

RESULTS OF PER PROTOCOL ANALYSIS

| Per Protocol p<.001 | Number (%) of Completed Patients | | |
|------------------------|----------------------------------|-------------|-------|
| | Completed Monotherapy | Escaped | Total |
| LTG | 28 (56%) | 22 (44%) | 50 |
| VPA | 13 (20%) | 51 (80%) | 64 |

Conversely, more than twice as many patients on VPA met escape criteria, compared to those on LTG, a significant difference ($p < 0.001$). The most common escape criteria in both treatment groups (see Table 6) were doubling of the highest 2-day seizure frequency and doubling of the monthly seizure frequency. The proportion of patients meeting each these criteria were similar for the LTG-treated patients (8/22, or 36%); whereas, for VPA patients, the proportions were 20/51 (39%) and 16/51 (31%), respectively. The emergence of a new and worse seizure type occurred twice as frequently among the VPA (16/51; 31%) as LTG (4/22; 18%) patients. Prolongation of generalized tonic-clonic seizures was more often found with LTG (5/22; 23%) than VPA (3/51; 6%) patients.

Following are efficacy results for the per-protocol population when data from each of the 36 centers contributing to the study were also combined on a geographical basis into four regions (v 5, p 42):

EFFICACY RESULTS BY GEOGRAPHICAL REGION OF THE UNITED STATES

| Per Protocol | LTG Number (%) of Patients | | | VPA Number (%) of Patients | | |
|-----------------|-------------------------------|------------|-------|-------------------------------|-------------|-------|
| | Completed | Escaped | Total | Completed Monotherapy | Escaped | Total |
| Northeastern US | 5 (42%) | 7 (58%) | 12 | 4 (27%) | 11 (73%) | 15 |
| Southeastern US | 7 (54%) | 6 (46%) | 13 | 2 (13%) | 14 (88%) | 16 |
| Midwestern US | 9 (53%) | 8 (47%) | 17 | 5 (24%) | 16 (76%) | 21 |
| Western US | 7 (88%) | 1 (13%) | 8 | 2 (17%) | 10 (83%) | 12 |

The proportion of patients meeting escape criteria during weeks 13-28 were similar among the geographical regions in both treatment groups, except for western US (see also Table 11).

Dr. Sue-Jane Wang has reviewed the data in her biostatistical review and has voiced no objection.

Intent-to-treat and worst-case analyses, although not specified in the protocol, were conducted on a *post-hoc* basis. In the intent-to-treat analysis (v 5, p 151), more than twice as many LTG patients completed 12 weeks on monotherapy as VPA-treated patients, a statistically significant difference ($p = 0.003$) that obtained when adjustments were made for center ($p = 0.007$):

RESULTS OF INTENT-TO-TREAT ANALYSIS

| Intent-to-Treat p = .003 | Number (%) of Patients | | |
|-----------------------------|--------------------------|------------------|-------|
| | Completed Monotherapy | Failed Treatment | Total |
| LTG | 28 (37%) | 48 (63%) | 76 |
| VPA | 13 (16%) | 67 (84%) | 80 |

Escape was the most common reason for treatment failure (22/48, or 46%, for LTG; 51/67, or 76%, for VPA); see Table 6. Other than escape, the most common reason for treatment failure was patient withdrawal due to AE (15/48, or 31%, for LTG; 6/67, or 9%, for VPA). The worst-case analysis involved the monotherapy period and counted LTG dropouts as escaped and VPA dropouts as completers. No difference (p=0.890) was observed between LTG and VPA: 28/76 (37%) LTG and 29/80 (36%) VPA patients completed 12 weeks on monotherapy. The sponsor explains the results by reference to the large number of premature withdrawals from both treatment arms. According to the sponsor, geographical adjustments for both the intent-to-treat and worst-case analyses, as with the per-protocol analysis, also showed a similar pattern of patients meeting escape criteria during weeks 13-28.

The sponsor has presented the efficacy data from two different perspectives -- an "escapers" and a "completers" -- and both, for this reviewer, have fundamental problems, raising serious questions about the validity of the results. Moreover, matters are further confused when the summary page of the study report, in reference to the primary outcome measure, mentions only the "escapers" analysis: "Efficacy was based on the proportion of patients who discontinued treatment due to meeting one of the 'escape' criteria" (v 5, p 110). The two perspectives will now be examined separately.

With respect to the "escapers" endpoint, it appears that more than twice as many LTG patients dropped out for safety reasons (11 vs 4) during the add-on period, prior to monotherapy. This fact would point to a *bias in favor of* the LTG group: a large number of LTG patients did not get an opportunity to test efficacy on LTG monotherapy (*ie*, to drop out for reasons of lack of efficacy). Had the worst-case scenario proved to be statistically significant, the present results might prove more easily acceptable. But, as no difference was shown between the two treatments, the bias in favor of LTG stands.

With respect to the "completers" analysis, the problem involves the fact that only 37% of the population finished the monotherapy period: the drug, in other words, failed in its intended effect in two-thirds of the population. LTG may have achieved statistical significance when evaluated against an active placebo, but it has not demonstrated clinically significant efficacy as monotherapy. Furthermore, given that one-third of the intent-to-treat population failed for safety reasons and another third due to lack of efficacy, a profile of the patient who would benefit by LTG monotherapy may be difficult to determine. The sponsor has not provided an evaluation of the data that might help resolve this issue.

It should be noted that the Felbamate monotherapy study, upon which the design of the LTG protocol was based, employed an escapers analysis for the primary outcome measure. However, unlike the LTG study, Felbamate monotherapy use was based on *two* trials (one multicenter and one smaller single center) and, in each trial, there were few withdrawals for safety reasons during the add-on period (in the multicenter trial, 5/56 (9%) felbamate and 3/55 (5%) VPA patients dropped out for safety reasons during the add-on period; in the single-center trial, the numbers were 1/22 and 1/22, respectively).

