 years old, but occurred only in placebo-treated patients in the older age groups. Interpretations were limited due to small sample sizes.

AE by Age in LGS Double-blind with Open-label Extension Subgroup

The incidence of adverse events reported by 10% or more of the patients was presented by age group in Sponsor's Table 6.3-6, ISS. The incidences of somnolence, fatigue, and aggression appeared to increase across the 3 age groups in this population, whereas the incidence of constipation appeared to decrease. The remaining events showed no consistent relationship to age. Small sample sizes restricted interpretations.

AE by Age in Other Population Subgroups

Results for the other analysis populations was presented in Sponsor's Appendix I, Tables 6.6.1-8 (mono-therapy substitution studies), 6.9.1-8 (double-blind studies in pediatric patients), and 6.10.1-8 (double-blind studies in pediatric patients, with open-label extensions). These were not integrated.

Adverse Events by Sex

AE by Sex in All Double-blind Study Subgroup

The incidences of the very common adverse events were summarized in Sponsor's Table 6.3-7, ISS for all male and female patients with epilepsy (double-blind studies). The pattern of results for rufinamide versus placebo was similar for the two groups, except with respect to nausea, which showed a larger difference between treatment groups in females than in males.

AE by Sex in All Studies Combined

The incidences of the very common adverse events were summarized in Sponsor's Table 6.3-8, ISS for all male and female patients with epilepsy. Headache, dizziness, nausea, and upper respiratory tract infection occurred in higher percentages of female patients than male patients. The remaining very common adverse events occurred in similar percentages of female and male patients.

AE by Sex in Adult Double-blind Studies Subgroup

The incidences of the very common adverse events were summarized in Sponsor's Table 6.3-9, ISS for all male and female adults with partial seizures (double-blind studies). Any adverse event, headache, dizziness, fatigue, and nausea occurred in higher percentages of female patients than male patients. Nausea occurred in higher percentages of rufinamide-treated female patients than placebo-treated female patients (16.6% vs. 12.7%), whereas nausea occurred in similar percentages of rufinamide- and placebo-treated male patients.

AE by Sex in Adult Double-blind with Open-label Extension Subgroup

The incidences of the very common adverse events were summarized in Sponsor's Table 6.3-10, ISS for all male and female patients in this population. Headache, dizziness, fatigue, and nausea occurred in higher percentages of female patients than male patients. The remaining very common adverse events occurred in similar percentages of female and male patients.

AE by Sex in LGS Double-blind Subgroup

The incidences of the very common adverse events were summarized in Sponsor's Table 6.3-11, ISS for all male and female patients with LGS (double-blind studies). The percentage of patients with at least one adverse event was similar with rufinamide and with placebo for both males and females. Somnolence and vomiting occurred at higher rates with rufinamide than with placebo in both males and females. Pyrexia occurred at a higher rate with placebo than rufinamide in male patients, but at similar rates with both treatments in female patients. Diarrhea occurred at a higher rate with placebo than rufinamide in female patients, but at similar rates with both treatments in male patients.

AE by Sex in LGS Double-blind with Open-label Extension Subgroup

The incidences of the very common adverse events were summarized in Sponsor's Table 6.3-12 IS for all male and female patients in this population. Pyrexia, somnolence, upper respiratory tract infection, fatigue, constipation, and aggression occurred in higher percentages of female patients than male patients. Vomiting occurred in a higher percentage of male patients than female patients. The remaining very common adverse events occurred in similar percentages of female and male patients.

AE by Sex in Other Population Subgroups

Results for the other analysis populations was presented in Sponsor's Appendix I, Tables 6.6.1-9 (mono-therapy substitution studies), 6.9.1-9 (double-blind studies in pediatric patients), and 6.10.1-9 (double-blind studies in pediatric patients, with open-label extensions). These were not integrated.

Adverse Events by Race

As discussed in Demographics (Table 7.2.1.2.A), 58% of the patients in the all-treated population were white, 4% were black, 0.3% were oriental, and 5% were of other races. The remaining 33% did not have race reported, which according to the sponsor, was primarily because enrollment in these studies did not require collecting information on race. Most of the latter studies were conducted in Europe or Eastern Europe, so it is likely that a majority of the patients without race recorded were white.

For the analysis of adverse events by race, the patients were categorized into three race subgroups: white, black, and other. "Other" included the patients for whom race was not recorded. These results by race must therefore be interpreted with caution.

AE by Race in All Double-blind Study Subgroup

The incidences of the most commonly reported adverse events were summarized in Sponsor's Table 6.3-13, ISS for this population, by race. The pattern of results for rufinamide versus placebo within each race subgroup was generally similar to that for the entire population, i.e., adverse events occurred in higher percents of rufinamide-treated patients than placebo-treated patients.

AE by Race in All Studies Combined

The incidence of the very common adverse events was summarized by race in Sponsor's Table 6.3-14, ISS for all treated patients with epilepsy. Somnolence was noted to occur at the highest incidence in the black population.

AE by Race in Adult Double-blind Subgroup

The incidence of adverse events reported by 10% or more of adults with partial seizures (double-blind studies) was presented by race in Sponsor's Table 6.3-15, ISS. In white patients, all of the very common adverse events occurred in higher percentages of rufinamide-treated patients than placebo-treated patients. This was also true for headache and dizziness among black patients, and for dizziness and somnolence among patients of other races (patients whose race was not reported). Fatigue, somnolence, and nausea occurred at similar rates in the 2 treatment groups in black patients, as did headache, fatigue, and nausea in patients of other races.

AE by Race in Adult Double-blind with Open-label Extension Subgroup

The incidence of the very common adverse events was summarized by race in Sponsor's Table 6.3-16, ISS for adults with partial seizures who received rufinamide during a double-blind or open-label study.

AE by Race in LGS Double-blind Subgroup

The incidence of very common adverse events was presented by race in Sponsor's Table 6.3-17, ISS for patients with LGS (double-blind study). A majority of the patients were white, and the pattern of results for that group was similar to that for all patients in this population, i.e., somnolence and vomiting occurred in higher percentages of rufinamide-treated patients than placebo-treated patients, pyrexia occurred in higher percentages of placebo-treated patients than rufinamide-treated patients, and diarrhea occurred in similar percentages of patients in the 2

treatment groups. The numbers of patients who were black or of other races were too small for conclusions to be drawn.

AE by Race in LGS Double-blind with Open-label Extension Subgroup

The incidence of very common adverse was presented by race in Sponsor's Table 6.3-18, ISS for all patients with LGS who received rufinamide in the double-blind or open-label part of the study. A majority of the patients were white, and the pattern of adverse events in that subgroup was similar to the pattern described above (see Appendix Table 5; Sponsor's Table 6.2-29, ISS) for all patients in this population.

AE by Race in Other Population Subgroups

Results for the other analysis populations was presented in Sponsor's Appendix I, Tables 6.6.1-10 (mono-therapy substitution studies), 6.9.1-10 (double-blind studies in pediatric patients), and 6.10.1-10 (double-blind studies in pediatric patients, with open-label extensions). The results were not integrated.

Reviewer Comments

See comments in the demographic section of the review. While the race based AE analyses shed some light on incidences based on race (mostly restricted to a majority of white, very limited black or other), small sample sizes limited interpretations upon which conclusions could be drawn. Even within this limited analyses, there was an increased incidence of somnolence in the black compared to white in the adult subgroup. The overall concerns on the lack of adequate exposures in number of African (black) patients (and Hispanic/Latino) prevail and it is recommended that the concern be reflected in the label.

Adverse Events by Concomitant AED

General Comments

Based on the sought indication, it is intended that rufinamide will be administered adjunctively to patients with epilepsy who are receiving one or more standard AEDs but are failing to attain satisfactory seizure control. Most of the double-blind studies in the clinical development program mandated that patients receive stable doses of 1 to 3 AEDs throughout their treatment with rufinamide. The notable exceptions to this were the double-blind mono-therapy and mono-therapy substitution studies, although patients in the largest of those studies (016) received one concomitant AED for the first 6 weeks of treatment, with reduction of the dose over time. Most patients in open-label extensions of double-blind studies continued to receive standard AEDs, but doses and medications were allowed to be changed at the discretion of the investigators.

It should be noted that the clinical studies were not designed to investigate possible interactions between rufinamide and the standard AEDs. In addition, most patients received more than one AED. Despite these limitations, analysis of the rates of adverse events in subgroups of patients who received different AEDs could suggest potential interactions that might be encountered in clinical practice and can also indicate events that may be attributed, at least in part, to the standard AED regimen rather than to rufinamide. To provide meaningful numbers of patients, these analyses were performed by the sponsor for all AEDs that were taken by at least 10% of

the rufinamide-treated patients in the relevant population. The relationship of plasma concentrations and AE with concomitant AEDs as co-variants is discussed below separately.

AE by Concomitant AED in All Double-blind Subgroup

The incidence of very common adverse events was presented by concomitant AED in Sponsor's Table 6.3-19, ISS for all treated patients with epilepsy (double-blind studies).

Within most of the AED subgroups, the percentages of patients with at least one adverse event were similar in the rufinamide and placebo treatment groups. For the 5 very common adverse events in this population, the results within each AED subgroup were generally similar to those for all treated patients, i.e., generally, adverse events occurred in higher percentages of patients in the rufinamide group than in the placebo group. Headache occurred at comparable rates in the 2 groups among patients who received concomitant carbamazepine, phenytoin, or vigabatrin, and at a higher rate in the placebo group than the rufinamide group among those who received concomitant clonazepam. Nausea occurred at the lowest rates in both rufinamide- and placebo-treated patients who received concomitant vigabatrin. Generally, the incidence rates were higher for rufinamide compared to placebo in patients who received lamotrigine for headache (30.6% vs. 16.8), dizziness (21.6% vs. 9.9%), fatigue (11.9% vs. 5.0%), somnolence (16.4% vs. 8.95) and nausea (17.2% vs. 4.0%). Like wise, the incidence rates were higher for rufinamide compared to placebo in patients who received vigabatrin for dizziness (13.6% vs. 7.1 %), fatigue (21.6% vs. 17.9%), somnolence (11.2% vs. 3.6%) and nausea (5.6% vs. 3.6%).

AE by Concomitant AED in All Studies Combined

The incidence of very common adverse events was presented by concomitant AED in Sponsor's Table 6.3-20, ISS for all treated patients with epilepsy.

Headache and somnolence occurred at comparable rates in all of the concomitant medication groups. Dizziness occurred at the lowest rate with concomitant clonazepam and the highest rates with concomitant lamotrigine and lorazepam. Fatigue and nausea occurred at the lowest rates with concomitant clonazepam and the highest rates with concomitant lorazepam.

AE by Concomitant AED in Adult Double-blind Studies Subgroup

The incidence of very common adverse events was presented by concomitant AED in Sponsor's Table 6.3-21, ISS for the adults with partial seizures who received study drug in double-blind studies.

Within the AED subgroups shown, the percentages of patients with at least one adverse event were similar in the rufinamide and placebo treatment groups (rufinamide > placebo). For the 5 very common adverse events in this population, the results within each AED subgroup were generally similar to those for all treated patients, i.e., dizziness, fatigue, and somnolence occurred in higher percentages of patients in the rufinamide group than in the placebo group, whereas headache and nausea occurred in similar percentages of patients in the 2 groups. In the subgroups of patients receiving phenytoin or clonazepam, all of the very common adverse events occurred at similar rates in the 2 treatment groups or at higher rates with placebo than with rufinamide (except for somnolence in the subgroup that received clonazepam).

AE by Concomitant AED in Adult Double-blind with Open-label Extension Studies Subgroup

The incidence of very common adverse events was presented by concomitant AED in Sponsor's Table 6.3-22, ISS for adults with partial seizures who received rufinamide.

Headache occurred at the highest rates in the valproate and diazepam subgroups. The rates of dizziness, nausea, and somnolence were lowest in the subgroup of patients who received concomitant vigabatrin. The rate of diplopia was lowest in the phenytoin subgroup and highest in the diazepam subgroup.

AE by Concomitant AED in LGS Double-blind (Study) Subgroup

The incidence of very common adverse events was presented by concomitant AED in Sponsor's Table 6.3-23, ISS.

Within most of the AED subgroups, the percentages of patients with at least one adverse event were similar in the rufinamide and placebo treatment groups. There were a few exceptions: no patients in the rufinamide group who used concomitant phenytoin and no patients in the placebo group who used concomitant diazepam had any adverse events. In the remaining subgroups, the pattern of the very common adverse events generally followed that seen in the total population, i.e., somnolence and vomiting occurred in higher percentages of patients who received rufinamide, whereas pyrexia and diarrhea occurred in higher percentages of patients who received placebo. One notable exception was the subgroup of patients who received clonazepam, in whom the rates of these events in the rufinamide group were similar to, or lower than, the rates in the placebo group. Small sample sizes limited meaningful interpretations.

AE by Concomitant AED in LGS Double-blind with Open-label Extension Studies Subgroup

The incidence of very common adverse events was presented by concomitant AED in Sponsor's Table 6.3-24, ISS for all patients with LGS who received rufinamide. The percentages of patients with at least one adverse event were fairly comparable across the subgroups, as were the percentages of patients with individual very common adverse events. Vomiting occurred in the highest percentages of patients in the carbamazepine and diazepam subgroups. Somnolence occurred in a higher percentage of patients who received carbamazepine than the other AEDs. Aggression occurred in a higher percentage of patients who received lorazepam. Diarrhea occurred in the highest percentages of patients in the diazepam, topiramate, and lorazepam subgroups.

AE by Concomitant AED in Other Population Subgroups

Results for pediatric patients were presented in Sponsor's Appendix I, Tables 6.9.1-11 (double-blind studies in pediatric patients) and 6.10.1-11 (double-blind studies in pediatric patients, with open-label extensions). The results were not integrated.

7.1.5.1 Eliciting adverse events data in the development program

Review of the safety assessments and monitoring plan were discussed under section 7.1.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The preferred terms for the events under different sections and subset analyses appear appropriate.

7.1.5.3 Incidence of common adverse events

See 7.1.5.

7.1.5.4 Common adverse event tables

See 7.1.5.

7.1.5.5 Identifying common and drug-related adverse events

See 7.1.5.

7.1.5.6 Additional analyses and explorations

The additional analyses and explorations that were conducted are discussed in the respective sections- e.g., 7.1.1 (Deaths) 7.1.2 (SAE), 7.1.3 (AE → DC- Treatment Emergent Adverse Events that led to Discontinuations), 7.1.3.3 (Other Significant AE), etc.

7.1.6 Less Common Adverse Events

See 7.1.5.

7.1.7 Laboratory Findings

Reviewer Comments

The normal ranges and clinically notable criteria used in the analyses of individual studies, and reported in the individual CSRs, varied. For consistency and accuracy, the sponsor chose a single set of age-adjusted normal ranges and clinically notable criteria to integrate the safety data. The age-adjusted normal ranges (Mayo Medical Laboratories Test Catalog recommendations) used in the analyses were presented in Sponsor's Appendix I, Table 8.1-0. The definitions of clinically notable laboratory values are shown in Appendix Table 2.

For purposes of easy reference, the sponsor's normal laboratory values (age-adjusted normal ranges [lowest and highest values] from Mayo Medical Laboratories Test Catalog [Sponsor's Appendix I, Table 8.1-0]) used in the analyses were compared to those from The Merck Manual, 17th edition, pp. 2526-2543. These sponsor's lowest and highest values are italicized and presented alongside the normal values from the Merck Manual.

The data for LGS double-blind and LGS double-blind with open-label extension subgroups came from a single study and its extension (Study 022/022E). Because the normal ranges and clinically notable criteria used in the CSR and the ISS differed, the shift tables and tables of clinically notable values presented in the ISS, according to the sponsor, may show findings that differ from those presented in the CSR. The sponsor considers the results included in the ISS to provide the best and most accurate representation of the laboratory data from the LGS study.

Hepatic and thyroid related laboratory assessments were comprehensively investigated in the clinical program for potential abnormalities because of species-specific toxicology pre-clinical findings. These were centri-lobular hepatic hypertrophy and disturbance of the pituitary-thyroid

axis in rats, cholestasis in dogs, gallbladder crystals in monkeys, liver tumors in mice and thyroid follicular adenomas in rats. There was also an increased incidence of benign bone tumors (osteomas) at 400 mg/kg in rat carcinogenicity study that was considered species specific by the sponsor. There was no special clinical safety monitoring mechanisms in this program that the sponsor effectively sought to address this preclinical concern. As an indirect measure, elevations in serum alkaline phosphatase, which normally comes from the liver and the bone, may be indicative of liver or bone pathology in adults. Due to rapid bone growth in pediatric and adolescent populations, there is an age-dependent increase in alkaline phosphatase levels and hence interpretations of elevated levels in the pediatric and adolescents should make allowances for such physiological aspects. The technique of distinguishing bone alkaline phosphatase from that of the liver is not considered a simple process. However, when elevations of 5'-nucleotidase, that is restricted to the hepatic membrane, are accompanied with increases in alkaline phosphatase, it is strongly suggestive of the residence of the problem in the liver. None of these considerations were entertained by the sponsor.

For more information, see Module 2.4, Nonclinical Overview. These pre-clinical concerns were discussed with the Agency Pharm-tox Reviewer and it is the understanding of this reviewer (as does the sponsor) that these findings are species specific.