An even more fundamental problem with US30/31 centers on the apparent misclassification of three LTG patients as withdrawals for adverse events when they in fact met efficacy escape

criteria earlier in the study (patients 30-1-01038 who met the criterion for doubling the highest 2-day seizure frequency on 3/16-17/95; 31-6-06046 who met the criterion for doubling the highest 4-week seizure frequency for the period 5/1-31/95; and 31-26-26161 who met the criterion of doubling the highest 2-day seizure frequency for 5/2-3/95). Furthermore, inadequate documentation of seizure diaries (*ie*, missing data) occurred in three additional LTG patients (30-15-15017 for the period 2/5-19/95; 31-14-14026 for the period 2/22-28/95; and 31-17-17041 for the period 16-25/95) and one VPA patient (30-15-15074 for the 2/1-7/96). These omissions represent substantial lacunae which could potentially involve efficacy failures.

Please see the addendum to the biostatistical review of Dr. Sue-Jane Wang (Biostatistics), who plans to reanalyze the data by including the three misclassified efficacy failures. She also plans to conduct a new worst-case analysis which would consider the three LTG cases with missing data as efficacy failures.

SECONDARY EFFICACY MEASURES: With respect to secondary efficacy results, both the per-protocol and intent-to-treat survival analyses demonstrated significantly longer time to escape for LTG than for VPA patients ($p=0.001$), as follows (v 1, p 105).

Time to Treatment Failure

| Population Analyzed | Median Days to Failure | | p-Value |
|---------------------|------------------------|-----|---------|
| | LAMICTAL | VPA | |
| Per protocol | >168 ^a | 57 | 0.001 |
| Intent-to-treat | 80 | 58 | 0.027 |
| Worst case | 80 | 64 | 0.324 |

^b The length of the study (*i.e.*, the maximum days to failure which could be detected in this study) was 168 days.

With the IGE, another secondary outcome measure, the investigator compared the patient's clinical status (AEs, seizure frequency, etc.) at the time of the evaluation to his condition at Baseline by means of a 7-point scale. For statistical analyses, all subcategories of deterioration are combined as the deterioration category, and all subcategories of improvement as well as "no change" are grouped together to make up the "improvement category." The proportion of patients in each treatment arm with improvement or no change were compared (see Tables 19 and 20). According to the sponsor, there were no differences between the treatment groups at any time point (v 5, p 153). It should be noted that the IGE includes only those patients who remained in the study and presumably were doing well; patients who met escape criteria or dropped out for any other reason no longer contributed data to later assessments. In the per-protocol analysis, there was a statistically significant difference ($p=0.019$) in favor of the LTG in the proportion of patients in each treatment arm with improvement or no change (33/50, or 60%, for LTG, compared to 28/64, or 44%, for VPA). However, for the intent-to-treat analysis, no difference was observed ($p=0.193$).

Finally, as to the results of the patient QOL and SS surveys (the third of the secondary outcome measures), the sponsor reports "no significant differences between treatment groups" (v 5, p 156); for more details, see Tables 44 and 47).

PHARMACOKINETIC DATA: With regard to LTG concentrations and trough concentrations of CBZ or PHT, no consistent differences in were detected between patients who finished monotherapy and those who escaped (v 1, p 158); see Tables 54 and 55.

Mean LTG concentrations increased, during dose escalation, from baseline through study week 12 (week 4 of Treatment Transition), and continued to increase through study week 24 with the gradual withdrawal of concomitant AEDs; see Tables 60 and 61. The new LTG steady state

was not attained until study week 24 (week 8 of Monotherapy), or 12 weeks after the dose reduction of CBZ and PHT and 8 weeks after the complete withdrawal of concomitant AEDs. The mean change in LTG for the CBZ population was 1.4 ug/ml or 19% for study weeks 20-24; but the corresponding changes for the PHT group "could not be precisely estimated due to the small sample size," although they appeared to be slightly lower than for CBZ. The mean trough plasma concentrations of CBZ and PHT remained about the same after study week 12 (week 4 of Treatment Transition), when the dosage reductions for concomitant AEDs were initiated.

Finally, the conclusions reached by Vijay K. Tammara, PhD, in his 15 June 1997 biopharmaceutical review essentially agree with the information the sponsor has submitted: "Mean steady state plasma concentrations of Lamictal were higher (8.0 to 10.0 ug/ml) when administered alone as monotherapy compared to when given with concomitant AEDs (4.0 to 6.0 ug/ml). In addition, it was also observed that mean plasma concentrations of Lamictal were comparable between completers and escapers during Lamictal monotherapy phase. Therefore, patient escape from the study did not appear to be caused by lower or higher plasma concentration of Lamictal and concomitant AEDs. Further, pharmacokinetics of carbamazepine and phenytoin were not affected by dose escalation of Lamictal during the first 4 weeks of treatment transition. This inference may be incorporated into the labeling of this drug."

SUBGROUP EFFICACY ANALYSES: Subgroup analyses of efficacy by age (two groups: adolescents, aged 13-<18, and adults, aged 18-59), baseline AED (CBZ vs PHT), race (white vs "other"), and gender indicated that subgroup factors of interest did not have an effect on treatment outcome (see Table 23).

Nevertheless, the results for some of the subgroups may be questionable based on patient number. There were only 5 adolescents, too few to attain validity. As for race, the sponsor made no distinction between such disparate groups as blacks and orientals. Even when all non-whites were grouped together, their number totalled less than half that of whites (49 vs 107).