The disposition of patients with clinically notable values (changes from baseline), were not specified. How these patients were managed, followed and the outcome was not provided. *It is recommended that this information be requested from the sponsor.*

Treatment Emergent Hepatobiliary (LFT) Laboratory Changes

Reviewer Comments

The parameters that were evaluated under this panel were albumin, alkaline phosphatase, γ -GTP, LDH, SGOT/AST, SGPT/ALT and Total Bilirubin. The number of patients who were evaluated varied depending on the assessed parameter, the analysis subgroup and the treatment (rufinamide or placebo). For e.g., in the All double-blind subgroup (N=1240 patients), SGOT/AST was assessed in 1186 and γ -GTP in only 15 patients. γ -GTP was not assessed in several of the subgroup analyses. These numbers varied further between the rufinamide and placebo treatment groups for the same parameter. In some subgroups analyses, the LFT panel was incomplete- e.g., γ -GTP was not measured in the LGS study. Hence, the interpretation of the results required allowances for such variations in the denominators.

The data (mean changes) was presented using SI units for albumin (normal SI units = 35-50 g/L [*sponsor 35-50*] [normal conventional units = 3.5-5.0 g/dL]) and total bilirubin (normal SI units = $\leq 22 \mu\text{mol/L}$ [*sponsor 1.71 to 17.1*] [normal conventional units = $\leq 1.3 \text{mg/dL}$]). Mean changes in the remainder of the parameters under this panel was expressed in conventional units (U/L). The results were presented as Mean Changes, Shift Table Changes and Clinically Notable Changes.

Treatment Emergent LFT Lab Changes in All Double-blind Studies Subgroup

Mean Changes

Sponsor's Table 8.1-1, ISS displayed mean values for hepatobiliary laboratory parameters at baseline, the last visit for each patient (termination), and the change between those 2 visits. Mean changes were small and were similar in the rufinamide and placebo groups for all parameters except albumin. These changes were not clinically meaningful (a mean change of 34.5 in albumin, mean changes that were lower (-) at study termination for several of the parameters) or significantly different than placebo. According to the sponsor, the relatively high mean for albumin was due to the inclusion of an erroneous lab value. Further, the rates of shifts relative to the normal range and of clinically notable changes in albumin were small in the rufinamide group and nearly identical to the rates in the placebo group. See below and sponsor's Tables 8.1-2 and 8.1-3, ISS for further details on albumin related changes. Discernable differences in mean that were clinically meaningful were not seen.

Shift Table Changes

The numbers of patients with shifts in hepatobiliary parameters, relative to the normal range, was summarized in Sponsor's Table 8.1-2, ISS for all treated patients with epilepsy who received study drug in double-blind studies. In the majority of patients in both treatment groups, no shifts relative to the normal range between baseline and the last post-baseline evaluation were noticed. Increases in hepatobiliary parameters occurred in $\leq 3.5\%$ of the rufinamide-treated patients and in $\leq 6.0\%$ of the placebo-treated patients. For most individual parameters, the percentages of patients with upward or downward shifts were similar for rufinamide and placebo. The largest differences between the treatment groups occurred in SGPT: 4.9% of rufinamide-treated patients and 3.3% of placebo-treated patients had decreases; 2.6% and 6.0%, respectively, had increases. Discernable differences that were clinically meaningful were not seen.

Clinically Notable Changes

The incidence of patients with normal values for hepatobiliary parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.1-3, ISS for all double-blind subgroup. Clinically notable values occurred in $\leq 1.0\%$ of the rufinamide-treated patients and $\leq 1.4\%$ of the placebo-treated patients. For individual parameters, the incidences of patients with clinically notable values were comparable between the treatment groups.

Discernable differences that were clinically meaningful were not seen.

There were no serious adverse events related to hepatobiliary laboratory tests or the hepatobiliary system in either treatment group. One rufinamide-treated patient (0005-02670 in Study 022) discontinued due to hepatic enzymes increased. This case is discussed under Other Significant AE (Skin Rash/Hypersensitivity).

Treatment Emergent LFT Lab Changes in All Subgroups Combined

Mean Changes

Sponsor's Table 8.1-4, ISS, displayed the mean values for hepatobiliary laboratory parameters at baseline, the last visit for each patient (Termination), and the change between those 2 visits. Mean changes were similar to those seen in the All double-blind subgroup and did not suggest any trends. See comments under All Double-blind subgroup.

Shift Table Changes

The numbers of patients with shifts in hepatobiliary parameters, relative to the normal range, was summarized in Sponsor's Table 8.1-5 for all treated patients with epilepsy (all subgroups combined). Shifts from within the normal range at baseline to above the normal range at the last evaluation occurred in $\leq 3.6\%$ of the patients. The highest rate of such upward shifts occurred with alkaline phosphatase (3.5%) and SGOT (3.6%). *Interpretation was limited by the absence of a consistent increase in each of the LFT parameters that typically represents the LFT panel and by the absence of placebo treatment arm for comparison.*

Clinically Notable Changes

The incidence of patients with normal values for hepatobiliary parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.1-6, ISS for All Subgroups Combined (all treated patients with epilepsy). Such notable values occurred in $\leq 2.5\%$ of the rufinamide-treated patients.

All patients in this population with clinically notable values for albumin were identified in Sponsor's Appendix I, Table 8.6-1, and all patients with clinically notable values for SGOT, SGPT, or total bilirubin were identified in Sponsor's Appendix I, Table 8.6-7. These tables displayed, for each of the patients, demographic information, treatment information, and laboratory results for SGOT, SGPT, bilirubin, and alkaline phosphatase.

The clinical significance of the noted changes in albumin were not meaningful and its relevance unknown.

The patients with an SGOT or SGPT value that was more than 5 times the upper limit of the normal range were further reviewed by the sponsor. There were 11 patients with increased SGOT and 12 with increased SGPT. Four patients had increases in both parameters. None of these patients had elevated bilirubin values more than 1.5 times the upper limit of the normal range, except for those described below. Of the 11 patients with elevations in SGOT, 3 had elevations at a single time while receiving placebo (1 of these later had a single elevation while receiving open-label rufinamide), 5 had single elevations with several normal values before and after while receiving rufinamide, 2 had elevated values at the last laboratory evaluation, and 1 had elevations both before and after randomization. Of the 12 patients with elevations in SGPT, one had an elevation at a single time while receiving placebo, one had the elevation at baseline, 6 had single elevations with several normal values before and after while receiving rufinamide, 3 had elevated values at the last laboratory evaluation, and one (the same patient noted in the SGOT group) had elevations before randomization that worsened during rufinamide treatment.

Three patients had a value for either SGOT or SGPT that was 2 or 3 times the upper limit of normal and a value for bilirubin that was 1.5 times the upper limit of normal, which were chronologically contiguous. These 3 patients are described below.

Patient 0005-04408 (Study 021PE) – this patient, a 12 year old female, has been discussed under Other Significant AE (Skin Rash/Hypersensitivity)

Patient 1274-03159 (Study 021PE)

This patient was a 13-year-old female who received rufinamide during the Double-blind Phase of Study 021P and then entered the open-label Extension Phase. Laboratory tests obtained approximately 3 weeks later revealed all values within the normal ranges. The next laboratory evaluation, which was performed after the patient had been in the Extension Phase for about 6

weeks and was receiving a dose of 3600 mg/day of rufinamide, revealed elevated values for SGOT (160 U/L; normal range, 20-40 U/L) and total bilirubin (41.04 µmol/L; normal range, 1.71-17.1 µmol/L), but not SGPT (26 U/L; normal range, 9-29 U/L). Alkaline phosphatase was 215 U/L, LDH was 1474 U/L, and creatinine was 1.6 mg/dL. The serum was grossly hemolyzed. The patient was reported to have an adverse event of environmental allergies, rated mild and coded to the Preferred Term of hypersensitivity, approximately 6 weeks before this laboratory evaluation. The event resolved with treatment in one day and was not considered related to study drug. She had no other adverse events around the time of the elevated laboratory values. The patient completed the study, receiving rufinamide at doses of 3200 or 3600 mg/day for more than one year in the Extension Phase, with all remaining laboratory evaluations showing normal values for SGOT, SGPT, and total bilirubin.

Patient 0002-08019 (Study AE/ET1)

This patient was a 28-year-old male who was randomly assigned to receive rufinamide 200 mg/day in Study AE/ET1. He had slightly elevated values for SGOT (67 U/L) and SGPT (114 U/L) approximately 3 months prior to study entry, but the values for those parameters were normal at an evaluation performed on the first day of study treatment. Approximately 10 days after the start of therapy, he experienced a prolonged secondarily generalized seizure with post-ictal hemiparesis and dysphasia. He also had post-ictal muscle entrapment syndrome. He was hospitalized. On admission, his platelet count was 190 x 10⁹/L, SGOT was 1314 U/L (normal range, 12-31 U/L), SGPT was 1056 U/L (normal range, 10-45 U/L), and bilirubin was 32 µmol/L (normal range, 1.71-17.1 µmol/L). Serum fibrin-degradation products and fibrinogen were normal. There was no evidence of cerebral infarction on CT scans, but regional cerebral blood flow investigation revealed hypoperfusion of the frontal part of the left hemisphere. The patient discontinued treatment 2 days after the seizure occurred. Blood parameters reportedly returned to normal in approximately 2 weeks.

Adverse events related to hepatobiliary laboratory tests occurred in fewer than 1% of rufinamide-treated patients (Sponsor's Appendix I, Table 6.10.1-1). One patient had a serious adverse event related to the hepatobiliary system (cholecystitis; Patient 0045-00022 in Study 0101). One patient discontinued due to hepatitis toxic (0001-04618 in Study 021PE), and another patient (0005-02670 in Study 022) discontinued due to hepatic enzymes increased. Patient 0005-02670 is discussed under Other Significant AE (under Rash/Hypersensitivity). Short narratives for Patients 0045-00022 and 0001-04618 are presented below:

Patient 0045-00022 (Study 0101): SAE Cholecystitis

Patient was a 38-year-old Caucasian female with a diagnosis of seizures NOS. Concomitant AED therapy included lamotrigine and carbamazepine. On Day 459 of rufinamide therapy, while receiving 2000 mg/day of rufinamide, the patient was admitted to a hospital with abdominal and epigastric pain. An ultrasound did not reveal any abnormalities. Routine blood tests revealed mildly elevated AST and gamma-GTP. A diagnosis of acute cholecystitis was made, and the patient was treated with antibiotics and analgesics. She was discharged 3 days later, judged to have made a complete recovery. No change in study treatment was made due to the event.

Reviewer Comments

In concurrence with the investigator's opinion, the acute cholecystitis was probably not related to study medication.

Patient 0001-04618 (Study 021PE) Discontinuation Toxic Hepatitis

This was a 12-year-old Caucasian male with a diagnosis of refractory partial seizures. Concomitant AEDs during the Extension Phase included carbamazepine. The only concomitant non-AED administered was albendazole for parasitosis. On Day 212 of the Extension Phase, while the patient was being treated with rufinamide 1000 mg/day, his mother telephoned the study site to report some signs and symptoms (not specified in the report provided to the sponsor). Hepatitis A was tentatively diagnosed because of the symptoms and because there was currently an epidemic of the infection in the area. Laboratory evaluations performed the next morning (Day 213) revealed normal values for SGOT (20 U/L), SGPT (12 U/L), alkaline phosphatase (190 U/L), and GGT (17 U/L), with negative results for hepatitis A and hepatitis B immunoglobulins. The investigator reported these findings as an adverse event of toxic hepatitis, which was considered mild and not serious, and was suspected of being related to study drug. Due to this adverse event, the patient received his last dose of study drug 11 days later. The event was considered resolved approximately 4 weeks later. Values for liver enzymes were within normal ranges in laboratory evaluations performed before and approximately 4 weeks after the event.

Reviewer Comments

In both the cases described under hepatobiliary lab related AE in the All Subgroup Combined analyses, the sequence of events based on the clinical diagnosis and their relation to abnormal LFTs were not congruent and meaningful. Their relationship to rufinamide at best was remote.

Treatment Emergent LFT Lab Changes in Adult Double-blind Subgroup

As mentioned above, it should be noted that gamma-GTP was not measured in any of the studies included in the adult double-blind subgroup.

Mean Changes

Sponsor's Table 8.1-7, ISS, displayed mean values for hepatobiliary laboratory parameters at baseline, the last visit for each patient (Termination), and the change between those 2 visits. Mean changes were small and were similar in the rufinamide and placebo groups for all parameters except albumin. According to the sponsor, the relatively high mean for albumin was due to the inclusion of an erroneous lab value. The observed changes were not clinically meaningful (a mean change of 58.1 albumin, mean changes that were lower (-) at study termination for several of the parameters) or significantly different than placebo. According to the sponsor, the relatively high mean for albumin was due to the inclusion of an erroneous lab value. Further, the rates of shifts relative to the normal range and of clinically notable changes in albumin were small in the rufinamide group and nearly identical to the rates in the placebo group. *Discernable differences that were clinically meaningful were not seen.*

Shift Table Changes

The numbers of patients with shifts in hepatobiliary parameters, relative to the normal range, was summarized in Sponsor's Table 8.1-8, ISS, for adult double-blind partial seizures subgroup.

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. Similar percentages of patients in the 2 groups had upward shifts in albumin, LDH, and bilirubin. Higher percentages in the placebo group than in the rufinamide group had upwards shifts in alkaline phosphatase, SGOT, and SGPT. *Discernable differences that were clinically meaningful were not seen.*

Clinically Notable Changes

The incidence of patients with normal values for hepatobiliary parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.1-9, ISS for adult double-blind subgroup. Clinically notable values occurred in $\leq 0.7\%$ of the rufinamide-treated patients and $\leq 2.0\%$ of the placebo-treated patients. For individual parameters, the incidences of patients with clinically notable values were comparable between the treatment groups. *Discernable differences that were clinically meaningful were not seen.*

There were no serious adverse events or discontinuations due to adverse events related to hepatobiliary laboratory tests or the hepatobiliary system in either treatment group in the adult double-blind subgroup population.

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

Mean changes between baseline and the last post-baseline value were small for every hepatobiliary laboratory parameter (Ref: Sponsor's Appendix I, Table 8.1.1-46). Increases from normal at baseline to above the normal range at the last post-baseline evaluation occurred in $<4\%$ of the patients (Ref: Sponsor's Appendix I, Table 8.4.10-1). Clinically notable increases occurred in $<2\%$ of the patients. The highest rate of such increases was for LDH, which increased from a normal value at baseline to a clinically notable level at sometime during treatment in 5 (1.9%) patients (Ref: Sponsor's Appendix I, Table 8.3.1-46). There were no serious adverse events or discontinuations due to adverse events related to hepatobiliary laboratory tests or the hepatobiliary system.

Treatment Emergent LFT Lab Changes in Mono-therapy Double-blind Subgroup

Mean changes between baseline and the last post-baseline value were small for every hepatobiliary laboratory parameter and were generally similar in the rufinamide and placebo groups (Ref: Sponsor's Appendix I, Table 8.1.1-31). Increases relative to the normal range occurred in higher percentages of placebo-treated patients than rufinamide-treated patients for both SGOT (16.4% versus 9.1%) and SGPT (20.9% versus 5.3%). Increases in other parameters occurred in $<5\%$ of the patients in either group (Ref: Sponsor's Appendix I, Table 8.4.7-1). In the rufinamide group 2 (1.0%) patients had clinically notable increases in LDH, 2 (1.0%) patients had clinically notable increases in SGOT, and 6 (3.1%) patients had clinically notable increases in SGPT (Ref: Sponsor's Appendix I, Table 8.3.1-31). In the placebo group, 1 (1.6%) patient had a clinically notable increase in SGPT. There were no other clinically notable values in this population. There were no serious adverse events or discontinuations due to adverse events related to hepatobiliary laboratory tests or the hepatobiliary system in either treatment group.

Treatment Emergent LFT Lab Changes in LGS Double-blind Subgroup

As mentioned above, it should be noted that gamma-GTP was not measured in the LGS Double-blind subgroup / study (single LGS study constituted the subgroup).

Mean Changes

Sponsor's Table 8.1-10, ISS, displayed mean values for hepatobiliary laboratory parameters at baseline, the last visit for each patient (Termination), and the change between those 2 visits. Mean changes were small and were similar in the rufinamide and placebo groups. The mean change in SGOT/AST with rufinamide was 0.9 and -2.1 with placebo. The mean change in LDH was 2.7 with rufinamide and 0.3 with placebo. The mean changes in remainder of parameters were (-) for both treatment groups. Small sample sizes limited the interpretation of the results. *Discernable differences that were clinically meaningful, however, were not seen.*

Shift Table Changes

The numbers of patients with shifts in hepatobiliary parameters, relative to the normal range, was summarized in Sponsor's Table 8.1-11, ISS for the LGS double-blind subgroup. 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. Shifts from within the normal range at baseline to above the normal range at the last evaluation occurred in small percentages of patients (<5%) in both groups. For individual parameters, the percentages of patients with upward or downward shifts were generally similar for rufinamide and placebo. Shifts (baseline normal to post-treatment high) for SGOT was 4.1 and 1.6 for rufinamide and placebo respectively. Greater shifts with placebo were seen for albumin, alkaline phosphatase, and SGPT. Small sample sizes limited the interpretation of the results. *Discernable differences that were clinically meaningful, however, were not seen.*

Clinically Notable Changes

The incidence of patients with normal values for hepatobiliary parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.1-12, ISS for patients in the LGS double-blind study. Two (2.9%) rufinamide-treated patients and 1 (1.6%) placebo-treated patient had a clinically notable decrease in albumin, and 1 (1.5%) rufinamide-treated patient had a clinically notable increase in LDH. There were no other clinically notable values in either treatment group. Small sample sizes limited the interpretation of the results. *Discernable differences that were clinically meaningful, however, were not seen.*

Adverse events related to hepatobiliary laboratory tests occurred in fewer than 1% of rufinamide-treated patients (Ref: Sponsor's Appendix I, Table 6.7.1-3). No patient in either treatment group had a serious adverse event. One patient in the rufinamide group (Patient 0005-02670 in Study 022) discontinued treatment due to rash, fatigue, vomiting, and hepatic enzymes increased (moderate increased in SGOT and SGPT); the increase in hepatic enzymes was not considered the primary reason for discontinuation (see discussion and narrative under Other Significant AE [Rash/Hypersensitivity] section for this patient).

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

Mean changes between baseline and the last post-baseline value were small for every hepatobiliary laboratory parameter (Ref: Sponsor's Appendix I, Table 8.1.1-11). Increases from normal at baseline to above the normal range at the last post-baseline evaluation occurred in <5% of the patients (Ref: Sponsor's Appendix I, Table 8.4.5-1). Higher percentages of patients had decreases in alkaline phosphatase and SGOT than had increases. Similar percentages had increases and decreases in SGPT. Twenty-one (16.5%) patients had clinically notable decreases in albumin, 5 (3.9%) patients had clinically notable increases in alkaline phosphatase, and 5 (3.9%) patients had clinically notable increases in LDH (Ref: Sponsor's Appendix I, Table 8.3.1-11). There were no other clinically notable values in this population. There were no serious adverse events related to hepatobiliary laboratory tests or the hepatobiliary system. As discussed previously (under other significant AE- rash), Patient 0005- 02670 in Study 022 had hepatic enzymes increased which was not the primary reason for discontinuation.

Treatment Emergent LFT Lab Changes in Pediatric Double-blind Subgroup

As mentioned above, it should be noted that gamma-GTP was not measured in the Pediatric Double-blind subgroup.

Mean Changes

Sponsor's Table 8.1-13, ISS, displays mean values for hepatobiliary laboratory parameters at baseline, the last visit for each patient (Termination), and the change between those 2 visits for the pediatric double-blind subgroup. Mean changes were small and were generally similar in the rufinamide and placebo groups. Further, the mean post-treatment changes across all the parameters in the rufinamide treatment subgroup were (-) / lower compared to baseline and in 3 parameters, the mean changes were (-) / lower compared to placebo. *Discernable differences that were clinically meaningful were not seen.*

Shift Table Changes

The numbers of pediatric double-blind patients with shifts in hepatobiliary parameters, relative to the normal range, was summarized in Sponsor's Table 8.1-14, 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. Shifts from within the normal range at baseline to above the normal range at the last evaluation occurred in small percentages of patients (<4%) in both groups. For most individual parameters, the percentages of patients with upward or downward shifts were similar for rufinamide and placebo. A higher percentage of patients in the rufinamide group than the placebo group had decreases from normal to below the normal range for SGOT (6.6% versus 4.6%); the percentages with increases were similar (2.4% versus 1.5%). A lower percentage of patients in the rufinamide group than the placebo group had increases from normal to above the normal range in SGPT (0.9% versus 3.6%); the percentages with decreases were similar (3.8% versus 2.5%). The three parameters (albumin, SGOT and bilirubin) the shifts from normal baseline to high post-rufinamide treatment were greater than comparable shifts in the post-placebo treatment arm. *Discernable differences that were clinically meaningful, however, were not seen.*

Clinically Notable Changes

The incidence of patients with normal values for hepatobiliary parameters at baseline and at least one post-baseline, clinically notable change were summarized in Sponsor's Table 8.1-15, ISS for

patients in the pediatric double-blind subgroup. The only clinically notable values in the rufinamide group occurred in 2 (1.1%) patients with decreases in albumin and 1 (0.6%) patient with an increase in LDH. In the placebo group, a decrease in albumin and increases in alkaline phosphatase, SGOT, and SGPT each occurred in 1 (0.6%) patient. There were no other clinically notable values in this population. There were no serious adverse events related to hepatobiliary laboratory tests or the hepatobiliary system in either treatment group. As noted above and discussed under other significant AE, patient 0005-02670 (Study 022) had hepatic enzyme increased that was not the primary reason for discontinuation.

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

Mean changes between baseline and the last post-baseline value were small for every hepatobiliary laboratory parameter (Ref: Sponsor's Appendix I, Table 8.1.1-16). Increases from normal to above the normal range for individual parameters occurred in <4% of the patients (Ref: Sponsor's Appendix I, Table 8.4.4-1). Similar percentages of patients had increases and decreases in alkaline phosphatase (3.3% versus 4.9%) and SGPT (2.8% versus 2.6%). The percentage of patients with increases in SGOT (2.8%) was lower than the percentage with decreases (9.2%). Clinically notable increases or decreases in these parameters occurred in \leq 3.0% of the patients (Ref: Sponsor's Appendix I, Table 8.3.1-16). There were no serious adverse events related to hepatobiliary laboratory tests or the hepatobiliary system. One patient (0001-04618 in Study 021PE- discussed previously) discontinued due to hepatitis toxic, and another patient (0005-02670 in Study 022- discussed previously) discontinued due to hepatic enzymes increased.

Treatment Emergent Renal Laboratory Changes

Reviewer Comments

The parameters that were evaluated under this panel were BUN and creatinine. 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. Hence, the interpretation of the results required allowances for such variations in the denominators.

The data (mean changes) was presented using SI units for BUN (normal SI = 2.5-10.7 mmol/L [*sponsor 2.14 to 8.57*] [normal conventional units = 7-30 mg/dL]) and creatinine (normal SI = \leq 106 μ mol/L [*sponsor 17.68 to 79.56*] [normal conventional units = \leq 1.2mg/dL]). The results were presented as Mean Changes, Shift Table Changes and Clinically Notable Changes.

Treatment Emergent Renal Lab Changes in All Double-blind Studies Subgroup

Mean Changes

Sponsor's Table 8.2-1, ISS, displayed mean values for renal laboratory parameters at baseline, the last visit for each patient (Termination), and the change between those 2 visits in the All Double-blind studies subgroup. Mean changes were small and were similar in the rufinamide and placebo groups. While the mean change in creatinine in the placebo group was 0.9, the rufinamide mean change was 2.7 (an increase in mean from baseline with rufinamide compared to placebo in the all double-blind subgroup).

Shift Table Changes

The numbers of patients with shifts in renal parameters, relative to the normal range, was summarized in Sponsor's Table 8.2-2, ISS for all treated patients with epilepsy who received study drug 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. Shifts from within the normal range at baseline to above the normal range at the last evaluation occurred in small percentages of patients (<4%) in both groups. The percentages of patients with upward or downward shifts were similar for rufinamide and placebo. The shifts from normal baseline to high post-treatment were greater in the placebo group for both BUN and Creatinine than the rufinamide group.

Clinically Notable Changes

The incidence of patients with normal values for renal parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.2-3, ISS for all treated patients with epilepsy who received study drug in double-blind studies. The incidences of clinically abnormal values for BUN and creatinine were similar in the rufinamide group and the placebo group with an increase in BUN for the rufinamide (1.8 vs. 1.6).

There were no serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events, in either treatment group.

Treatment Emergent Renal Lab Changes in All Subgroups Combined

Mean Changes

Sponsor's Table 8.2-4, ISS displayed mean values for renal laboratory parameters at baseline, the last visit for each patient (Termination), and the change between those 2 visits. Mean changes were small. The lack of a placebo arm made meaningful interpretations difficult.

Shift Table Changes

The results for all treated patients with epilepsy (Sponsor's Table 8.2-5, ISS) were similar to those seen in the double-blind studies. Upward and downward shifts from normal in BUN occurred in similar percentages of patients (2.9% and 2.5% respectively), as did upward and downward shifts in creatinine (3.4% and 4.5%, respectively).

Clinically Notable Changes

Forty-three (2.4%) patients had clinically notable increases in BUN and 1 (0.1%) patient had a clinically notable decrease, as shown in Sponsor's Table 8.2-6, ISS. Fifteen (0.8%) patients had clinically notable increases in creatinine, and none had decreases. The lack of a placebo arm made meaningful interpretations difficult.

All patients in this population with clinically notable values for creatinine were identified in Sponsor's Appendix I, Table 8.6-8. The table displayed, for each of these patients, demographic information, treatment information, and laboratory results for creatinine and BUN. Of the 15 patients with increased creatinine, 14 had one or two isolated elevated values. Thirteen of the 14

patients continued therapy and had normal values at later evaluations; the 13th patient had relatively high creatinine values throughout treatment, with a minor increase relative to the other values. One of 15 patients had multiple values that were elevated. This patient had fluctuating values throughout placebo and rufinamide treatment; the baseline creatinine value was the same as the final on-therapy value.

Adverse events related to renal laboratory tests or renal disorders occurred in fewer than 1% of the rufinamide-treated patients (Ref: Sponsor's Appendix I, Table 6.10.1-1). One patient (0514-00005, Study 0101) had a serious adverse event of renal failure acute. This case is discussed below.

Patient 0514-00005 (Study 0101): SAE Acute Renal Failure

Patient was a 23-year-old Caucasian male who on day 285 of rufinamide therapy, while receiving rufinamide 2000 mg/day, lamotrigine, and phenytoin; experienced a prolonged seizure and developed rhabdomyolysis resulting in anorexia and dehydration. The patient was admitted to the hospital for acute renal failure. His BUN at admission was 158 and his creatinine was 1.2 (units and normal ranges were not provided). Study medication was temporarily interrupted upon admission. The patient was eventually discharged and the acute renal failure was assessed as completely resolved 17 days after the onset of the seizure. The investigator assessed this serious adverse event as not related to rufinamide treatment. Renal experts at the hospital attributed the acute renal failure to the prolonged seizure, which resulted in dehydration. The patient was subsequently restarted on rufinamide.

There were no discontinuations due to renal adverse events.

Treatment Emergent Renal Lab Changes in Adult Double-blind Subgroup

Mean Changes

Sponsor's Table 8.2-7, ISS, displayed mean values for renal laboratory parameters at baseline, the last visit for each patient (Termination), and the change between those 2 visits. While mean changes were small and were similar in the rufinamide and placebo groups, the mean change in creatinine was 2.3 and 0.9 with rufinamide and placebo respectively in the adult double-blind subgroup.

Shift Table Changes

The numbers of patients with shifts in renal parameters, relative to the normal range, were summarized in Sponsor's Table 8.2-8, ISS for patients in the adult 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. Shifts from within the normal range at baseline to above the normal range at the last evaluation occurred in small percentages of patients (<3%) in both groups. But these shifts were greater with rufinamide compared to placebo (2.6 vs. 2.1 for BUN and 1.0 vs. 0.3 for creatinine) in the adult double-blind subgroup.

Clinically Notable Changes

The incidence of patients with normal values for renal parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.2-9, ISS, for adults with partial seizures who received study drug in double-blind studies. The incidences of clinically abnormal values for BUN and creatinine were similar in the rufinamide group and the placebo group and no clinically meaningful discernable trends were observed.

There were no serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events, in either treatment group.

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

Mean changes between baseline and the last post-baseline evaluation were small for both BUN (0.0 mmol/L) and creatinine (1.2 μ mol/L) (Ref: Sponsor's Appendix I, Table 8.1.1-47). Downward shifts in BUN occurred in 1.7% of the patients, whereas upward shifts occurred in 4.8% (Ref: Sponsor's Appendix I, Table 8.4.10-2). Shifts in creatinine occurred in 6.9% and 1.1% of the patients, respectively. Of the 867 patients with normal baseline values for BUN, 0.1% had a clinically notable decrease and 4.6% had a clinically notable increase. Of the 923 patients with normal baseline values for creatinine, none had a clinically notable decrease and 1.0% had clinically notable increases (Ref: Sponsor's Appendix I, Table 8.3.1-47). The lack of a placebo arm made meaningful interpretations difficult. There were no serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events.

Treatment Emergent Renal Lab Changes in Mono-therapy Double-blind Subgroup

Mean changes between baseline and the last post-baseline evaluation were small and were comparable in the rufinamide and placebo groups: -0.1 mmol/L in the rufinamide group and -0.0 mmol/L in the placebo group for BUN, and 4.0 and 2.2 μ mol/L, respectively, for creatinine (Ref: Sponsor's Appendix I, Table 8.1.1-32). Downward shifts in BUN occurred in 3.4% of the rufinamide-treated patients and 0% of the placebo-treated patients, whereas upward shifts occurred in 1.0% and 3.0%, respectively (Ref: Sponsor's Appendix I, Table 8.4.7-2). Downward shifts in creatinine occurred in 1.0% of the rufinamide-treated patients and 3.0% of the placebo-treated patients, whereas upward shifts occurred in 1.4% and 4.5%, respectively. No patient in either treatment group had a normal baseline value for BUN or creatinine and at least 1 post-baseline, clinically notable value (Ref: Sponsor's Appendix I, Table 8.3.1-32). There were no serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events, in either treatment group.

Treatment Emergent Renal Lab Changes in LGS Double-blind Subgroup

Mean Changes

Sponsor's Table 8.2-10, ISS, displayed mean values for renal laboratory parameters at baseline, the last visit for each patient (Termination), and the change between those 2 visits. Mean changes were small and were similar in the rufinamide and placebo groups. *Discernable differences that were clinically meaningful, however, were not seen.*

Shift Table Changes

The numbers of patients with shifts in renal parameters, relative to the normal range, was summarized in Sponsor's Table 8.2-11, ISS, for patients in the double-blind LGS study. Both upward and downward shifts from normal in BUN occurred in lower percentages of patients in the rufinamide group than the placebo group. Both upward and downward shifts from normal in creatinine occurred in higher percentages of rufinamide-treated patients than placebo-treated patients. The creatinine upward shift was 8.1 and 1.6 for rufinamide and placebo respectively. Upward shifts in BUN, however, were greater with placebo (10.9 vs. 2.7). Sample sizes were small.

Clinically Notable Changes

No patient in either treatment group had a post-baseline, clinically notable value for BUN or creatinine (Ref: Sponsor's Appendix I, Table 8.3.1-7). There were no serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events, in either treatment group.

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

Mean changes between baseline and the last post-baseline evaluation were small for both BUN (-0.4 mmol/L) and creatinine (1.6 μ mol/L) (Ref: Sponsor's Appendix I, Table 8.1.1-12). Shifts to below the normal range occurred in 4.4% of the patients for BUN and 3.7% of the patients for creatinine (Ref: Sponsor's Appendix I, Table 8.4.5-2). Shifts to above the normal range occurred in 3.7% and 5.2%, respectively. No patient had a post-baseline, clinically notable value for creatinine (Appendix I, Table 8.3.1-12). Two (1.6%) had clinically notable increases in BUN. The lack of a placebo arm made meaningful interpretations difficult. There were no serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events.

Treatment Emergent Renal Lab Changes in Pediatric Double-blind Subgroup

Mean Changes

Sponsor's Table 8.2-12, ISS, displayed mean values for renal laboratory parameters at baseline, the last visit for each patient (Termination), and the change between those 2 visits. Mean changes in BUN were small and were identical in the rufinamide and placebo groups. The mean change in creatinine was greater in the rufinamide group (2.7) than in the placebo group (0.3) in the pediatric double-blind subgroup.

Shift Table Changes

The numbers of patients with shifts in renal parameters, relative to the normal range, were summarized in Sponsor's Table 8.2-13, ISS, for pediatric patients in double-blind studies. The percentages of patients with upward or downward shifts in BUN and creatinine were similar for the rufinamide and placebo groups. The shift in creatinine from normal baseline to high post treatment in the pediatric double-blind subgroup was greater with rufinamide than placebo (10.8 vs. 8.1).

Clinically Notable Changes

No patient in either treatment group had a clinically notable value for BUN. One (0.6%) of 168 patients in the placebo group and none of 185 patients in the rufinamide group had a clinically notable increase in creatinine. (Ref: Sponsor's Appendix I, Table 8.3.1-22).

There were no serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events, in either treatment group.

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

Mean changes between baseline and the last post-baseline evaluation were small for both BUN (-0.0 mmol/L) and creatinine (4.0 μ mol/L) (Ref: Sponsor's Appendix I, Table 8.1.1-17). Upward and downward shifts in BUN, relative to the normal range, each occurred in 2.3% of the patients (Ref: Sponsor's Appendix I, Table 8.4.4-2). Upward shifts in creatinine occurred in 10.7% of the patients, whereas downward shifts occurred in 2.0%. Three (1.0%) patients had clinically notable increases in BUN, and 4 (1.1%) patients had clinically notable increases in creatinine (Ref: Sponsor's Appendix I, Table 8.3.1-17). The lack of a placebo arm made meaningful interpretations difficult. There were no serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events.

Treatment Emergent Hematology Laboratory Changes

Reviewer Comments

The parameters that were evaluated under this panel were RBC, WBC, Platelets, Hb, HCT, and a differential WBC. 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. Hence, the interpretation of the results required allowances for such variations in the denominators.

The data (mean changes) was presented using % for the WBC differential, SI counts for RBC (SI units = $10^{12}/L$ [sponsor 3.9 to 5.72] [conventional units = $10^6/\mu L$]), SI units for WBC (SI units = $10^9/L$ [sponsor 3.4 to 10.8] [conventional units = $10^3/\mu L$]) and SI units for Platelets (SI units = $10^9/L$ [sponsor 150-450] [conventional units = $10^3/\mu L$]), SI units for Hb (SI units = g/L [sponsor 7.45 to 10.86] [conventional units = g/dL]) and conventional units (%) for HCT [sponsor 33 to 47.3]. The results were presented as Mean Changes, Shift Table Changes and Clinically Notable Changes.