Results of the per-protocol, intent-to-treat, and worst-case efficacy analyses for patients presenting with secondarily generalized seizures at Baseline showed no statistically significant differences between treatment groups for any of the selected parameters, namely, escape categories (double monthly seizure rate, double highest 2-day seizure frequency, emergence of new or worse seizure type, or significant prolongation of generalized tonic-clonic seizures); IGE; age; race; gender; or baseline AED (CBZ vs PHT); for more details, see Tables 29, 30, and 37.

LTG MONOTHERAPY IN NEWLY DIAGNOSED PATIENTS: Equivalence trials were conducted in the UK in newly diagnosed (treatment-naive) patients with partial or primary generalized epilepsy, comparing LTG directly with either CBZ (UK49, UK89) or PHT (UK74).

UK49 and 89 were identical double-blind, parallel-group studies which stratified patients on the basis of clinical history into two groups, partial seizures and generalized tonic-clonic. Patients were then randomly assigned to LTG or CBZ treatment for 48 weeks. Study drug dosage was titrated upwards over 2 weeks to an initial maintenance total daily dose, for LTG, of 150 mg, and for CBZ, of 600 mg. Doses were subsequently adjusted on the basis of efficacy, adverse experiences, or coded plasma concentrations. Initial recruitment included patients aged 15-65 with partial seizures or generalized tonic-clonic seizures (at least two in the previous 6 months and at least one in the past 3 months) who had not been treated with any AED, but protocol amendments extended the age range to 14 years or older.

UK74 was a multicenter, double-blind, parallel-group trial similar in design to UK49 and 89 but using PHT as the comparative drug. Patient stratification, based on clinical history, divided subjects into 3 groups: partial seizures without secondary generalization, secondary generalized seizures, and primary generalized seizures. Within each group, patients were randomized to LTG or PHT for 48 weeks, and study drug was escalated over 2 weeks to an initial maintenance total daily dose, for LTG, of 150 mg, or for PHT, of 300 mg. Doses were subsequently adjusted on

the basis of efficacy, adverse experiences, or coded plasma concentrations. Initial recruitment included patients aged 15-65, with at least two in the previous 6 months and at least one in the past 3 months, who had not been treated with any AED; protocol amendments extended the age range to 75 years.

No statistically significant difference in efficacy was shown between treatments, and the sponsor has offered these trials for help in determining an appropriate dosing regimen for LTG monotherapy (see below).

III. SAFETY

Safety data are presented for the period 7 April 1994-31 August 1996. The LTG adult monotherapy cohort consists of 1052 unique subject exposures from a total of 27 clinical studies, achieving monotherapy either by AED withdrawal or by monotherapy in newly diagnosed epilepsy patients. The primary safety population (868) included patients who participated in completed monotherapy studies (9 controlled and uncontrolled studies; LTG dose 200 mg per day).

Of the 868 unique patients, 353 (40.7%) withdrew from LTG for any reason during participation in either a primary study or a continuous study, including 116 patients (13.4%) who dropped out due to AEs. There were four deaths among LTG patients. A total of 181/867 received LTG for at least 52 weeks, 27 for at least 104 weeks, and 1 for 152 weeks. The mean average total daily dose among the 867 patients was 200 mg, and the modal total daily dose was 218 mg. There were 589.6 patient years of exposure.

In the pivotal monotherapy study (US30/31), 76 patients were exposed to LTG (target dose: 500 mg per day) and 80 to VPA (target dose: 1000 mg per day). Of these, 15/75 (19.7%) and 6/80 (7.5%) withdrew due to AEs. 12 of the 15 patients who discontinued were treated with CBZ at baseline, and nearly all of them withdrew during the Treatment Transition (add-on) Phase. One patient randomized to LTG (31-17-17006) received only VPA placebo for 3 weeks beginning from randomization and was then withdrawn due to the protocol violation. The patient's efficacy and safety data are included in the intent-to-treat and safety analyses but the patient was not counted in exposure tables; see v 5, p 158).

53/75 LTG patients in US30/31 received study drug for at least 8 weeks, 32 for at least 20 weeks, and 15 for 22 weeks. During the add-on period, the mean and modal average total daily LTG doses were respectively 379 and 452 mg; and during the monotherapy period, respectively 491 and 493 mg. This accounts for a total of 8.2 patient years of exposure to LTG. The sponsor suggests, as a possible explanation for the large number of dropouts from the LTG group, that these patients received a higher dose of anticonvulsant, with consequently more attendant AEs. However, in the migraine study (discussed below), there were also a large number of dropouts, and doses were half those in US30/31. Large numbers of dropouts in that study, the sponsor felt, were due to the rapid dose escalation (over 2 instead of 4 weeks).

In monotherapy studies in newly diagnosed patients (equivalence trials), 446 unique patients received LTG in four controlled studies and 1 in an uncontrolled study. Of these, 42 (9.4%) withdrew due to AEs. Among the 247 patients receiving CBZ, 91 (36.8%) withdrew, 47 (19%) of these because of AEs; among the 95 who received PHT, 50 (52.6%) withdrew, 17 (17.8%) due to AEs. Of the 447 patients receiving LTG, 78 received study medication for at least 52 weeks, 20 for at least 104 weeks, and 1 for 152 weeks. The mean modal and average total daily LTG doses were 147 and 134 mg, respectively, accounting for 235.2 patient years of exposure. (The mean modal and average total daily CBZ doses were 511 and 488 mg, and for PHT, 298 and 292 mg respectively.)

Demographic characteristics for the 868 patients in the completed monotherapy studies show 415 (47.8%) males and 453 (52.5%) females. Most (788/868, or 90.8%) were between the ages

of 16 and 59. Of the 868 patients, 828 (95.4%) were white, 9 (1.0%) black, 13 (1.5%) Asian, (0.5%) oriental, and 14 (1.6%) "other." The mean duration of epilepsy at study initiation was 11 years, an average of 17-22 years in the conversion to monotherapy studies and 2-4 years in the monotherapy studies for newly diagnosed patients.

It must be emphasized that the data base in the submission does not distinguish unique monotherapy exposures from add-on exposures and, in addition, includes (though the number is presumably small) subjects between the ages of 13 and 16.

DEATHS: There was one death during US30/31 (v 5, p 161): patient 30-1-1039, a 22-year-old white male randomized to receive VPA in addition to his concomitant AED, phenytoin. After 36 days of treatment with study drug (or 3 days after the phenytoin taper was begun), he was found dead in the morning. No cause was discovered during post-mortem, and the death was classified as "sudden unexplained death in epilepsy" (SUDEP).

If completed monotherapy (n=868) and add-on trials (n=1052) are summed, there are a total of 17 recorded in the present submission; four have been attributed to SUDEP while on LTG. The ratio of 3/1920 for SUDEP agrees with information found in current LTG labeling. (This denominator was arrived at in phone conversations with Elizabeth McConnell, Glaxo-Wellcome, on 12/2/97 and 12/10/97. See also Tables 6.22 and 6.22.1.)

A description of all 17 deaths can be found in the sponsor's reports reproduced in the addendum; the remaining 13 deaths were not attributable to study drug or SUDEP by the investigator or sponsor. Following are the sponsor's case reports for the 3 deaths on LTG classified as SUDEP:

(1) 41-year-old female, without significant past medical history, was on LTG monotherapy (300 mg/day) for 10 months. There were no reported AEs, significant abnormalities in labs or vitals, or EKG changes at baseline. Three days after she presented to clinic with "perfect" seizure control and no AEs, she was found dead in bed.

(2) 30-year-old male, in good heart and without history of heart disease, was on LTG 400 mg/day for 355 days when he was found dead on the farm where he worked "about 10 minutes after death." Although the general practitioner ascribed death to myocardial infarction, the investigator reported the event as SUDEP.

(3) 56-year-old male, receiving LTG 600 mg/day in an open-label treatment protocol, died after a "typical complex partial seizure."

SERIOUS ADVERSE EVENTS: In the pivotal monotherapy study (US30/31; see Table 76), SAEs were reported by 4 (5%) in the LTG group (2 during the add-on phase and 2 while on monotherapy), all of whom withdrew from the study; and there were 5 (6%) in the VPA group, 3 of whom withdrew (see Tables 78 and 79). Two patients on LTG (2.6%) reported serious rash leading to hospitalization (one of which was classified as Stevens-Johnson). The most common SAE in the VPA group was "reaction aggravated" (2 patients, 3%). Because "reaction aggravated" refers to worsening seizures, the question arises as to whether these patients may have actually met escape criteria and so should fall under the category of dropouts due to lack of efficacy, rather than as withdrawals for safety reasons.

Following are incidences of major SAEs experienced by LTG patients in other monotherapy studies:

--for completed monotherapy studies (see Table 6.22 and 6.22.1), 56/868 (6.5%) reported SAEs, most commonly (1) "reaction aggravated" (9 patients; 1%), a category defined as "persistent, recurring, or prolonged seizures, status epilepticus, increase in seizure frequency or intensity, and hospitalization for seizures" (v 1, p 112); and (2) rash (6; 0.7%), consisting of "serious rash" (6; 0.7%), "serious maculo-papular rash" (1; 0.1%), and Stevens-Johnson Syndrome (1; 0.1%). A total of 21/868 (2.4%) withdrew from LTG because of SAEs. Note that 9 serious adverse events (SAEs) that occurred in a completed

monotherapy study were not captured in the database, because "the investigators... did not indicate that the AE was serious on the patient's case report form" (v 1, p 112). --for monotherapy studies in newly diagnosed patients (see Table 6.28), 22 (5%) on LTG, (7 (3%) on CBZ, and 12 (13%) on PHT reported SAEs. Among LTG patients, the most common SAE was "reaction unevaluable" (4; 1%), including right knee arthroscopy, acute appendicitis, hysterectomy, and CO poisoning. Among CBZ patients, neoplasm (2; <1%). Among PHT patients, abdominal pain and asthenia (2; 2% for each). 2/446 LTG patients experienced "serious" rash.

WITHDRAWALS DUE TO AEs: 116/868 (13.4%) LTG patients in all monotherapy studies withdrew because of AEs, most commonly "all rash" (6.1%), asthenia (1.5%), dizziness (1.4%), headache (1%), and diplopia (1%). (See Table 6.16.)

In the pivotal trial (US30/31), 15 (20%) LTG and 6 (8%) VPA patients dropped out due to AEs. With respect to the LTG group, 12/15 were on CBZ at baseline, in contrast to 2/6 withdrawals from the VPA. The most common among LTG patients were "all rash" (8%) and dizziness (4%). Most of the dropouts for safety reasons occurred during the add-on period. AEs leading to withdrawal during the monotherapy period were dizziness, diplopia, and rash; diplopia and dizziness are higher in patients receiving LTG and CBZ, according to the sponsor (v 1, p 113). (For more details, see Table 80).

TREATMENT-EMERGENT AEs: 605/868 (69.7%) of LTG patients in completed monotherapy studies reported treatment-emergent AEs during their course of treatment (see Table 6.18). The five most common were headache (16.7%), asthenia (13.6%), "all rash" (13.5%), dizziness (12.7%), and nausea (9.1%). The category "all rash" included the following COSTART terms: rash, pustular rash, macular papular rash, urticaria, Stevens-Johnson Syndrome, and vesicular bullous rash.