Treatment Emergent Hematology Lab Changes in All Double-blind Studies Subgroup

Mean Changes

Sponsor's Table 8.3-1, ISS, displayed mean values for hematology laboratory 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 similar in the rufinamide and placebo groups. *Discernable differences that were clinically meaningful, however, were not seen.*

Shift Table Changes

The numbers of patients with shifts in hematology parameters, relative to the normal range, was summarized in Sponsor's Table 8.3-2, ISS, for all treated patients who received study drug 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. 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 hematology parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.3-3, ISS for all patients with epilepsy who received study drug in double-blind studies. The incidences of such values were similar with rufinamide and placebo. *Discernable differences that were clinically meaningful were not seen.*

Serious adverse events related to hematology, which occurred in the rufinamide group, were leukopenia (2 patients), neutropenia (2 patients), and anemia (1 patient). One rufinamide-treated patient discontinued due to disseminated intravascular coagulation, and one discontinued due to neutropenia. For discussion and label recommendations, see All Subgroups below. No placebo-treated patient had a serious adverse event related to hematology or discontinued due to such events.

Treatment Emergent Hematology Lab Changes in All Subgroups Combined

Mean Changes

Sponsor's Table 8.3-4, ISS, displayed mean values for hematology laboratory parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2 visits. Mean changes were small for every parameter and were similar to those seen in the double-blind studies. *Discernable differences that were clinically meaningful, however, were not seen.*

Shift Table Changes

The numbers of patients with shifts in hematology parameters, relative to the normal range, was summarized in Sponsor's Table 8.3-5, ISS for all treated patients who received study drug in all subgroups combined. A majority of the patients had no shifts relative to the normal range between baseline and the last post-baseline evaluation. Two hundred fifteen (10.9%) patients had downward shifts in monocytes, 180 (9.1%) patients had downward shifts in hemoglobin, and 154 (7.8%) patients had downward shifts in RBCs. Fewer than 6% of the patients had upward or downward shifts in the remaining parameters. The lack of a placebo arm made meaningful interpretations difficult.

Clinically Notable Changes

The incidence of patients with normal values for hematology parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.3-6, ISS for all patients with epilepsy who received study drug in all subgroups combined. The incidences of

such values were generally higher than those in the double-blind studies, reflecting the longer duration of treatment in this population. The lack of a placebo arm made meaningful interpretations difficult.

A series of tables were included in Sponsor's Appendix I identifying patients in this population (all subgroup combined) with clinically notable values (Table 8.6-2 [neutrophils or WBCs], Table 8.6-3 [hematocrit, hemoglobin, or RBCs], Table 8.6-4 [platelet count], Table 8.6-5 [eosinophils], and Table 8.6-6 [lymphocytes]). These tables displayed, for each of the patients, demographic information, treatment information, and relevant hematology laboratory results.

The following is a summary of these clinically notable changes in labs -

Neutrophils as a Clinically Notable Change- low value

There were at least 20 patients out of 26 (Appendix Table 2 for definition) in whom the final neutrophil count was categorized as clinically notable drop than the previous ones. While the temporal relation to the last dose was not provided, the shortest interval between the noted abnormal value and the preceding value was 4 weeks, implying that the earliest time at which neutropenia was seen was 4 weeks. In the remainder 6 patients with clinically notable low neutrophil value, it was not possible to make such determinations.

Hematocrit, Hb or RBC as a Clinically Notable- low value

In 5 patients, the final counts were categorized as clinically notable low value. All clinically notable values occurred at only one or 2 evaluations with subsequent values that were not clinically notable or were within normal ranges, with no evidence of progressive decline, except in 5 patients who had clinically notable values for RBCs at the final evaluation.

Platelets as a Clinically Notable Change- low value

Abnormal platelet values that were considered clinically notable included the following subgroups-

- f) The clinically abnormal values were reported for 19 patients. These were likely laboratory errors, i.e., very low values (0-4,000 platelets) with no thrombocytopenia reported as an adverse event, and the patients continued in the study with subsequent values that were not clinically notable.
- g) ~ 23 patients had one determination with low platelets (<150,000) before drug intake, that were subsequently followed by values of >100,000. Two patients had an AE of thrombocytopenia. In one, the AE was thought to be due to valproate.
- h) 3 patients had low values at one determination, which was the final laboratory evaluation performed. The reported values were 1000 (patient M7143W-00105), 2600 (this patient 0008-08071 discontinued due to fatigue and was also on valproate), and 73000.
- i) Seven patients had thrombocytopenia as an adverse event. Two of the 7 had clinically notable values (see above). The remaining 5 had values that were not clinically notable.
- j) There were no serious adverse events of thrombocytopenia and no discontinuations due to adverse events related to thrombocytopenia.

Reviewer Comments

In a majority of the cases of thrombocytopenia, valproate was thought to be the primary cause (in the label for valproate [2006 PDR, p. 413], thrombocytopenia is listed as a warning).

Laboratory-related AE

Anemia was reported as an adverse event in 2.1% of female patients who were treated with rufinamide and 0.6% of male patients (Ref: Sponsor's Appendix I, Table 6.3.1-9). All other adverse events related to hematology laboratory parameters occurred in fewer than 1% of the rufinamide-treated patients (Ref; Sponsor's Appendix I, Table 6.10.1-1).

Serious adverse events related to hematology were leucopenia (3 patients: 0003-06026 in Study AE/ET1, 1553-02028 in Study 022, 1747-02023 in Study 022E), neutropenia (2 patients: 0002-04024 in Study AE/ET1, 1553-02028 in Study 022), anemia (1 patient: 1276-05044 in Study 021A), hemolytic anemia (1 patient: 1747-02023 in Study 022E), and leukocytosis (1 patient: 0001-07515 in Study AE/ET1E). Note that more than one SAE occurred in the same patient (s).

Discontinuations related to hematology included anemia (1 patient: 0512-00001 in Study 0101), disseminated intravascular coagulation (1 patient: 0004-04209 in Study 021P), hemolytic anemia (1 patient: 1747-02023 in Study 022E), leukopenia (1 patient: 0512-00001 in Study 0101), and neutropenia (1 patient: 0003-04265 in Study AE/ET1). Note that more than one event occurred in the same patient.

Patient 0003-06026 (Study AE/ET1): SAE Leucopenia and discontinuation

This 18 year old F, on carbamazepine since 1992, was started on 400 mg rufinamide in Jan 04. Base line labs were- WBC = 4.6×10^9 , HCT = 37, Plt = 194×10^9 . Three days after starting rufinamide, the WBC was 3.4×10^9 and ~ 4 weeks later it was 2.7×10^9 (HCT=34 and Plt= 168×10^9). Patient was discontinued and 5 days later the WBC count was 6.5×10^9 .

Reviewer Comments

SAE of leucopenia and discontinuation in Patient 0003-06026 (Study AE/ET1) is most likely related to rufinamide administration.

Reviewer Comments

See label recommendations below.

Patient 1553-02028 (Study 022): SAE Leucopenia and Neutropenia

This was a 13-year-old male patient with a diagnosis of Lennox-Gastaut syndrome and baseline WBC of $5.8 \times 10^9/L$ and neutrophils of 63.15%. Following therapy with cefixime (400 mg/day) for streptococcal pharyngitis and one day prior to receiving rufinamide (on the day of randomization) the laboratory tests revealed a WBC of $2.9 \times 10^9/L$ with 7.24% neutrophils. Concomitant medications were lamotrigine 500 mg/day, and carbamazepine 600 mg/day. On the following day, prior to the knowledge of the abnormal results of the WBC count from the previous day, patient received a single dose of 600 mg of rufinamide. Rufinamide and cefixime were discontinued and patient was hospitalized for observation and monitoring. Within 5 days of the onset of adverse experience, the patient was discharged from the hospital in improved

condition. The patient remained off rufinamide until the neutropenia was resolved. Approximately 16 days after discharge from the hospital WBC was $4.4 \times 10^9/L$ with 35.73% neutrophils. On 05-Nov-1998 the patient reinitiated blinded rufinamide treatment.

Reviewer Comments

SAE of leucopenia and neutropenia in Patient 1553-02028 (Study 022) is not related to rufinamide administration because these events occurred before the patient was exposed to rufinamide.

Patient 1747-02023 (Study 022E): SAE Leucopenia, Hemolytic anemia and Discontinuation

This 14-year-old Caucasian 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. 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 25-Aug-99. Concomitant AEDs included clonazepam, lamotrigine and tiagabine. Concomitant non-AEDs included alendronate sodium, amoxicillin, bisacodyl, cefuroxime axetil, chloral hydrate, clavulin, diphenhydramine, epinephrine, folic acid, ibuprofen, lorazepam, methylprednisolone, multivitamins, naproxen, paracetamol, prednisone and Respire SR-120. On 25-Aug-99 (Day 83 of double-blind treatment), while receiving 1000 mg/day of rufinamide, the patient developed a rash. Total and differential white blood counts and bilirubin remained within normal limits. The rash completely resolved on 29-Aug-99.

On 09-Jun-00 (Day 372 of rufinamide), while receiving 1400 mg/day of rufinamide, leukopenia was reported. She had an abnormally low absolute neutrophil count ($0.473 \times 10^9/L$) and WBC ($1.8 \times 10^9/L$) on that day. A bone marrow biopsy performed on 16-Jun-00 revealed no cancer cells and an abundance of neutrophils.

On 09-Sep-00 (Day 464 of rufinamide), while receiving 1400 mg/day of rufinamide, antinuclear antibody and anti-DS-DNA tests were positive. The diagnosis of systemic lupus erythematosus (SLE) was made on 29-Sep-00 by a pediatric immunologist. She was started on naproxen, prednisone and alendronate. On 17-Oct-00, her white blood cell count was $4.1 \times 10^9/L$ and neutrophils were $1.763 \times 10^9/L$. Although the values for white cells, neutrophils and bilirubin were within the normal range both total and direct bilirubin were elevated over previous values on 14-Sep-00 and by 17-Oct-00 the total bilirubin was $17.10 \mu\text{mol/L}$. The investigator assessed this adverse event as not related to rufinamide because anti-DS-DNA is not expected to be found in drug-induced SLE. On _____ of rufinamide), while receiving 1400 mg/day of rufinamide, the patient's hematocrit had fallen to 22% and she was diagnosed with hemolytic anemia secondary to systemic lupus erythematosus and hyperbilirubinemia secondary to hemolytic anemia. She was admitted to the hospital for treatment with intravenous methylprednisolone. The hematocrit increased to 26 percent after the first intravenous dose. Due to the diagnosis of SLE, rufinamide was discontinued after 511 days of treatment. The hemolytic anemia was reported as resolved by 31-Oct-00. After rufinamide was discontinued for 76 days, the white blood cell count was $4.4 \times 10^9/L$, neutrophils were $1.09 \times 10^9/L$, and total bilirubin was at the pre-study level.

b(6)

Reviewer Comment

In this complex case, with underlying immunosuppressive medical condition of SLE and concurrent poly-drug treatment, it is difficult to determine the extent of the role of rufinamide particularly in the context of its prolonged use. *While direct relationship either to leucopenia or hemolytic anemia is unlikely, the possibility of a remote association either because of the presence of other medications or underlying lupus cannot be fully excluded.*

Patient 0002-04024 (Study AE/ET1): SAE Neutropenia

A 31 year F on carbamazepine, 27 days after initiation with rufinamide, was noted to have neutropenia WBC= 4.5×10^9 and neutrophil = 1.08×10^9 (baseline WBC= 5.0×10^9 and Neutrophil= 2.0×10^9). With no treatment or intervention, repeat values ~ 4 weeks later, the counts were WBC 4.9×10^9 and neutrophils were 2.35×10^9 .

Reviewer Comment

While the report at ~ 4 week post-exposure showed improvement, whether based on this single value one can conclude that rufinamide was not the cause for the SAE of neutropenia can be questioned. However, under the assumption that rufinamide was not discontinued (if no treatment of intervention also means no changes in medications) the resolution of the values towards baseline is re-assuring. Without further information, whether rufinamide was or was not the cause of neutropenia is not determinable.

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

This patient has been discussed under the all double-blind subgroup treatment emergent chemistry lab changes (see below). Details of the description of the anemia were not provided other than a single HCT and Hb value (hematocrit [33%] and hemoglobin [10.8 g/dl]). The primary SAE of concern was metabolic (hyponatremia) and it appears that anemia was a coincidental finding that was listed automatically as a SAE along with the others.

Reviewer Comments

The SAE of anemia, as listed, was probably not the main event of concern.

Patient 0001-07515 (Study AE/ET1E): SAE Leukocytosis

This 61-year-old female patient, with a history involving multiple medical problems, on multiple non-AEDs and AEDs, entered the double-blind phase of the study AE/ET1 with a diagnosis of inadequately controlled partial seizures. On Day 2520 of rufinamide therapy, while receiving 3200 mg/day of rufinamide, the patient was noted to have leukocytosis (results not available). WBCs at study entry and throughout the study period were within the normal range and the last recorded value was $6.4 \times 10^9/L$. The patient was withdrawn from the study due to the abnormal laboratory value, with the last dose taken on Day 2547 of rufinamide therapy (value not provided). The patient was subsequently diagnosed with chronic myeloid leukemia.

Reviewer Comments

In a majority of the cases of thrombocytopenia, valproate was thought to be the primary cause (in the label for valproate, thrombocytopenia is listed under the).

Patient 0512-00001 (Study 0101): Discontinuation Leucopenia and Anemia

The patient had underlying SLE which was the most likely cause for the leucopenia and anemia. The actual cause for discontinuation was most likely fever.

Patient 0004- 04209 (Study 021P): Discontinuation DIC

This 6-year-old male patient entered the study with a diagnosis of partial seizures. The patient's significant medical history included mild mental retardation. The patient began rufinamide on 23-Sep-1998. Approximately  after entry into the double-blind phase, the patient was alone taking a bath when his parents found him unconscious in the water. The rufinamide dose at the time of the adverse event was 1000 mg/day. Concomitant medications were phenobarbital 60 mg/day and valproic acid 1000 mg/day. The patient was hospitalized and intubated. Disseminated intravascular coagulation was diagnosed. Rufinamide and valproic acid were stopped on the same day the patient was discontinued from the study. Within 8 days of the onset of the adverse event, the patient completely recovered from asphyxia.

b(6)

Reviewer Comments

The primary inciting cause for DIC was most likely related to the shock as a result of profound systemic cardiovascular and respiratory decompensation due to asphyxia rather than rufinamide related. The asphyxia and unconsciousness was probably due to an un-witnessed seizure.

Patient: 0003-04265 (Study AE/ET1): Discontinuation Neutropenia

This 36 year old F patient with history of partial seizures on clobazam (benzodiazepine not approved in the US) and phenytoin (x ~ 8 months) was enrolled and started on 1600 mg of rufinamide. The following were the WBC ($\times 10^9$)/neutrophil (%) counts and associated events following rufinamide administration-

Day 3 = 5.7/56, Day 13 = 4.2/58, Day 28 = 7.3/61, Day 29 – developed furuncles, Day 55 = 3.5/43% and developed lingual mycosis. Following this, patient was discontinued. There was no further follow up.

Reviewer Comments

The patient continued to receive phenytoin and rufinamide while leucopenia and neutropenia was being monitored. In the absence of other information, it is not possible to determine the actual cause. Cessation of one medication at a time with continued WBC/differential monitoring may have provided the answer. However, it is also likely that the combination of phenytoin and rufinamide may have resulted in this problem.

Downward WBC shifts from a normal baseline that were greater than placebo were seen (4.3 vs. 2.4) in the adult double-blind subgroup analysis (see below) suggesting a tendency for rufinamide to cause leucopenia. Clinically notable decreases in WBCs occurred in 37 (5.2%) rufinamide-treated patients and 6 (2.1%) placebo-treated patients in the adult double-blind subgroup analysis (see below). These coupled with the findings from Patient 0003-04265 (Study AE/ET1) who discontinued due to neutropenia that was associated with furuncle and localized

mycosis and the discontinuation of Patient 0003-06026 (Study AE/ET1) due to SAE of leucopenia raises the concern further.

It is recommended that the greater incidence of shifts from normal baseline or clinically notable changes in the occurrence of leucopenia and neutropenia compared to placebo and the development of furuncles and localized mycosis that led to discontinuation in a patient who was also receiving phenytoin _____

b(4)

Patient 1747-02023 who discontinued was discussed under SAE above.

Treatment Emergent Hematology Lab Changes in Adult Double-blind Subgroup

Mean Changes

Sponsor's Table 8.3-7, ISS, displays mean values for hematology laboratory 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 similar in the rufinamide and placebo groups. *Discernable differences that were clinically meaningful, however, were not seen.*

Shift Table Changes

The numbers of patients with shifts in hematology parameters, relative to the normal range, was summarized in Sponsor's Table 8.3-8 for adults with partial seizures who received study drug 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. The percentages of patients with upward or downward shifts from normal were similar in the two treatment groups. The largest percentages of patients with shifts in both groups were for hemoglobin (downward shifts for 9.9% of the rufinamide-treated patients and 10.7% of the placebo treated patients) and monocytes (downward shifts for 10.4% and 13.4%, respectively). Upward and downward WBC shifts from a normal baseline that were greater than placebo were seen (upward 1.8 vs. 0 and downward 4.3 vs. 2.4).

Reviewer Comments

See label recommendations above.

Clinically Notable Changes

The incidence of patients with normal values for hematology parameters at baseline and at least 1 post-baseline, clinically notable value was summarized in Sponsor's Table 8.3-9, ISS, for adults with partial seizures who received study drug in double-blind studies. Clinically notable decreases in WBCs occurred in 37 (5.2%) rufinamide-treated patients and 6 (2.1%) placebo-treated patients. All other incidences of clinically notable values were <3% and were comparable in the 2 treatment groups with no discernable trends.

Serious adverse events related to hematology, which each occurred in one patient in the rufinamide group, were leukopenia, neutropenia, and anemia. One rufinamide-treated patient discontinued due to neutropenia. These were described and discussed above under all subgroups

combined including label recommendations. No placebo-treated patient had a serious adverse event related to hematology or discontinued due to such events.

Reviewer Comments

See label recommendations above under all subgroups combined.

Treatment Emergent Hematology 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 8.1.1-48). Downward shifts from normal occurred in hemoglobin (10.7% of patients), monocytes (10.4%), and RBCs (8.7%). For the remaining parameters, all upward and downward shifts occurred in $\leq 5.4\%$ of the patients (Ref: Sponsor's Appendix I, Table 8.4.10-3). At least 1 post-baseline, clinically notable decrease in WBCs occurred in 6.5% of 918 patients with data. For the remaining parameters, clinically notable increases or decreases occurred in $<5\%$ of the patients (Ref: Sponsor's Appendix I, Table 8.3.1-48). Serious adverse events related to hematology occurred in 4 patients: leukopenia in Patient 0003-06026 (Study AE/ET1), neutropenia in Patient 0002-04024 (Study AE/ET1), anemia in Patient 1276-05044 (Study 021A), and leukocytosis in Patient 0001-07515 (Study AE/ET1E). One patient (0003-04265 in Study AE/ET1) discontinued due to neutropenia. These cases were described and discussed above including label recommendations under all subgroups combined. The lack of a placebo arm made meaningful interpretations difficult.

Treatment Emergent Hematology 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 for the rufinamide and placebo groups (Ref: Sponsor's Appendix I, Table 8.1.1-33). 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 8.4.7-3).

Clinically notable increases in eosinophils occurred in 5 (2.8%) rufinamide-treated patients and no placebo-treated patients (Ref: Sponsor's Appendix I, Table 8.3.1-33). Other clinically notable values occurred in, at most, 1 to 3 patients per group. No patient in either group had a serious adverse event related to hematology, and there were no discontinuations due to hematology-related adverse events.

Treatment Emergent Hematology Lab Changes in LGS Double-blind Subgroup

Mean Changes

Sponsor's Table 8.3-10, ISS, displayed mean values for hematology laboratory 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 comparable in the rufinamide and placebo groups. *Discernable differences that were clinically meaningful, however, were not seen.*

Shift Table Changes

The numbers of patients with shifts in hematology parameters, relative to the normal range, was summarized in Sponsor's Table 8.3-11, ISS for the LGS study. 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. Higher percentages of patients in the rufinamide group than in the placebo group had downward shifts in hemoglobin (13.5% versus 3.1%) and RBCs (10.8% versus 4.7%). *Discernable differences that were clinically meaningful, however, were not seen.* Small sample sizes further limited interpretations.

Clinically Notable Changes

The incidence of patients with normal values for hematology parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.3-12, ISS for the double-blind adjunctive therapy study in LGS. The rates were generally similar in the two treatment groups. *Discernable differences that were clinically meaningful, however, were not seen.* Small sample sizes further limited interpretations.

Serious adverse events of leukopenia and neutropenia each occurred in one rufinamide-treated patient (patient: 1553-02028 in Study 022) which was probably not related to rufinamide (low counts were reported the day prior to the patient receiving rufinamide and with re-instatement and maintenance on rufinamide for 14 months there were no problems- see description and discussion above under all subgroups combined). No placebo-treated patient had a serious adverse event related to hematology. No patient in either treatment group discontinued due to such events.

Treatment Emergent Hematology 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 comparable to those seen in the double-blind study (Ref: Sponsor's Appendix I, Table 8.1.1-13). 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 8.4.5-3). Twenty (14.8%) patients had downward shifts in hemoglobin, 14 (10.4%) patients had downward shifts in hematocrit, and 12 (8.9%) patients had downward shifts in monocytes. All other upward and downward shifts occurred in $\leq 7.4\%$ of the patients. The rates of clinically notable values were somewhat higher than those seen during the Double-blind Phase, reflecting the longer duration of treatment in this population (Ref: Sponsor's Appendix I, 8.3.1-13). Serious adverse events of leukopenia and neutropenia occurred in the same patient (1553-02028 in Study 022- described above), and an additional patient had a serious adverse event of hemolytic anemia on Day 511 of rufinamide therapy (1747-02023 in Study 022E- see description and discussion above under all subgroups combined). The latter patient was the only patient whose treatment was discontinued due to an adverse event related to hematology.

Treatment Emergent Hematology Lab Changes in Pediatric Double-blind Subgroup

Mean Changes

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 8.1.1-23).

Shift Table Changes

The numbers of patients with shifts in hematology parameters, relative to the normal range, was summarized in Sponsor's Table 8.3-13, ISS for the pediatric patients who received study drug 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. 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 (9.4%) than in the placebo group (5.6%) had downward shifts in hemoglobin.

Clinically Notable Changes

The rates of clinically notable values were generally similar in the two treatment groups (Ref: Sponsor's Appendix I, Table 8.3.1-23). Serious adverse events of leukopenia and neutropenia each occurred in one rufinamide-treated patient (patient: 1553-02028 in Study 022-see above). One rufinamide-treated patient (0004- 04209 in Study 021P) discontinued due to disseminated intravascular coagulation, which occurred on Day 35 of rufinamide therapy, after immersion asphyxia (see description and discussion above under all subgroups combined. No placebo-treated patient had a serious adverse event related to hematology or discontinued due to such events.

Treatment Emergent Hematology 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 8.1.1-18). 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 8.4.4-3). Thirty-six (9.2%) patients had downward shifts in hemoglobin, and 36 (9.2%) patients had downward shifts in RBCs. Fewer than 7.5% of the patients had upward or downward shifts in any other parameters. The rates of clinically notable values were higher than those seen in the double-blind studies, reflecting the longer duration of treatment in this population (Appendix I, Table 8.3.1-18). Serious adverse events related to hematology were leukopenia (Patients 1553-02028 in Study 022 and 1747- 02023 in Study 022E), neutropenia (Patient 1553-02028 in Study 022), and hemolytic anemia (Patient 1747-02023 in Study 022E). One rufinamide-treated patient discontinued due to disseminated intravascular coagulation (Patient 0004-04209 in Study 021P), and one discontinued due to hemolytic anemia (Patient 1747-02023 in Study 022E). These cases were described and discussed including label recommendations above under all subgroups combined.

Treatment Emergent General Chemistry Lab Changes

Reviewer Comments

The parameters that were evaluated under this panel were Bicarbonate, Calcium, Chloride, Cholesterol, Glucose, Potassium, Sodium and Uric acid. 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. Bicarbonate and cholesterol were not measured in the LGS study. Hence, the interpretation of the results required allowances for such variations in the denominators.

The data (mean changes) was presented using SI counts for Calcium (normal SI units = 2.12 - 2.57 [*sponsor 2.22 to 2.64*] [conventional units = 8.5-10.3mg/dL]), SI units for glucose (normal SI units = < 6.1 mmol/L [*sponsor 3.89 to 5.55*] [conventional units = < 110 mg/dL]) and SI units for Uric acid (normal SI units = 238-506 mmol/L [*sponsor 124 to 475.84*] [conventional units = 4.0-8.5 mg/dL]), while the remainder were expressed in conventional units (*sodium sponsor 135 to 145 mEq/L*). The results were presented as Mean Changes, Shift Table Changes and Clinically Notable Changes.

Treatment Emergent General Chemistry Lab Changes in All Double-blind Studies Subgroup

Mean Changes

Sponsor's Table 8.4-1, 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 comparable in the rufinamide and placebo groups. *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 8.4-2, 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.* However, the shifts in sodium from normal baseline to low post-treatment in this all double-blind subgroup (rufinamide = 26 [2.1%] and placebo = 11 [1.7%]), may have any significance in the context of the SAE described below (Patient 1276-05044 [Study 021A])

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 8.4-3, ISS for the all double-blind studies subgroup. The rates were generally similar in the two treatment groups. *Discernable differences that were clinically meaningful, however, were not seen.*

Two patients had serious adverse events of hyponatremia (0008-01168 in Study AE/ET1 and 1276-05044 in Study 021A), and 1 patient had a serious adverse event of hypochloremia (1276-05044 in Study 021A); these patients were all in the rufinamide group. These are described below. One additional hyponatremia patient (1284-5033) was reported in the June 2006 safety addendum submission under the SAE update. Further information (patient narrative) could not be accessed via the provided hyperlink. In a TCON on Sep 11, 2006, this information was

sought. The sponsor acknowledged that the hyperlink was not working. However, sponsor identified the narrative in another folder of the submission.

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

A 39 year old F, 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, by her own choice, stopped taking only rufinamide. 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.

Label recommendations- see below under comments for patient 00081-01168.

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 ~~06-Mar-98~~ 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 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 1 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.

b(6)

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 1 _____ 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.

b(6)

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.

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 (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.

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).

7.1.7.1 Overview of laboratory testing in the development program

See 7.1.7 and 7.1.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See 7.1.7 and 7.1.

7.1.7.3 Standard analyses and explorations of laboratory data

See 7.1.7 and 7.1.

7.1.7.3.1 Analyses focused on measures of central tendency

See 7.1.7 and 7.1.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

See 7.1.7 and 7.1

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

See 7.1.7 and 7.1.

7.1.7.4 Additional analyses and explorations

See 7.1.7.

7.1.7.5 Special assessments

See 7.1.7.

7.1.8 Vital Signs

Reviewer Comments

Only clinically notable changes in vitals were presented. The definitions of clinically notable changes in vital signs and weight are shown in Appendix Table 3. 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 criteria 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. In this context, the more meaningful information on the mean changes and shifts in vital signs were not integrated. In order to address this limitation further, this reviewer explored for data pertaining to changes in mean. 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 in mean changes did not raise specific concerns in any of the population subsets including the diabetic neuropathy and healthy volunteer subgroups. Hence, the findings based on the presented clinically notable changes should be interpreted accordingly.*

Treatment Emergent Vital Signs Changes in All Double-blind Studies Subgroup

The mean changes in vital signs and weight that occurred between baseline and the last post-baseline evaluation were small, were similar in the rufinamide and placebo groups, and were therefore not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-0). The numbers of patients with clinically notable changes in vital signs and body weight by age were summarized in Sponsor's Table 9.1-1, ISS. The results were generally similar for rufinamide and placebo within each age group. In patients who were 16 years or younger, weight increases occurred at a higher rate in the placebo group than the rufinamide group, whereas weight decreases occurred at a higher rate in the rufinamide group than the placebo group. *Discernable differences that were clinically meaningful were not seen.*

Treatment Emergent Vital Signs Changes in All Subgroups Combined

The mean changes in vital signs and weight that occurred between baseline and the last post-baseline evaluation were small and were not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-1). The numbers of patients with clinically notable changes in vital signs and body weight by age were summarized in Sponsor's Table 9.1-2, ISS. The youngest subgroup of patients (<12 years old) had higher rates of decreases in pulse rate and increases in systolic and diastolic blood pressure than did all 3 of the older age groups. Increases in weight occurred at higher rates in patients who were 16 years or younger, whereas decreases in weight occurred at the lowest rate in the youngest subgroup of patients.

Treatment Emergent Vital Signs Changes in Adult Double-blind Subgroup

The mean changes in vital signs and weight that occurred between baseline and the last post-baseline evaluation were small, were similar in the rufinamide and placebo groups, and were therefore not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-2). The numbers of patients with clinically notable changes in vital signs and body weight by age were summarized in Sponsor's Table 9.1-3, ISS. No patient in this population was younger than 12 years, and the overwhelming majority of the patients were between the ages of 17 and 64 years. The results were similar for rufinamide and placebo within that age group. *Discernable differences that were clinically meaningful were not seen.*

Treatment Emergent Vital Signs Changes in Adult Double-blind with Open-label Extension Subgroup

The mean changes in vital signs and weight that occurred between baseline and the last post-baseline evaluation were small and were not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-3). The numbers of patients with clinically notable changes in vital signs and body weight by age were summarized in Sponsor's Table 9.1-4, ISS. No patient in this population was younger than 12 years, and the overwhelming majority of the patients were 17 to 64 years old.

Treatment Emergent Vital Signs Changes in Mono-therapy Double-blind Subgroup

The mean changes in vital signs that occurred between baseline and the last post-baseline evaluation were small, were similar in the rufinamide and placebo groups, and were therefore not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-4). The numbers of patients with clinically notable changes in vital signs and body weight by age were summarized in Sponsor's Table 9.1-5, ISS. The overwhelming majority of patients in this population were between the ages of 17 and 64 years. The results for pulse and blood pressure were similar for rufinamide and placebo within that age group. Only a few placebo-treated patients (all from Study 039) had weight recorded at baseline and at 1 or more post-baseline evaluations. *Discernable differences that were clinically meaningful were not seen.*

Treatment Emergent Vital Signs Changes in LGS Double-blind Subgroup

The mean changes in vital signs and weight that occurred between baseline and the last post-baseline evaluation were small, were similar in the rufinamide and placebo groups, and were therefore not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-5). The numbers of patients with clinically notable changes in vital signs and body weight by age were summarized in Sponsor's Table 9.1-6, ISS. The numbers of patients with increases or

decreases in vital signs and weight were small and were generally comparable between the treatments and age groups. *The only potentially noteworthy difference between treatments was for increases in body weight among patients who were 12 to 16 years old. These occurred in 3 rufinamide-treated patients and 1 placebo-treated patient.*

Treatment Emergent Vital Signs Changes in LGS Double-blind with Open-label Extension Subgroup

The mean changes in vital signs and weight that occurred between baseline and the last post-baseline evaluation were small and were not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-6). The subgroup of patients who were less than 12 years old had the highest rates of changes in pulse and blood pressure (increases in 10.0% to 18.3% of patients) (Sponsor's Table 9.1-7, ISS). The numbers of patients with clinically notable changes in the older age subgroups were small (1 to 4 patients).

Treatment Emergent Vital Signs Changes in Pediatric Double-blind Subgroup

The mean changes in vital signs and weight that occurred between baseline and the last post-baseline evaluation were small, were similar in the rufinamide and placebo groups, and were therefore not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-7). The numbers of patients with clinically notable changes in vital signs and body weight by age were summarized in Table 9.1-8, ISS. Compared with patients who were older, those who were <12 years old had higher rates of clinically notable decreases in pulse rate, increases in systolic blood pressure, and increases in diastolic blood pressure, but this occurred in both the rufinamide and placebo groups. Older patients in both treatment groups had higher rates of decreases in systolic blood pressure and weight increases. There were few differences between the treatment groups in the incidences of clinically notable values. Rufinamide-treated patients who were 12 years or older had somewhat higher rates of decreases in diastolic blood pressure (4.4%), compared to placebo-treated older patients (1.2%). Decreases in weight occurred only in rufinamide-treated patients, whereas increases in weight occurred at higher rates in placebo-treated patients regardless of age. *Discernable differences that were clinically meaningful were not seen.*

Treatment Emergent Vital Signs Changes in Pediatric Double-blind with Open-label Extension Subgroup

The mean changes in vital signs and weight that occurred between baseline and the last post-baseline evaluation were small and were not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-8). The subgroup of patients who were less than 12 years old had higher rates of clinically notable decreases in pulse and increases in blood pressure, compared to the subgroup who were 12 to 16 years old. The older subgroup had higher rates of decreases in systolic blood pressure compared to the younger subgroup (Ref: Sponsor's Appendix I, Table 9.2.1-8).

Treatment Emergent Vital Signs Changes in Diabetic neuropathy and Healthy Volunteer Subgroup

Diabetic neuropathy

The mean changes in vital signs and weight that occurred between baseline and the last post-baseline evaluation were small, were similar in the rufinamide and placebo groups, and were therefore not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-9).

Eighty-eight (71.5%) of the 123 patients in this study were 17 to 64 years old, and weight was not recorded at both baseline and post-baseline. At most, one patient in either treatment and age subgroup had a clinically notable change in pulse rate, systolic blood pressure, or diastolic blood pressure (Ref: Sponsor's Appendix I, Table 9.2.1-9).

Healthy volunteers

Vital signs data were not available for studies 0233, 0184, 0202, and 0237. In the remaining studies, only 20 placebo-treated subjects had vital signs data at both baseline and at least 1 post-baseline evaluation, so no comparisons between the groups could be made. The mean changes in vital signs and weight that occurred in the rufinamide group between baseline and the last post-baseline evaluation were small and were therefore not clinically meaningful (Ref: Sponsor's Appendix I, Table 9.1.1-10). Clinically notable changes in pulse rate occurred in 8 (3.1%) of 256 rufinamide-treated subjects with data; all 8 subjects had increases in pulse rate. Three (1.2%) of 256 subjects with data had a clinically notable increase in diastolic blood pressure, whereas no subject had an increase in systolic blood pressure; clinically notable decreases occurred in 15 (5.9%) and 4 (1.6%) subjects, respectively. Clinically notable increases in body weight occurred in 2 (3.2%) of 63 subjects with data, and decreases occurred in 3 (4.8%) subjects (Ref: Sponsor's Appendix I, Table 9.2.1-10).

7.1.8.1 Overview of vital signs testing in the development program

See 7.1.8 and 7.1.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See 7.1.8 and 7.1.