With respect to the pivotal trial (US30/31; see Tables 66 and 67), 57 (75%) of LTG and 63 of (79%) VPA patients reported treatment-emergent AEs, most commonly dizziness (24% LTG, 26% VPA), coordination abnormal (17% LTG, 0% VPA), nausea (18% LTG, 20% VPA), headache (17% LTG, 20% VPA), vomiting (16% LTG, 9% VPA), asthenia (14% LTG, 13% VPA), tremor (11% LTG; 16% VPA), somnolence (9% LTG, 16% VPA), nystagmus (9% LTG, 0% VPA), amblyopia (9% LTG, 5% VPA), and diplopia (9% LTG, 6% VPA). Following are the incidences of rash: rash (8% LTG, 8% VPA), rash macular papular (3% LTG, 0% VPA), rash vesicular bullous (1% LTG, 0% VPA), Stevens-Johnson (1% LTG, 0% VPA). AEs possibly associated with rash also occurred more frequently in the LTG group: lymphadenopathy (5% LTG, 0% VPA) and pruritus (5% LTG, 0% VPA). Although the sponsor breaks down incidences of adverse events by occurrence during Treatment Transition, Monotherapy, and Follow-up, "interpretation of the data collected during monotherapy is limited by small sample sizes" (v 5, p 161).

With regard to the monotherapy equivalence trials in newly diagnosed patients, AE rates for LTG were similar to those for CBZ and PHT: asthenia (16%, 24%, 29% respectively), headache (20%, 17%, 19%), somnolence (8%, 20%, 28%), "all rash" (14%, 15%, 11%), dizziness (8%, 14%, 12%), and nausea (10%, 10%, 4%). Note, however, that the patient population and LTG dosing schedule (200 mg, as opposed to 500 mg, per day) were different from the pivotal trial.

ALL ADVERSE REACTIONS: There is no listing of all adverse events. The labeling found with the present submission, however, is unchanged from the one in current use. It appears that the same panoply of AEs were seen in patients who received monotherapy LTG (US30/31) as adjunctive therapy LTG (in light of current labeling), only the rates were generally higher with the latter. But number of subjects involved in the monotherapy trial (US30/31) is very small.

ADDITIONAL CONCERNS -- RASH: In the completed monotherapy studies, 117/868 (13.5%)

reported an event classified as "all rash," broken down as follows (v 43, p 97):

**Incidence of Rash in Patients on LTG in
Completed Monotherapy**

| COSTART Term | No. of Patients | Maximum Intensity | | |
|-----------------|-----------------|-------------------|----------|--------|
| | n=868 | Mild | Moderate | Severe |
| Rash | 96 (11%) | 46 | 39 | 11 |
| Rash mac pap | 11 (1%) | 4 | 4 | 3 |
| Urticaria | 3 (<1%) | 1 | 0 | 2 |
| Stevens-Johnson | 1 (<1%) | 0 | 0 | 1 |
| Rash vesic bull | 6 (<1%) | 4 | 2 | 0 |
| All Rash | 117 (13%) | 55 | 45 | 17 |

Including current ongoing studies (n=696) may provide a more accurate survey and raises the denominator to 1564. The ongoing studies recognize 11 additional cases of serious rash, 3 of them classified as Stevens-Johnson (v 43, pp 196-201). This brings the total number cases of serious rash to 27 (incidence: 1 in 175) and of Stevens-Johnson to 4 (incidence 1 in 400). (The denominators were arrived at through personal communication with Elizabeth McConnell, Glaxo-Wellcome, 12/2/97 and 12/3/97).

In the pivotal trial, US30/31 (76 on LTG, 80 on VPA), 10/76 experienced rashes (v 43, p 98) -- two were considered severe, leading to hospitalization, and one of these was classified as Stevens-Johnson:

Incidence of Rash in Patients on LTG in US 30/31

| COSTART Term | No. of Patients | Maximum Intensity | | |
|-----------------|-----------------|-------------------|----------|--------|
| | n=76 | Mild | Moderate | Severe |
| Rash | 6 (8%) | 3 | 3 | 0 |
| Rash mac pap | 2 (3%) | 0 | 1 | 1 |
| Stevens-Johnson | 1 (0.1%) | 0 | 0 | 1 |
| Rash vesic bull | 1 (1%) | 1 | 0 | 0 |
| All Rash | 10 (13%) | 4 | 4 | 2 |

(Note, however, that only 75 of the 76 patients randomized to LTG actually received the study drug; see above.)

Thus, on the basis of the evidence submitted in the current submission, the incidence of serious rash leading to hospitalization appears to range from _____ and of Stevens-Johnson from _____. These incidences in adults are similar to those found in children, according to current labeling and information with which the sponsor recently provided the FDA. However, the data base in the present supplemental NDA does not distinguish unique monotherapy exposures from add-on exposures and, in addition, includes (though the number is presumably small) subjects between the ages of _____

According to the sponsor's report, the serious rashes seem to have occurred after 2-8 weeks on LTG. There are no reports of rashes progression to intubation, TEN, severe hematological disturbances, irreversible consequences, multiorgan failure, or death.

It is difficult to determine an exact denominator for the population under consideration, because the sponsor lists cases of specific AEs inconsistently throughout the submission. Rash is a prime example: although the above table classifies at least 17 cases of rash as "serious" among the completed monotherapy trials, the sponsor gives brief narratives for no more than 11 in the section entitled "All Serious Rashes" which includes both completed and ongoing studies (v 43, pp 196-200). Elizabeth McConnell (Glaxo-Wellcome) has promised to send a new data set with life tables which should clarify some of the problems (phone conversation, 12/10/97). Following are the 11 cases:

STEVENS-JOHNSON

(1) Patient 31-10-10081 (from US30/31), a 56-year-old male on CBZ and randomized to LTG. About 2 weeks after initiating study drug, he developed a rash later diagnosed as Stevens-Johnson. He was admitted 4 days after the onset of the rash and treated with IV methylprednisone, oral diphenhydramine, and topic hydrocortisone. He was discontinued from the study; the investigator classified the events as "possibly attributable to study drug treatment" (v 5, p 163). No follow-up information is provided.

(2) Patient 105-1-1137: 39-year-old female developed an erythematous rash with pustules and pruritus after 13 days on LTG (on 25 mg/d x 4 days at AE onset), which was stopped 4 days later. Hospitalized 3 days later, she was diagnosed with Stevens-Johnson and treated with prednisone. No follow-up provided.

(3) Patient 29-4-30030: 23-year-old female, with history of CBZ allergy, developed a "severe blotchy rash with mucosal involvement" after 4 weeks on LTG 100 mg/d. Diagnosed with Stevens-Johnson, she was hospitalized and treated with IV methylprednisolone, hydroxyzine, and prednisone. "At the time of this reporting, a dermatologist expected the event to resolve over the next 2-3 weeks." No further follow-up.

(4) Patient 405-01092: 24-year-old female, who received LTG 25 mg/d x 2 weeks increasing to 50 mg/d, developed Stevens-Johnson 2 days after the dose increase (on day 19 of LTG treatment). She was hospitalized x 6 days and treated with brompheniramine maleate, Betadine mouthwash, betamethasone ointment, neomycin+gramicidin, trimeprazine, and ampicillin. The event resolved after 15 days.

OTHER SERIOUS RASH

(1) Patient 31-9-9023 (from US30/31), a 34-year-old male on CBZ and randomized to LTG. About 2 weeks after initiating study drug, he developed a rash and high fever and was discontinued from the study because the investigator deemed the events as "possibly attributable to study drug treatment" (v 5, p 163). No follow-up information is provided.

(2) Patient 105-1-11203: 43-year-old female was hospitalized for rash 6 weeks after starting LTG treatment (at the time of rash, on 100 mg/d x 14 days) and treated with astemizole, terfenadine, and prednisolone. The rash resolved 3 days after LTG discontinuation.

(3) Patient 105-1-3203: 26-year-old female, with history of thrombocytopenia, developed a rash of the forearms and thighs with paresthesias and pruritus 2 months after starting LTG (on 50 mg/d x 9 days at AE onset). No other information provided.

(4) Patient 105-1-7502: 56-year-old male, with history of PHT allergy and thrombocytopenia on CBZ, developed a sore throat after 9 days on LTG (on 100 mg/d x 10 days at AE onset) and was treated with amoxicillin 2 days later for fever and tonsillitis. After 3 days, the tonsillitis and rash ("maculopapular exanthema") worsened, the fever continued, and thrombocytopenia developed. LTG was subsequently withdrawn. No further information.

(5) Patient 74-1-1120: 45-year-old male developed a rash after 26 days on LTG; he was withdrawn from the study and begun on VPA. The rash resolved 3 days later. No further information.

(6) Patient 74-1-5011: 26-year-old male developed a maculopapular rash 18 days after starting LTG (dose at AE onset: 150 mg/d x 9 days). CBZ was substituted for LTG, but the rash had still not resolved 28 days later. No further follow-up.

(6) Patient 405-01137: 16-year-old male was hospitalized with urticaria after 76 days on LTG 200 mg/d. LTG was continued, and the rash resolved 24 hours later. The rash was attributed to an allergic reaction to prawns by the investigator.

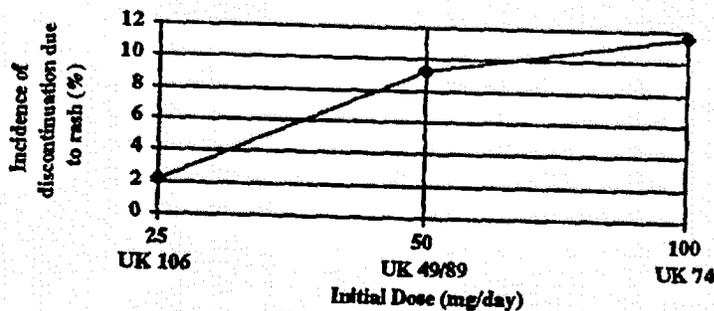
MONOTHERAPY STUDY IN MIGRAINE: This was a 12-week randomized, reportedly double-blind, placebo-controlled study (LTG:placebo::37:40). The initial 18 subjects received LTG 200 mg/day from randomization. After an increased incidence of rash, the dosing regimen was amended (25 mg weeks 1-2, 50 mg weeks 3-4, 200 mg weeks 5-16) and the following 19 subjects received LTG according to the new schedule. (The sponsor does not explain how the dose change was effected in a double-blind study.) Of the 77 subjects randomized, 23 LTG and 30 placebo patients completed the 12-week treatment phase. Withdrawals included 8 (21.6%) LTG and 3 (7.5%) placebo patients; among them, 12 patients (11 on LTG, 1 placebo) developed a rash but none was considered serious by the investigator. The sponsor has attributed the large number of rash reports to the high initial starting dose, since twice as many subjects who had been dosed without escalation were involved (v 1, p 117):

Incidence of Rashes in Patients on LTG in UK 78

| | Number of Patients | Number of Patients (%) with skin rash |
|-----------------------|--------------------|---------------------------------------|
| Total patients on LTG | 37 | 11 (29.7%) |
| Non-dose escalated | 18 | 7 (38.9%) |
| Dose escalated | 19 | 4 (21%) |

According to the sponsor, "rapid dose escalation and a high initial starting dose are clearly risk factors for rash" (v 1, 118).