7.1.8.3 Standard analyses and explorations of vital signs data

See 7.1.8 and 7.1.

7.1.8.3.1 Analyses focused on measures of central tendencies

See 7.1.8 and 7.1.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

See 7.1.8 and 7.1.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

See 7.1.8 and 7.1.

7.1.8.4 Additional analyses and explorations

See 7.1.8 and 7.1.

7.1.9 Electrocardiograms (ECGs)

These have been reviewed by Dr. Jones (safety team). The primary findings of concern stem 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. Although there were no reports of fatal arrhythmias, the potential exists with rufinamide. The shortened QT will impact the risk-benefit assessments (see section 1.3.3 safety summary). Reference is made to Dr. Jones' review for further details on the methods and analyses. See 1.3.3 safety summary on the discussions on short QT and its impact on the rufinamide safety profile.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

See 7.1.9.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See 7.1.9.

7.1.9.3 Standard analyses and explorations of ECG data

See 7.1.9.

7.1.9.3.1 Analyses focused on measures of central tendency

See 7.1.9.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

See 7.1.9.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

See 7.1.9.

7.1.9.4 Additional analyses and explorations

These are discussed under the individual sections (CNS/Neuropsychiatric AE, Rash/hypersensitivity reaction, Sudden death [SUDEP], Status, etc). These essentially involved comparisons of AEs of rufinamide with that of some of the approved antiepileptics to get a perspective of the safety profile of rufinamide relative to the others. This approach further helped identify differences in the format of the rufinamide label that led to some of the label recommendations. In addition, such comparisons helped in the assessments of determining the risks with rufinamide relative to the others with similar indications.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

See preclinical comments by Agency pharm-tox reviewer. See 3.2.

7.1.12 Special Safety Studies

Special safety studies (assessments) that were conducted in this program can be broadly classified as those that were conducted in special populations (e.g., effects of rufinamide in subjects with special conditions such as hepatic or renal impairment) or those studies designed to assess for special effects (such as CVS/QTc).

The special population assessments (including those related to gender, age, race, elderly, pediatrics, renal impairment, hepatic impairment, pregnancy, etc.) are discussed in section 8.3.

The special effects safety assessments involved the evaluation for the Potential for Prolongation of Cardiac Repolarization (effects on CVS, ECG and QTc). This is discussed in the review by Dr. Jones.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal Effects

The sponsor, in accordance with common medical practice for AEDs, recommends that discontinuation of rufinamide should be accomplished by gradual dose reduction to avoid the possibility of recurrence of seizures on withdrawal. Gradual dose reduction was recommended in the clinical studies. *Abrupt withdrawal was not studied.*

The protocols for the clinical studies recommended that the dose of study drug be tapered, if possible, when a patient either prematurely discontinued treatment or completed the study. Tapering was accomplished by reducing the total daily dose of study drug by approximately 25% every other day.

Adverse events that had their onset during tapering were evaluated to assess the potential occurrence of withdrawal effects. Sponsor's Table 16.1-1, ISS, summarized adverse events that started during the tapering period for all treated patients with epilepsy who tapered from either rufinamide or placebo and who had at least 1 study visit during the tapering period. This table included taperings that occurred when patients completed a double-blind study and did not choose to enter an open-label extension, and when patients completed open-label extensions. The relatively low number of patients in the placebo group reflected the fact that most patients who completed the double-blind studies participated in open-label extensions and therefore did not have tapering of their double-blind medication. The table showed the events that occurred in 1.0% or more of the patients in either group. *At least one adverse event began during tapering in 176 (19.9%) of the patients tapering from rufinamide and 5 (13.9%) of those tapering from placebo.* All events were reported in <3% of the rufinamide-treated patients. The most frequently reported events were headache (2.0%), vomiting (1.4%), somnolence (1.1%), and insomnia (1.1%).

Adverse events that occurred during tapering were severe in 19 (2.2%) of the rufinamide-treated patients and 1 (2.8%) of the placebo-treated patients (Ref: Sponsor's Appendix I, Table 7.6.1-2).

In the rufinamide group, 3 patients had severe headache, 2 patients had severe diarrhea, 2 patients had severe convulsions, and one patient each had severe vomiting, somnolence, fatigue, contusion, depression, aggression, rash, abdominal pain upper, hypertension, bronchitis, anxiety, appendicitis, back pain, oppositional defiant disorder, and thermal burn. The one severe event that occurred during placebo tapering was tremor.

The adverse events that occurred during tapering were considered by the investigators to be serious adverse events in 6 (0.7%) of the rufinamide-treated patients and 1 (2.8%) of the placebo-treated patients (Ref: Sponsor's Appendix I, Table 7.6.1-4). In the rufinamide group, this included the following patients:

1078-00105 (Study 018): convulsion; 1136-00056 (Study 018): aggression, depression, oppositional defiant disorder; 0002-04962 (Study 021): appendicitis, vomiting; 0002-06628 (Study 021): thermal burn; 0010-04705 (Study 021): headache, vomiting; 1265-05032 (Study 021): anxiety.

The one patient in the placebo group with a serious adverse event was Patient 0007-04217 (Study 021), who had grand mal convulsion. Details about these patients were presented in Sponsor's Appendix I, Table 7.6.1-3.

Reviewer Comments

Although a formal withdrawal study was not conducted, these data, although limited, did not suggest that there was strong evidence of a worrisome withdrawal syndrome.

Note: In the proposed label, under the precaution section, the following language regarding withdrawal has been included-

“As with all antiepileptic drugs INOVELON® should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus. If abrupt discontinuation of the drug is medically necessary, the transition to another AED should be made under close medical supervision. In clinical trials INOVELON® discontinuation was achieved by reducing the dose by approximately 25% every two days”.

Drug Abuse and Dependence

The abuse and dependence potential of INOVELON® was not evaluated in human studies in this program.

7.1.14 Human Reproduction and Pregnancy Data

Formal studies in pregnant women were not performed. Please refer to the preclinical section for effect on reproduction and pregnancy in animal studies.

Pregnancy

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 – 

b(4)

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, one 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.

7.1.15 Assessment of Effect on Growth

Please refer to the preclinical section for effect on growth in animal studies.

7.1.16 Overdose Experience

The chemical and PK properties related to overdose were addressed by the sponsor in an anecdotal manner that relied on, amongst others, physicochemical and PK properties of rufinamide, or based on incidental accidental extra doses.

According to the sponsor the extent of rufinamide absorption varies with the dose administered, irrespective of the formulation. The CSF and FMI tablets displayed decreasing bioavailability with increasing dose, both when administered as a single dose and as multiple doses in healthy subjects and in patients.

According to the sponsor, a similar less-than-proportional increase in exposure with increasing dose was observed in animal pharmacokinetic studies, with no significant gender differences.

The rate of absorption of rufinamide from the tablet was estimated by compartmental modeling of multiple-dose data collected in healthy subjects (rich pharmacokinetic profiles), and in patients with epilepsy (rich pharmacokinetic profiles with the CSF tablet, sparse pharmacokinetic profiles with the FMI). The rate constant of absorption had a K_a of approximately 0.2 h^{-1} for the

FMI tablets (Study E2080-A001-001, Module 5). This, according to the sponsor, might provide a margin of safety in case of overdose.

In a clinical trial in healthy volunteers, rufinamide doses up to 7200 mg/day were tolerated (Study E2080-A001-001, Module 5). In clinical trials, 2 (0.1%) of 1978 rufinamide-treated patients had an adverse event that coded to the Preferred Term of overdose. Patient 0001-01622 in Study AE/ET1E experienced a phenytoin overdose while receiving rufinamide 1600 mg/day; this was reported as a serious adverse event, and the narrative was presented in the CSR in Module 5. Patient 0074-06303 in Study 021A took 7200 mg of rufinamide in 1 day (the maximum recommended dose in the study was 3200 mg/day); this was not considered a serious adverse event, nor did it lead to discontinuation. Neither patient experienced any significant adverse events in conjunction with the overdose.

The following recommendation has been made by the sponsor regarding overdose- “after an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for rufinamide. Treatment should be supportive and may include hemodialysis (Study 029, Module 5). No data are available on overdoses exceeding 7200 mg of rufinamide”.

Note: The following language regarding overdose has been included in the proposed label-

“Because strategies for the management of overdose are continually evolving, it is advisable to contact a Certified Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

One overdose of 7200 mg/day INOVELON® was reported in an adult during the clinical trials. The overdose was associated with no major signs or symptoms, no medical intervention was required, and the patient continued in the study at the target dose.

Treatment Or Management of Overdose: There is no specific antidote for overdose with INOVELON®. If indicated, elimination of unabsorbed drug should be attempted by induction of emesis or gastric lavage. Usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

Hemodialysis: Standard hemodialysis procedures may result in limited clearance of rufinamide. Although there is no experience to date in treating overdose with hemodialysis, the procedure may be considered when indicated by the patient’s clinical state.”

7.1.17 Post marketing Experience

Currently, rufinamide, according to the sponsor, is not marketed anywhere in the world.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary clinical safety data that were summarized and integrated to evaluate safety are shown below. In addition to the 1978 unique epilepsy patients, the sponsor also submitted information on the patients in the diabetic neuropathy studies and subjects from the healthy volunteer studies. Section 4.1 and 4.2 provides information on the sources of the clinical data and the listing of the clinical studies.

7.2.1.1 Study type and design/patient enumeration

Study Type, Design and Methodology

The general features of designs of the rufinamide clinical studies and clinical pharmacology studies that provided data for this ISS is summarized below, including the key inclusion and exclusion criteria under the broad headings of- A) All treated patients with epilepsy, B) Diabetic Neuropathy and C) Healthy Volunteers.

A) All treated patients with epilepsy

The studies conducted in patients with epilepsy can be grouped by design into four categories:

- 1) Double-blind, placebo-controlled adjunctive therapy studies
- 2) Double-blind, controlled mono-therapy or mono-therapy substitution studies
- 3) Open-label adjunctive therapy or mono-therapy studies
- 4) Open-label extensions of double-blind, controlled studies

Double-blind, placebo-controlled adjunctive therapy studies

The designs of all double-blind, placebo-controlled adjunctive therapy studies were similar. Each study included a Baseline Phase, during which the diagnosis was established and the baseline seizure frequency was documented. Patients who completed the Baseline Phase and met entry criteria were then randomized to a treatment group and entered the Double-blind Phase. In some studies, the dose of study drug was titrated to the study target dose during the first 7 to 14 days of the Double-blind Phase (Titration Period). The dose at the end of the Titration Phase was the dose that the patient was to receive for the remainder of the Double-blind Phase. In other studies, the patients began double-blind treatment at the target dose, which was not to change during the remainder of the Double-blind Phase. The duration of the double-blind, controlled adjunctive therapy studies ranged from 28 to 140 days. The patients in the adjunctive therapy studies were required to be taking one to three concomitant, stable-dose AEDs during double-blind treatment. Table 3.1-1 (ISS, p. 47) in the submission summarizes the designs of all double-blind, controlled adjunctive therapy studies in patients with epilepsy. Additional details are presented in APPENDIX TABLE 1.

Double-blind, controlled mono-therapy or mono-therapy substitution studies

The 3 controlled studies that evaluated rufinamide mono-therapy or mono-therapy substitution had the basic goal of determining whether rufinamide as a single agent had anti-convulsant efficacy. The designs employed, however, differed.

Study 038 was a 10-day study in patients with refractory seizures who had been weaned off their concomitant AEDs to undergo in patient evaluation for epilepsy surgery. After the patients completed that evaluation, they entered a 48-hour Baseline Phase when no AEDs (except low-

dose lorazepam) could be taken. Patients who experienced 2 to 10 seizures during the Baseline Phase were randomly assigned to receive double-blind rufinamide (3200 mg/day) or placebo. The patients continued in the study until they had either completed 10 days of double-blind treatment or had met one of four exit criteria defined by the protocol, all indicating increased severity or frequency of seizures. These patients were then eligible to enter an open-label extension (see below).

Study 016 enrolled patients with inadequately controlled partial seizures who were receiving one or two concomitant AEDs, one given at a therapeutic level and the second, if present, at a sub-therapeutic level. Baseline seizure frequency on this regimen was established during a 56-day Baseline Phase. Eligible patients were then randomized to receive one of two dose levels of rufinamide (3200 or 300 mg/day) during the 112-day Double-blind Phase. The dose of rufinamide was titrated during the first 7 days of the Double-blind Phase in patients who were assigned to receive 3200 mg/day. The dose of the AED administered at a therapeutic level was tapered over the first 42 days and then discontinued. The second AED, if present, was discontinued on Day 4. Thus, patients received rufinamide mono-therapy from Day 43 on. The patients continued in the study until they either had completed double-blind treatment or had met one of four exit criteria defined by the protocol, all indicating increased severity or frequency of seizures. These patients were then eligible to enter an open-label extension (see below).

Study 039 enrolled currently untreated patients with recent-onset partial seizures. Baseline seizures frequency was established during a 56-day Baseline Phase. Eligible patients were then randomized to receive rufinamide 1200 mg/day or placebo during the 56-day Double-blind Phase. The dose could be increased to 1600, 2000, and then to 2400 mg/day (or placebo equivalent) after occurrence of the first, second, and third seizures during the Double-blind Phase. Patients who completed the study, or received approval after experiencing 1 seizure, could enter the Extension Phase (see Section 3.1.1.4 below). Study 039 was terminated early because only 29 of the planned 188 patients were enrolled after 22 months of attempted enrollment.

Open-label adjunctive therapy or mono-therapy studies

There were two open-label studies that were not extensions of double-blind studies and had different goals and designs.

Study 027 was designed to study the safety and tolerability of short-term treatment with rufinamide in pediatric patients with inadequately controlled seizures. Patients were stratified to one of three groups based on age (≤ 6 years, 7-12 years, 13- <18 years). Each patient received rufinamide 10 mg/kg/day during Week 1 and rufinamide 30 mg/kg/day during Week 2. Patients who completed the 2-week study were eligible to enter an open-label extension (see below).

Study 0101 enrolled patients with any type of seizure, who may or may not have been receiving concomitant AEDs. During a 14-day Baseline Phase, the diagnosis was confirmed and the baseline seizure frequency was documented. Open-label treatment with rufinamide began after the Baseline Phase. The initial dose of 400 mg/day could be incrementally increased to 3200 mg/day based on individual efficacy and tolerability. Treatment for an individual patient could continue until rufinamide was registered and launched in the country where the patient was being treated or until its development in that country was terminated.

Open-label extension studies

As noted above, many studies included provisions for patients to continue receiving open-label rufinamide in an Extension Phase. The major requirements for continuing were that the patient had completed the double-blind study and that the investigator thought the patient would benefit from treatment with rufinamide. Patients could enter an extension regardless of the treatment they had received in the double-blind study. Some studies included a Conversion Period in which patients who had received placebo during the double-blind study were switched to rufinamide on a recommended titration schedule. Adjustments of the rufinamide dose during open-label treatment were generally allowed, based on efficacy and tolerance. Adjustments of the concomitant AEDs were allowed in most studies.

B) Diabetic neuropathy

Study 0201 was designed to evaluate the safety and efficacy of rufinamide 2400 mg/day relative to placebo in patients with chronic pain due to diabetic neuropathy. Patient eligibility was determined and baseline procedures were performed during a 1-week pre-randomization Phase. Eligible patients were then randomly assigned to receive either rufinamide 2400 mg/day or placebo during the 28-day Double-blind Phase, which included a 7-day Titration Period and a 21-day Maintenance Period. A 7-day Follow-up Period, during which no study drug was given, completed the study. No concomitant medications for neuropathic pain were allowed during the pre-randomization or Double-blind Phases, except acetaminophen or acetaminophen/codeine as rescue medication.

C) Healthy volunteers

The studies in healthy volunteers were pharmacokinetic and pharmacodynamic studies that evaluated different formulations of rufinamide, different dose levels, different numbers of doses, administration under different conditions, and drug interactions. Most of the studies were performed in healthy men, although healthy women were enrolled in selected studies. One study (029) enrolled both healthy men and women and male and female patients with chronic renal failure. Study 031 enrolled elderly subjects (65-80 years) and young subjects (18-45 years). The remaining studies enrolled only non-elderly subjects. The duration of rufinamide administration ranged from a single dose to multiple doses given for 4 weeks. Doses ranged from 100 to 7200 mg/day.

Study Protocol Inclusion and Exclusion Criteria

Criteria for Studies under All Treated Patients with Epilepsy

According to the sponsor, the inclusion/exclusion criteria were generally similar. Differences in the criteria primarily reflected differences in the target populations for the studies, i.e., whether both children and adults were to be enrolled, and what the specific diagnosis was to be. The most important inclusion/exclusion criteria are listed below, with differences noted between studies when present. Because the same inclusion/exclusion criteria applied to patients entering both a double-blind study and its open-label extension, for purposes of clarity, the sponsor's notations about differences were restricted to the double-blind studies.