Effect of Initial LTG Dose on Incidence of Discontinuation Due to Rash in Monotherapy Studies in Newly Diagnosed Patients



SAFETY LABS AND OTHER DATA: For US30/31, according to the sponsor, analyses of clinical lab evaluations, EKGs, vitals, and physical and neurological exams were not done, because this

information is available in NDA 20,241 and subsequent updates. However, a summary review of the raw data "did not reveal any findings which differed from those previously reported from the adjunctive use of LTG" (v 1, p 118).

Vitals appeared unremarkable. There were some abnormal EKG readings, either considered wrong or not serious: a computer-read tracing suggested a possible MI in a 35-year-old male, which, on review by a cardiologist, was considered unlikely; the tracing of a 47-year-old male was read by the computer as abnormal R-wave progression but classified by the cardiologist as a normal variant; a 44-year-old female had a tracing 29 days after beginning study drug which showed an IVCD and inferior ST-T wave, both of which were regarded by the investigator to be "mild in intensity, not serious, and not related to the use of study drug" (v 5, p 167); a 22-year-old female who, 30 days into study drug treatment, was found to have sinus tachycardia regarded by the investigator to be "mild in intensity, not serious, and not related to the use of study drug" (v 5, p 167).

There were a few abnormal labs in US30/31. Four patients had elevated CK levels: patient 30-20-20157 had a CK of 1304 U/l after 28 weeks on LTG; patients 30-20-16009 and 30-20-20158, respective CKs of 1391 and 3070 U/l after 16 weeks on VPA; and patient 30-4-4032, a normal baseline CK (73 U/l) which rose to 319 after 57 days on LTG (reported as a "mild and not serious adverse event" [v 5, p 165]). No further information is available about these patients. One patient (30-15-15074), randomized to VPA, was found to have elevated transaminases (ALT 423, AST 171) and subsequently withdrew after being diagnosed with hepatitis C.

Physical and neurological exams apparently revealed no findings of concern.

Finally, one patient, a 20-year-old female, became pregnant during UK30/31. She presented with complex partial seizures (21 seizures per 4-week baseline while on PHT) and was randomized to VPA. Her serum pregnancy test was negative at study week 28 but positive at week 31 (taper and follow-up), at which time she was withdrawn because she met escape criteria due to the doubling of her highest 2-day seizure frequency. The patient elected to terminate her pregnancy.

DOSING AND SAFETY DATA DERIVED FROM LTG MONOTHERAPY IN NEWLY DIAGNOSED PATIENTS: Equivalence trials in the UK were conducted in newly diagnosed patients with partial or primary generalized epilepsy, comparing LTG directly either with carbamazepine (double-blinded, placebo-controlled: UK49 and UK89; open-label: UK106) or with phenytoin (UK74). No statistically significant difference in efficacy was shown between treatments. It is difficult to know whether these trials were sufficiently powered. Nevertheless, the sponsor claims that these equivalence trials may provide relevant dosing and safety information with regard to initiating LTG monotherapy in treatment-naive patients:

Relationship Between Doses and Serum Levels in LAMICTAL Monotherapy Studies

| Study | Mean Maintenance dose mg/day | Mean Plasma Level µg/ml |
|-----------|---------------------------------|----------------------------|
| 30/31 | 410.4 | 8.7 |
| 49/89 | 172.8 | 3.3 |
| 74 | 172.3 | 3.4 |
| 106 (100) | 100.03 | 2.1 |
| 106 (200) | 193.96 | 3.58 |

UK49, 89, and 74 achieved maintenance dosing by titration on the basis of blinded plasma levels, with a maximum target level of 4.0 ug/ml. The sponsor recommends the following dosing schedule:

**Recommended dose escalation of LAMICTAL
for Adults on Monotherapy**

| Weeks 1 + 2 | Weeks 3 + 4 | Usual maintenance dose |
|-----------------------|-----------------------|--|
| 25 mg (once a day) | 50 mg (once a day) | 100-200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50-100 mg every 1-2 weeks |

The sponsor has proposed lower doses for safety reasons, using the equivalence trials to bolster its position (personal communication, Elizabeth McConnell, Glaxo-Wellcome, 12/1/97). Nonetheless, lower doses may compromise the efficacy of LTG as monotherapy. In US30/31, the target dose was 500 mg/day. Efficacy in controlling partial and secondarily generalized seizures, even on that higher dose, was not ideal, and it is difficult to derive adequate information from equivalence trials. Therefore, lower doses would not appear to be recommendable.

POST-MARKETING SAFETY EXPERIENCE: There have been 59 serious spontaneous adult cases where LTG was "the only epilepsy treatment reported" (v 43, p 112). According to the sponsor, it is not known whether these patients were truly on LTG monotherapy (personal communication, Betty McConnell, Glaxo-Wellcome, 12/1/97). Of those 59, 7 resulted in death (see below), 17 involved rash (Stevens-Johnson and/or toxic epidermal necrolysis, 10 cases; rash plus disseminated intravascular coagulation, 1 case), and 4 involving hematological abnormalities (neutropenia plus enlarged lymph nodes in the first 5 weeks of treatment, 1 case; DIC, as just cited, 1 case; agranulocytosis occurring within the first 3 months of treatment, 1 case; and anemia in an HIV patient, 1 case).

The 7 deaths comprised: overdose of LTG (2 patients), status epilepticus (1), anorexia (1), and SUDEP (3). Following are brief case histories (v 43, p 112; the sponsor has no further information):

--overdose of LTG (2 patients)

- (1) 22-year-old female, who took 15 g LTG in a suicide attempt, had an acute clonic seizure, heart failure, and cardiac asystole; despite CPR, she experienced brain death and was pronounced 2 days later.
- (2) 52-year-old female, with malignant cerebral tumor, died after receiving LTG 400 mg for 6 days. (Note, however, that UK30/31 subjects received higher doses for much longer periods.)

--status epilepticus (1)

- (1) 37-year-old male, who received LTG during a switch from other AED therapy, experienced status epilepticus and died.

--anorexia (1)

- (1) 69-year-old female, receiving LTG for 6 months, "developed severe, intractable anorexia and died."

--SUDEP (3)

- (1) 22-year-old female, having received LTG for 8 months, was found dead, cause unknown.
- (2) 38-year-old male, having received LTG for 13 months, was found collapsed in his bath; 2 days later he died of SUDEP.
- (3) 31-year-old male, receiving LTG, died of sudden unexplained causes.

IV. CONCLUSION

There does not appear, from this single trial, to be adequate data affirming the effectiveness of Lamictal as monotherapy in the treatment of partial and secondarily generalized seizures.

The sponsor has presented the efficacy data from two different perspectives -- an "escapers" and a "completers" -- and both, for this reviewer, have fundamental problems, raising serious questions about the validity of the results. With respect to the "escapers" endpoint, it appears that more than twice as many LTG patients dropped out for safety reasons (11 vs 4) during the add-on period, prior to monotherapy. This fact would point to a *bias in favor of* the LTG group: a large number of LTG patients did not get an opportunity to test efficacy on LTG monotherapy (*ie*, to drop out for reasons of lack of efficacy). Had the worst-case scenario proved to be statistically significant, the present results might prove more easily acceptable. But, as no difference was shown between the two treatments, the bias in favor of LTG stands. It should be noted that the Felbamate monotherapy trial, upon which the design of the LTG trial was based, also used an escapers analysis for the primary outcome measure. However, unlike the LTG trial, there were few withdrawals for safety reasons during the add-on period.

With respect to the "completers" analysis, the problem involves the fact that only 37% of the population completed the monotherapy period: the drug, in other words, failed in its intended effect in two-thirds of the population. LTG may have achieved statistical significance when evaluated against an active placebo, but it has not demonstrated clinically significant efficacy as monotherapy. Furthermore, given that one-third of the intent-to-treat population failed for safety reasons and another third due to lack of efficacy, a profile of the patient who would benefit by LTG monotherapy may be difficult to determine. The sponsor has not provided an evaluation of the data that might help resolve this issue.

An even more fundamental problem with US30/31 centers on the apparent misclassification of three LTG patients as withdrawals for adverse events when they in fact met efficacy escape criteria earlier in the study (patients 30-1-01038 who met the criterion for doubling the highest 2-day seizure frequency on 3/16-17/95; 31-6-06046 who met the criterion for doubling the highest 4-week seizure frequency for the period 5/1-31/95; and 31-26-26161 who met the criterion of doubling the highest 2-day seizure frequency for 5/2-3/95). Furthermore, inadequate documentation of seizure diaries (*ie*, missing data) occurred in three additional LTG patients (30-15-15017 for the period 2/5-19/95; 31-14-14026 for the period 2/22-28/95; and 31-17-17041 for the period 16-25/95) and one VPA patient (30-15-15074 for the 2/1-7/96). These omissions represent substantial lacunae which could potentially involve efficacy failures.

Please see the addendum to the biostatistical review of Dr. Sue-Jane Wang (Biostatistics), who plans to reanalyze the data by including the three misclassified efficacy failures. She also plans to conduct a new worst-case analysis which would consider the three LTG cases with missing data as efficacy failures.

Finally, significant prolongation of generalized tonic-clonic seizures (one of the escape criteria) was more common (a trend) among the LTG population than the VPA (despite the less than therapeutic dose used), although the US30/31 intent-to-treat sample size was small (38 LTG and 27 VPA patients had secondarily generalized seizures) and the total number of patients experiencing secondarily generalized seizures was tiny (5). If the LTG dose is lowered from 500 mg/day to 200 mg/day with the goal of decreasing the number of adverse events, as the sponsor suggests in its proposed labeling, the drug as monotherapy may prove less efficacious for seizure control -- for partial as well as secondarily generalized.

There are also some safety concerns, in particular rash. The incidence of serious rash leading to hospitalization ranges from 1 in 38 to 1 in 175, and of Stevens-Johnson from 1 in 76 to 1 in 400. These incidences in adults are similar to those found in children. However, the data base does not distinguish unique monotherapy exposures from add-on exposures and, in addition,

includes (though the number is presumably small) subjects between the ages of 13 and 16.

V. RECOMMENDATIONS

APPEARS THIS WAY
ON ORIGINAL

- (1) Await the biostatistical review of Dr. Sue-Jane Wang.
- (2) In view of the small number patients who finished US30/31, request an analysis from the sponsor providing patient profiles (in both the LTG and VPA groups) to determine the type of patient most likely to benefit from LTG monotherapy. Such an analysis might bolster the claim of monotherapy in a select population.
- (3) The sponsor should provide, if possible, a more reliable exposure data base in adults (unique exposures vs add-on exposures, and the denominator should express a population ≥ 16 years of age) in order to obtain rates for (a) serious rash leading to hospitalization, (b) Stevens-Johnson, and (c) SUDEP.

Richard M. Tresley MD
Medical Reviewer

NDA 20,241 Supplement (Monotherapy) div file/Katz R/Ware J/Tresley R/15 December 1997

APPEARS THIS WAY
ON ORIGINAL