The key criteria for recruitment of patients for the clinical efficacy (and safety) studies were as follows:

- Male or female patients.
- Aged 18 to 60 years (study AE/PT2), 15 to 65 years (study AE/ET1), 16 years or older (study 021A), 12 years or older (studies 038, 016, 0101), 4 to 30 years (study 022), 4 years or older (study 018), or 4 to less than 16 years (study 021P).
- Female patients of childbearing potential were not to be pregnant or nursing and were to be using reliable methods of contraception.
- Weight at least 18 kg (021A, 022, 018, 021P) or 45 kg (studies 038, 016, 0101). There was no weight restriction in Studies AE/PT2 and AE/ET1.
- In general good health (except seizure disorder).
- Had the diagnosis specified by the protocol:
 - Studies AE/ET1, 021A, 038, 016, 021P: inadequately controlled partial seizures with or without secondarily generalized seizures.
 - Study AE/PT2: PGTC or partial seizures.
 - Study 022: inadequately controlled LGS which must have included both atypical absence seizures and drop attacks; other seizure types may have included tonic, tonic-clonic, or myoclonic. Each patient's diagnosis was confirmed by direct 6- to 24-hour video-EEG recordings.
 - Study 018: inadequately controlled PGTC seizures.
 - Study 0101: seizures as defined in the International League Against Epilepsy (ILAE) classification of epileptic seizures.
- Receiving a stable dose of 1 or 2 concomitant AEDs (AE/PT2, 021A, 016, 018, 021P) or of 1 to 3 concomitant AEDs (AE/ET1, 022). In Study 038, patients could receive no AEDs during the 48 hours preceding randomization, except low-dose lorazepam.
- Experienced the minimum specified number of seizures before the start of double-blind treatment:
 - Study AE/ET1: 4 seizures per month during the 6 months prior to the 3-month Baseline Phase;
 - Studies 021A and 021P: at least 6 partial seizures in the 56-day Baseline Phase, with at least one partial seizure in each 28-day period.
 - Study 016: 1 to 40 partial seizures per 28 days during the 56-day Baseline Phase, with at least one complex partial seizure or partial seizure with secondary generalization.
 - Study 022: at least 90 seizures in the month prior to the 28-day Baseline Phase.
 - Study 018: at least 3 PGTC seizures in the 56-day Baseline Phase, with at least one PGTC seizure in each 28-day period.
 - No study entry requirements concerning seizure frequency were defined in the protocols for Studies AE/PT2, 038, and 0101.

Key exclusion criteria were:

- Treatable etiology of seizures (studies 021A, 038, 016, 022, 018, 021P, 0101).
- History of status epilepticus within 30 days (study 022), 2 months (studies 021A, 021P, 0101), 3 months (study 018), 24 months (studies AE/PT2, AE/ET1), or at any time (study 016) prior to study.
- Any clinically significant organic disease, psychiatric or mood disorder not associated with the primary diagnosis, malignancy or history of malignancy.
- Clinically significant laboratory abnormality or ECG abnormality.
- History of substance abuse (including alcohol) at any time (studies 021A, 038, 016, 022, 018, 021P, 0101) or within previous 12 months (studies AE/PT2, AE/ET1).

- History of rufinamide therapy (except for open-label extension studies).
- Use of felbamate at any time previously (study AE/ET1) or within 30 days (studies 021A, 018, 021P), 6 weeks (studies 038), or 2 months (studies 022, 0101) prior to study.
- Receiving any other investigational product or device within 30 days (studies 021A, 016, 022, 018, 021P, 0101), 6 weeks (studies 038), or 3 months (studies AE/PT2, AE/ET1) prior to study.
- Inability to maintain a seizure calendar and take medication either independently or with assistance.

Criteria for Studies under Diabetic Neuropathy Subgroup

Patients were eligible to enroll in Study 0201 if they were 18 to 65 years old (inclusive); had a clinical diagnosis of diabetes mellitus (type I or II) had a history of pain associated with diabetic neuropathy for 6 months to 3 years prior to study entry; had moderate pain of stable intensity; and had not taken analgesic medication other than acetaminophen or acetaminophen/codeine for at least 2 weeks prior to randomization. Female patients had to be post-menopausal, surgically incapable of bearing children, or practicing an acceptable method of birth control. Key exclusion criteria were neurologic disorders unrelated to diabetic neuropathy; history or evidence of severe medical disease or malignancy; and other pain that could have confounded the assessment of diabetic neuropathic pain.

Criteria for Studies under Healthy Volunteers Subgroup

Most of these studies enrolled men in good health as determined by medical history, physical examination, and baseline tests such as laboratory evaluations. Sterilized female volunteers were enrolled in Studies 037, 0102, 0104, and 0105. Healthy women who were not sterilized were enrolled in Studies HPH9029, 031, E2080-A001-001, and 014 (only female subjects enrolled in this drug-interaction study with an oral contraceptive). The acceptable age ranges differed with the protocol and covered the range of 18 to 60 years, although many studies were limited to younger subjects (18 to 35 years). Only Study 031 enrolled a cohort of elderly subjects (65 to 80 years). Study 029 enrolled 18 male and female subjects between the ages of 25 and 70 years: 9 healthy subjects and 9 subjects with severe chronic renal failure, with stable creatinine clearance <30 mL/min, requiring hemodialysis.

Patient Enumeration

Safety data that were summarized for the populations in safety assessments were subgrouped as discussed below and the number of patients under each subgroup, presented in tables.

All treated patients with epilepsy (double-blind studies)

This population included all patients with epilepsy who received at least one dose of study drug in a double-blind clinical study (N=1240 rufinamide-treated patients and N= 635 placebo-treated patients).

All treated patients with epilepsy

This population includes all patients with epilepsy who received at least one dose of rufinamide in a controlled or open-label clinical study or in an open-label extension (N=1978 rufinamide-

treated patients). Data that was obtained only while patients were receiving rufinamide were included in this pool.

Double-blind, adjunctive therapy studies in adults with partial seizures

This population included all adult patients who received at least one dose of rufinamide or placebo in Studies AE/PT2, AE/ET1, or 021A (N=720 rufinamide-treated patients and N=290 placebo-treated patients).

Double-blind, adjunctive therapy studies in adults with partial seizures (with open-label extensions)

This population includes all patients who 1) received double-blind rufinamide in Studies AE/PT2, AE/ET1 or 021A and did not enter the Extension Phase, and 2) received double-blind rufinamide or placebo in Studies AE/PT2, AE/ET1 or 021A, entered the Extension Phase, and received at least one dose of open-label rufinamide (N=932 rufinamide-treated patients). Data that was obtained only while patients were receiving rufinamide were included in this pool.

Double-blind mono therapy substitution studies

This population included all patients who received at least one dose of rufinamide or placebo in Studies 016, 038, or 039 (N=208 rufinamide-treated patients and N=67 placebo-treated patients).

Double-blind, adjunctive therapy study in LGS

This population included all patients who received at least one dose of rufinamide or placebo in double-blind Study 022 (N=74 rufinamide-treated patients and N=64 placebo-treated patients).

Double-blind, adjunctive therapy study in LGS (with open-label extension)

This population included all patients who 1) received double-blind rufinamide in Study 022 and did not enter the Extension Phase (Study 022E), 2) received double-blind rufinamide in Study 022, entered the Extension Phase, and received at least one dose of open-label rufinamide; and 3) received double-blind placebo in Study 022, entered the Extension Phase, and received at least one dose of open-label rufinamide (N=135 rufinamide-treated patients). Data that was obtained only while patients were receiving rufinamide were included in this pool.

Double-blind studies in pediatric patients

This population included all patients who received at least one dose of rufinamide or placebo and either were enrolled in double-blind Study 021P (pediatric patients only) or were ≤ 16 years old and enrolled in another double-blind study in epilepsy, including the LGS study (N=212 rufinamide-treated patients and N=197 placebo-treated patients).

Double-blind, adjunctive therapy study in pediatric patients (with open-label extensions)

This population included all patients in the preceding population who 1) received double-blind rufinamide only, 2) received double-blind rufinamide, entered an Extension Phase, and received at least one dose of open-label rufinamide; and 3) received double-blind placebo, entered an Extension Phase, and received at least one dose of open-label rufinamide (N=391 rufinamide-

treated patients). Data that was obtained only while patients were receiving rufinamide were included in this pool.

Although not included in the analyses for the sought indication in epilepsy, safety results from 2 additional analysis populations were discussed briefly by the sponsor in this application. These were-

Patients with diabetic neuropathy

This population includes all patients who received at least one dose of study drug in double-blind, placebo-controlled Study 0201 (N=60 rufinamide-treated patients and N=63 placebo-treated patients), which enrolled patients with diabetes mellitus and a history of pain associated with diabetic neuropathy.

Healthy volunteers

Safety data were pooled from 21 double-blind and open-label pharmacokinetic or clinical pharmacology studies in healthy volunteers (N=326 rufinamide-treated subjects and N=90 placebo-treated subjects).

Table 7.2.1.1.A shows the numbers of patients from each study population who were included in the safety database. The focus of this application is for an indication for epilepsy (including LGS) in adults and children (greater than 4 years of age) and the population that were evaluated for an epilepsy indication involved 1978 adult and pediatric patients. Table 7.2.1.1.B provides a further breakdown of these 1978 patients.

Reviewer Comments

The breakdown of analysis population by study that was provided in Table 1.2-3, ISS, p 42, did not match with the individual numbers. In essence, the sources that led to the 1978 referenced safety patients (combined adults and pediatrics) could not be identified. In a separate e-mail correspondence (Aug 25, 2006), this reviewer requested this information from the sponsor. This was received on August 30, 2006, but the presented information was not clear and discordant with the information presented in Table 1.2-3. In a TCON with the sponsor (Ms. Loretta Robertson) on August 30, 2006, these discrepancies were discussed and further clarification was sought. The need for clarity in the numbers was reiterated in a TCON on Sep 5, 2006. The sought clarity was provided via e-mail on Sep 5, 2006 and via TCON on Sep 6, 2006. Table 7.2.1.1.B includes information on the 1978 number clarification and Table 7.2.1.1.C on the demographic information.

SAFETY TABLE 7.2.1.1.A OVERVIEW ANALYSIS POPULATION (Patients N)		
	Rufinamide	Placebo
All Exposed Unique Epilepsy Patients	1978	--
All Patients with Epilepsy – Double Blind	1240	635
Adults with Partial Seizures – Double Blind	720	290
Adults with Partial Seizures – Double Blind + Open Label	932	290
Mono therapy – Double Blind	208	67
Patients with LGS – Double Blind	74	64
Patients with LGS – Double Blind + Open Label	135	64
Pediatric Patients – Double Blind	212	197

Pediatric Patients – Double Blind + Open Label	391	197
Diabetic Neuropathy - Double Blind	60	63
Healthy Volunteers (PK/PD) - Double Blind + Open label	326	90
Ref: Sponsor's Table 1.2-3, ISS, p. 42		
Note- Hatched areas are the populations whose incidences of AEs are reflected in the proposed label (Tables 4 and 5 in the proposed label).		

SAFETY TABLE 7.2.1.1.B		
OVERVIEW OF EPILEPSY ANALYSIS POPULATION (Patients N) BY SUBGROUPS		
Primary Subgroups	Rufinamide	Placebo
Adults– Double Blind + Open Label	932	290
Mono therapy – Double Blind	208	67
Patients with LGS – Double Blind + Open Label	135	64
Pediatric Patients – Double Blind + Open Label	391	197
Total Exposures from Primary Subgroups	1666	618
Patients counted more than once from primary subgroups	109	--
Unique Patients from primary subgroups	1557	--
Unique Patients from Other Studies (from outside the primary subgroups)	421	--
All Epilepsy Unique Patients	1978	635
Double-blind Subgroups		
Adults with Partial Seizures – Double Blind	720	290
Patients with LGS – Double Blind	74	64
Pediatric Patients – Double Blind	212	197
Mono therapy – Double Blind	208	67
Total Exposures from Primary Double-blind Subgroups	1214	618
Patients counted more than once from Primary Double-blind Subgroups	62	--
Unique Patients from Primary Double-blind Subgroups	1152	--
Unique Patients from Other Studies (from outside the primary double-blind subgroups)	88	--
All Epilepsy Double-Blind Unique Patients	1240	635
Ref: Sponsor's Table 1.2-3, ISS, p. 42; Subsequent Correspondences of Aug 30, 2006, Sep 5, 2006		
Note:		
The information presented in this table was obtained upon request from the sponsor during the review cycle (see comments in review).		
Hatched areas are the populations whose incidences of AEs are reflected		

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SAFETY TABLE 7.2.1.1.C		
OVERVIEW OF EPILEPSY POPULATION BY AGE, SUBGROUP, INDICATION		
Criteria	Pediatric (N) [Age < 16 yrs]	Adult (N) [Age ≥ 16 yrs]
Number of Unique Patients (N= 1978)	397	1581
All Double-blind (N = 1240)	203	1037
All Open-label	194	544
LGS Double-blind (N=74)	49	25
LGS Open-label	41	20
Partial Epilepsy Indication (double-blind) (N= 720)	4	716
LGS Indication (double-blind) (N= 74)	49	25
Ref: Sponsor's Information submitted Sep 7, 2006; See Table 7.2.1.2.A		

7.2.1.2 Demographics

The safety of rufinamide was evaluated in adult and pediatric patients with a variety of seizure disorders which included the seizure subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures, primary generalized seizures and seizures associated with the

LGS. In addition, healthy volunteers and patients with neuropathic pain related to painful diabetic neuropathy were studied.

Demographic information of the different subsets of the patient population that was analyzed as noted in the patient population analysis is discussed and presented in the Table 7.2.1.2.A below. An overview of information on concomitant medications that included AEDs and non-AEDs that was collected and analyzed is also discussed.

SAFETY TABLE 7.2.1.2.A												
OVERVIEW OF PATIENT DEMOGRAPHICS ALL STUDIES BY STUDY GROUPS												
		All DB		All	DOUBLE - BLIND							
		R	P		Adult		Monotherapy		LGS		Pediatric	
Treatment		R	P	R	R	P	R	P	R	P	R	P
Number Treated		1240	635	1978	720	290	208	67	74	64	212	197
		N	N	N	N	N	N	N	N	N	N	N
		(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Characteristics												
Sex	Male	620	338	999	364	156	78	28	46	40	121	114
		50.0	53.2	50.5	50.6	53.8	37.5	41.8	62.2	62.5	57.1	57.9
	Female	620	297	979	356	134	130	39	28	24	91	83
		50.0	46.8	49.5	49.4	46.2	62.5	58.2	37.8	37.5	42.9	42.1
Race^a	White / Caucasian	576	436	1139	130	138	173	49	62	53	174	176
		46.5	68.7	57.6	18.1	47.6	83.2	73.1	83.8	82.8	82.1	89.3
	Black	52	28	86	8	4	22	11	6	4	16	10
		4.2	4.4	4.3	1.1	1.4	10.6	16.4	8.1	6.3	7.5	5.1
	Oriental	5	2	6	3	0	1	1	1	0	1	1
		0.4	0.3	0.3	0.4	0	0.5	1.5	1.4	0	0.5	0.5
	Other	43	36	100	15	15	12	6	5	7	13	10
		3.5	5.7	5.1	2.1	5.2	5.8	9.0	6.8	10.9	6.1	5.1
Age (yrs)	Mean	31.7	28.6	31.3	35.8	37.7	38.3	37.7	14.5	13.6	10.4	10.6
	Range	3-81	4-87	1-81	14-72	17-68	12-81	12-87	4-35	4-37	3-16	4-17
	<12 ^c	119	112	234	0	0	0	0	31	33	119	112
		9.6	17.6	11.8	0	0	0	0	41.9	51.6	56.1	56.9
	≥12-16 ^c	93	84	183	9	0	3	4	19	17	93	84
		7.5	13.2	9.3	1.3	0	1.4	6.0	25.7	26.6	43.9	42.6
	≥17-64	1019	433	1534	709	287	198	60	24	14	0	1
		82.2	68.2	77.6	98.5	99.0	95.2	89.6	32.4	21.9	0	0.5
Weight (kg)	N	1232	630	1965	715	288	205	64	74	64	212	197
	Mean	67.6	64.2	66.8	72.2	74.7	77.3	83.0	44.1	40.2	39.9	40.5
	Range	15.5-158.3	16.2-176.3	13.2-158.3	36-129	34.6-145.4	44.8-158.3	44.6-176.3	15.5-138.5	16.2-86.0	15.5-138.5	16.2-118.7
	≤29	72	62	139	0	0	0	0	24	24	72	62
		5.8	9.8	7.1	0	0	0	0	32.4	37.5	34.0	31.5
	>29-50	161	104	275	49	9	13	3	25	20	93	81
		13.1	16.5	14.0	6.9	3.1	6.3	4.7	33.8	31.3	43.9	41.1
	>50	999	464	1551	666	279	192	61	25	20	47	54
	81.1	73.7	78.9	93.1	96.9	93.7	95.3	33.8	31.3	22.2	27.4	

Ref: Sponsor's Tables 4.1-1, 4.2-1, 4.3-1, 4.4-1, 4.5-1, 4.6-1, ISS, pp 57-67.

Note

DB= Double-blind; R= Rufinamide; P= Placebo; LGS= Lennox-Gastaut syndrome; a= The possible choices for race on the

rufinamide CRFs that collected this information were White/Caucasian, Black, Oriental, or Other; b = information about race was not collected in all studies. Hatched areas indicate areas of concern (see comments in review); c = breakdown of ages <16 yrs = Adolescents 12 to <16 yrs (for the sought partial epilepsy indication) = 4 patients; Pediatric and adolescents > 4 to < 16 yrs (for the sought LGS indication) = 49 patients (31 patients were < 12 years, 18 patients were 12 to <16 yrs).

Patient Demographics All Treated Patients with Epilepsy (Double-Blind Studies)

Table 7.2.1.2.A summarizes the demographic characteristics of all treated patients with epilepsy (double-blind studies). The results were similar for the 2 treatment groups. Approximately half of the patients were males. The mean age was 31.7 years in the rufinamide group and 28.6 years in the placebo group; a larger percentage of the patients in the rufinamide group (82.2%) than in the placebo group (68.2%) were between the ages of 17 and 64 years. The mean weights were 67.6 kg and 64.2 kg, respectively; more than 73% of the patients weighed more than 50 kg.

Sponsor's Tables 4.1-2 and 4.1-3, ISS, p. 58 provide a summary of the concomitant AEDs and non-AEDs respectively received by more than 5% and 10% of the patients respectively in either treatment group (rufinamide or placebo).

Most of the studies included in this pool enrolled patients who were receiving stable doses of 1 to 3 AEDs (patients in mono-therapy Studies 038 and 039 were not permitted to receive any concomitant AED, except low-dose lorazepam in Study 038). The concomitant AEDs used most frequently in both treatment groups were carbamazepine (55.6% of patients in the rufinamide group and 46.1% of patients in the placebo group) and valproate (27.6% and 29.8%, respectively). The percentages of patients who received other individual AEDs were generally similar in the 2 treatment groups.

Similar percentages of rufinamide-treated patients (73.7%) and placebo-treated patients (74.0%) received non-AED concomitant therapy. However, only 2 medications (paracetamol and ibuprofen) were taken by more than 10% of the patients in either group.

Patient Demographics All Treated Patients with Epilepsy

Table 7.2.1.2.A summarizes the demographic characteristics of all treated patients with epilepsy. Approximately half of the 1978 patients exposed to rufinamide were males. The mean age was 31.3 years, and 77.6% of the patients were between the ages of 17 and 64 years. The mean weight was 66.8 kg, and 78.9% of the patients weighed more than 50 kg.

Sponsor's Tables 4.2-2 and 4.3-3, ISS, pp 59-60 provide a summary of the concomitant AEDs and non-AEDs respectively received by more than 5% and 10% of the patients respectively. It is important to remember that most of the studies evaluated rufinamide as adjunctive therapy in patients receiving stable doses of 1 to 3 AEDs.

Overall, 98.2% of all treated patients with epilepsy received at least one AED concurrently with rufinamide. The patients were most often co-medicated with carbamazepine (52.9%), valproate (31.6%), phenytoin (22.9%), and clonazepam (19.7%).

Overall 78.8% of all treated patients with epilepsy received non-AED concomitant therapy. However, only 2 medications (paracetamol and ibuprofen) were taken by more than 10% of the patients.

Patient Demographics Double-Blind, Adjunctive Therapy Studies In Adults with Partial Seizures

The characteristics of the two treatment groups (rufinamide and placebo) in this population are as shown in Table 7.2.1.2.A. Approximately half of the patients were males. The mean age was 35.8 years in the rufinamide group and 37.7 years in the placebo group; more than 98% of the patients in each group were between the ages of 17 and 64 years. The mean weights were 72.2 kg and 74.7 kg, respectively; more than 93% of the patients weighed more than 50 kg.

Sponsor's Tables 4.3-2 and 4.3-3, ISS, p. 62 provided a summary of the concomitant AEDs and non-AEDs respectively received by more than 5% and 10% of the patients respectively.

All of the studies included in the AED pool, enrolled patients who were receiving stable doses of 1 to 3 AEDs. The most frequently used concomitant AEDs in both treatment groups were carbamazepine (68.3% of patients in the rufinamide group and 64.1% of patients in the placebo group), valproate (25.6% and 25.9%), and phenytoin (22.2% and 19.0%). The percentages of patients who received other concomitant AEDs were similar in the 2 treatment groups.

Overall, 65.4% of rufinamide-treated patients and 80.3% of placebo-treated patients received non-AED concomitant therapy. However, only one medication (paracetamol) was taken by more than 10% of the patients in either group.

Patient Demographics Double-Blind, Mono-therapy Substitution Studies

The demographic features of the 2 treatment groups in this population are shown in Table 7.2.1.2.A. A majority of the patients in each group were females; most patients were white. The mean age was 38.3 years in the rufinamide group and 37.7 years in the placebo group; more than 89% of the patients in each group were between the ages of 17 and 64 years. The mean weights were 77.3 kg and 83.0 kg, respectively; more than 93% of the patients weighed more than 50 kg.

The studies included in the population of mono-therapy substitution studies allowed patients to be taking 1 or 2 AEDs at study entry and for at least part of the study (Study 016), no AEDs other than low-dose lorazepam during the study (Study 038), or no AEDs (Study 039). All of the AEDs that were shown in Table 4.4-2, ISS, p. 64 were taken by patients from Studies 016 or 038. In addition, most of the patients in the rufinamide group were from Study 016 (which had no placebo group and which allowed patients to take concomitant AEDs for at least part of the study), whereas all of the patients in the placebo group were from Study 038. Therefore, the difference between the rufinamide group (72.1%) and the placebo group (10.4%) in the percentages of patients who received at least one concomitant AEDs were most likely due to differences in study designs. The most frequently taken AEDs in the rufinamide group were carbamazepine (42.8%) and phenytoin (20.7%).

Sponsor's Table 4.4-3, ISS, p. 64 summarized the concomitant non-AED medications and significant non-drug therapies received during the double-blind, mono-therapy substitution studies. Overall, 62.0% of rufinamide-treated patients and 76.1% of placebo-treated patients received non-AED concomitant therapy. However, only 2 medications (paracetamol and ibuprofen) were taken by more than 10% of the patients in either group.

Patient Demographics Double-Blind Adjunctive Therapy Study in LGS

Table 7.2.1.2.A, provides an overview of the demographic characteristics of the two treatment groups (rufinamide and placebo) in this population. In each group, approximately 62% of the patients were males. The mean age was approximately 14 years in each group, with 42% (rufinamide) and 52% (placebo) of the patients being less than 12 years old. The mean weight was 44.1 kg in the rufinamide group and 40.2 kg in the placebo group.

Patients in the LGS study were to be receiving stable doses of 1 to 3 AEDs. As shown in Table 4.5-2, ISS, p. 66 of the submission, the concomitant AEDs used most frequently in more than 5% of patients were the same in both treatment groups: valproate, lamotrigine, clonazepam, and topiramate.

As shown in Sponsor's Table 4.5-3, ISS, p. 66, the concomitant non-AED medications and significant non-drug therapies, overall, 81.1% of rufinamide-treated patients and 73.4% of placebo-treated patients received non-AED concomitant therapy. However, only 2 medications (paracetamol and amoxicillin) were taken by more than 10% of the patients in either group.

Patient Demographics Double-blind Studies in Pediatrics

Table 7.2.1.2.A, summarizes the demographic characteristics of all pediatric patients who were treated in double-blind epilepsy studies. Although this population included patients from several studies, the demographic characteristics of the patients who received rufinamide were similar to those of the patients who received placebo. Approximately 57% of the patients in each treatment group were males. The mean age was approximately 10.5 years, with approximately 56% of the patients being less than 12 years old. The mean weight was approximately 40 kg.

As shown in Sponsor's Table 4.6-2, ISS, p. 68 of the submission, 98.6% of the rufinamide-treated patients and 98.0% of the placebo-treated patients in this population received at least one concomitant AED. The medications used most frequently in more than 5% of patients were the same in both treatment groups: carbamazepine, valproate, clonazepam, and lamotrigine.

As shown in Sponsor's Table 4.6-3, ISS, p. 68, overall, 67.0% of rufinamide-treated patients and 60.9% of placebo-treated patients received non-AED concomitant therapy. However, only one medication (paracetamol) was taken by more than 10% of the patients in either group.

Reviewer Comments

The breakdown of ages for patients < 12 years, specifically for 4 and over for the sought LGS indication, was not provided in the submission. In a separate e-mail correspondence (Aug 25, 2006), this reviewer requested this information from the sponsor. This was submitted on August 30, 2006 for the 4-11 ages. For reasons alluded to regarding the discordance between the intended ages of use for each of the two sought indications and the breakdown of presented AEs by ages, the critical breakdown on demographics for the ages >12 to 16 and ≥ 16 and >4 to 16 and ≥ 16 were not presented. 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 email, the attached reformatted AE tables _____ that included the age breakdowns were provided. See note in Table 7.2.1.2.A. On Sep 6, 2006, in a separate e-mail, the demographic breakdown along the sought indication was provided. This is included in the Table 7.2.1.2.B below.

b(4)

The demographics of the most relevant population based on the two sought indications would include adolescents and adults for the partial epilepsy indication and pediatrics and adults for the LGS indication. As indicated in various sections of the review, following several interactions with the sponsor, this information on demographic information relevant to the sought indication that was presented, is summarized in Table 7.2.1.2.B.

SAFETY TABLE 7.2.1.2.B									
DEMOGRAPHICS OF POPULATION RELEVANT TO INDICATION									
Study Subgroup		Partial Seizures Double-blind				LGS Double-blind			
Population		Adolescent		Adult		Pediatric		Adult LGS	
Age Groups (years)		12 - < 16		≥ 16		4 - < 16		≥ 16	
Number Treated		N		N		N		N	
Percent		(%)		(%)		(%)		(%)	
Treatment		R = 4	P = 0	R = 716	P = 290	R = 49	P = 43	R = 25	P = 21
CHARACTERISTICS									
Sex	Male	3	0	361	156	29	28	17	12
		75	0	50.4	53.8	59.2	65.1	68.0	57.1
	Female	1	0	355	134	20	15	8	9
		25	0	49.6	46.2	40.8	34.9	32.0	42.9
Race ^a	White / Caucasian	0	0	130		39	34	23	19
		0	0	18.2		79.6	79.1	92.0	90.5
	Black	0	0	8		5	3	1	1
		0	0	1.1		10.2	7.0	4.0	4.8
	Oriental	0	0	3		0	0	1	0
		0	0	0.4		0	0	4.0	0
	Other	0	0	15		5	6	0	1
		0	0	2.1		10.2	14.0	0	4.8
Not reported ^b	4	0	560		0	0	0	0	
	100	0	78.2		0	0	0	0	
Age (yrs)	Mean	14.75	0	35.91	37.65	9.71	9.23	23.88	22.52
	Range	14-15	0	16-72	17-68	4-15	4-15	16-35	16-37
	Median	15	0	35	37	10.00	9.00	23	17
Weight (kg)	N	4	0	711	288	49	43	25	21
	Mean	51.75	0	72.27	74.70	34.06	31.19	63.74	58.77
	Median	48.0	0	71.0	72.15	29.10	27.0	61.80	64
	Range	36-75	0	40-129	34.60-145.40	15.50-138.50	16.20-76.0	34.60-113.40	34.10-86.00
	< 29	0	0	0	0	24	24	0	0
		0	0	0	0	49.0	55.8	0	0
	> 29-50	2	0	47	9	18	13	7	7
		50.0	0	6.6	3.1	36.7	30.2	28.0	33.3
	> 50	2	0	664	279	7	6	18	14
		50.0	0	92.7	96.2	14.3	14.0	72.0	66.7
Missing	5	2	0	0	0	0	0	0	
	0.7	0.7	0	0	0	0	0	0	

Ref: Sponsor's Post-text Tables 9 and 10, submitted Sep 6, 2006

Note:
a= The possible choices for race on the rufinamide CRFs that collected this information were White/Caucasian, Black, Oriental, or Other. b = information about race was not collected in all studies. Hatched areas indicate areas of concern (see comments in review); Treatment R= Rufinamide, P= Placebo

Patient Demographics Diabetic Neuropathy Studies

The demographic characteristics of the two treatment groups in the diabetic neuropathy study (Study 0201) were presented in Appendix I, Table 4.2-6 of the submission. Slightly more than half of the patients in each group were males. The mean age was 60.3 years in the rufinamide

group and 57.8 years in the placebo group, with approximately 71% of the patients being between the ages of 17 and 64. The mean weight was 98.3 kg in the rufinamide group and 94.6 kg in the placebo group, with more than 93% of the patients weighing more than 50 kg. Concomitant medications taken by the patients in this population were shown in Appendix I, Table 4.4-6.

Subject Demographics Healthy Volunteer Studies

The demographic characteristics of the subjects in the healthy volunteer studies were presented Appendix I, Table 4.2-7 of the submission. Most subjects in the rufinamide group (274/326; 84.0%) and in the placebo group (87/90; 96.7%) were males because many of the protocols limited enrollment to healthy male subjects. The mean age was 30.5 years in the rufinamide group and 26.4 years in the placebo group. Three hundred fifteen (96.6%) and 90 (100%) subjects, respectively, were between the ages of 17 and 64 years.

Reviewer Comments on Demographics

The 'Other' category under race included those for whom race was not recorded (Ref: Sec 6.3.3, p. 134, ISS). It should be noted that information on race was not collected in a large subset of patients. The predominant race was White/Caucasian.

The US population by race (as of July 1, 2005 based on Census 2000; (<http://www.infoplease.com/ipa/A0762156.html>) consists of, amongst others, 80.2% Whites, 12.8% Black/African Americans, 14.4% Hispanic/Latino, and 4.3% Asian. In this estimate, the percentages did not add up to 100% due to rounding and because Hispanics may have been counted under any race more than once depending on the country of their origin. Nonetheless, it gives an idea of an estimate of the three largest race groups sufficient to gauge whether the rufinamide exposed population was representative of the US population. It should be noted that several studies have shown a higher rate of epilepsy compared to whites among people in African countries or of African descent - (Ref- Neurology in Clinical Practice, Vol 2, 4th edition, The Epilepsies, p. 1954; Sander, JW, 2003- The Epidemiology of Epilepsy Revisited, Curr Opin Neurol, vol. 16, pp. 165-170) or amongst African Americans (<http://epilepsyontario.org/client/EO/EOWeb.nsf/web/Epilepsy+in+Africa+and+the+African+African+Community>). Further, the risk of sudden deaths in African Americans with epilepsy is higher than the Caucasians (<http://www.emedicine.com/neuro/topic659.htm>). Based on such background information involving African Americans (race = black) and epilepsy and its risks, it is important to note that this drug development program did not expose adequate African American patients with epilepsy representative of the US market population. Independent of whether such estimates of higher risks also exist in the Hispanic/Latino population, this population, the second largest in the US, was also not adequately studied. While the patient population probably was representative of patients with epilepsy in the geographic areas where the studies were conducted- in terms of demographic characteristics, diagnosis of epilepsy, and medications received before and during randomized treatment, whether they were representative of the population in the US is questionable. It is unknown if such lack of information due to in-homogeneity in exposure may have any underlying safety implications. *The potential risks of rufinamide for the intended African American and Hispanic population in the US are therefore unknown.*

It is therefore recommended that the label reflect this racial in-homogeneity in exposure with a precaution that the risks in Blacks/African Americans and Hispanic/Latinos were not adequately

studied.

7.2.1.3 Extent of exposure (dose/duration)

The overall extent of exposure is summarized by median dose, age and or sex for each of the epilepsy analysis population (All double-blind, All Epilepsy, Adult Double-blind, Adult Double-blind with open-label extension, Mono-therapy double-blind, LGS double-blind, LGS double-blind with open-label extension, Pediatric double-blind and Pediatric double-blind with open label extension). Although not part of the epilepsy population, an overview for the diabetic neuropathy subgroup and healthy volunteer subgroup is additionally presented.

Exposure All Double-blind

Extent of exposure for all patients with epilepsy who received rufinamide in all double-blind studies is summarized by median daily dose in Appendix Table 4 of this review (Table 5.1-1, ISS, p.69). Median doses were less than 1600 mg/day for 703 (56.7%) patients, 1600 to less than 2400 mg/day for 245 (19.8%) patients, 2400 to 3200 mg/day for 291 (23.5%) patients, and more than 3200 mg/day for 1 (0.1%) patients. The majority of patients within each median dose group were treated for less than 3 months. More than half of the patients who received median doses of 2400 to 3200 mg/day were treated for at least 3 months.

The total exposure to study drug in this population was 291.51 patient-years for rufinamide and 149.60 patient-years for placebo. The median duration of exposure was 2.8 months and 3.0 months, respectively (Ref: Sponsor's Appendix I, Table 5.2.1-1). The mean daily dose of rufinamide was 1373.28 mg/day, the median daily dose was 1000 mg/day, and the maximum daily dose was 1458.06 mg/day (mean) or 1200 mg/day (median). The daily dose given for the maximum duration per patient was a mean of 1395.89 mg/day (median, 1000 mg/day). Exposure to the rufinamide dose given for the maximum duration and to the maximum daily dose was similar to that shown above for the median dose (see Sponsor's Appendix I, Tables 5.2.1-2 and 5.2.1-4).

Exposure All Subgroups Combined

Extent of exposure to study drug for all rufinamide-treated epilepsy subgroups is summarized by median daily dose in Appendix Table 4 of this review (Table 5.2-1, ISS). Median doses were less than 1600 mg/day for 939 (47.5%) patients, 1600 to less than 2400 mg/day for 381 (19.3%) patients, 2400 to 3200 mg/day for 598 (30.2%) patients, and more than 3200 mg/day for 60 (3.0%) patients.

The duration of exposure to these median daily doses ranged from less than 1 month to 4 years or more. More than half of the 939 patients with median doses of less than 1600 mg/day were treated for at least 6 months. More than half of the 1039 patients with median doses of 1600 mg/day or more were treated for at least 12 months.

The total exposure to rufinamide in this population was 2552.96 patient-years. The mean daily dose of rufinamide was 1700.32 mg/day, the median daily dose was 1600 mg/day, and the maximum daily dose was 2084.98 mg/day (mean) or 2000 mg/day (median) (Ref: Sponsor's Appendix I, Table 5.3.1-1). The daily dose given for the maximum duration per patient was a mean of 1671.18 mg/day (median, 1600 mg/day). Exposure to the rufinamide dose given for the