CENTER FOR DRUG EVALUATION AND RESEARCH

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20-844/S-010

MEDICAL REVIEW

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

NDA Number	20,505
Generic (Brand) Name	Topamax (topiramate)
Sponsor	RW Johnson Pharmaceutical Research Institute
Indication	1. sNDA: adjunctive treatment for (a) pediatric partial-onset seizures (b) Lennox-Gastaut syndrome (c) generalized tonic-clonic seizures 2. Four-Month Safety Update 3. 20 March 1998 Update 4. 28 April 1998 Additional Analyses
Classification	S
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Clinical Reviewer	Richard M. Tresley, MD
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I. INTRODUCTION

Topamax (TOP) was approved as adjunctive therapy to treat partial seizures in adults with epilepsy on December 24, 1997. The sponsor has submitted three supplemental NDAs to support indications for use, as an adjunctive agent, in the treatment of (1) pediatric partial-onset seizures (single controlled trial), (2) Lennox-Gastaut syndrome (single controlled trial), and (3) primary generalized tonic-clonic seizures with or without other generalized seizure subtypes (two controlled trials). Each supplement will be discussed separately with respect to efficacy. A general safety assessment will be done for both pediatric and adult populations.

II. EFFICACY

(a) Pediatric Partial-Onset Seizures (Study YP)

TRIAL DESIGN: This Phase 3, multicenter (17 centers, 17 investigators), randomized, double-blind, placebo-controlled study was conducted in the United States and Costa Rica during the period 6/2/94-5/29/96. Its aim was to evaluate topiramate as adjunctive therapy in pediatric subjects with uncontrolled partial-onset seizures with or without secondary generalization. Four total daily (target) doses of topiramate were tested -- 125, 175, 225, and 400 mg/day -- based on subject weight to approximate 6 mg/kg/day.

The trial was divided into two phases (see Table 4 and Figure 2): baseline (56 days) and double-blind (112 days). During the baseline period, subjects received a constant dose of one or two anticonvulsants (AEDs), and the number and type of seizures were monitored on this regimen. Subjects met eligibility requirements for the double-blind portion if they had at least 6 partial-onset seizures during the 56 days, with at least one seizure per 28-day period. Those who were eligible were randomized in equal proportions at each center to placebo or topiramate arms while continuing their baseline AEDs.

The double-blind portion consisted of titration and stabilization phases, each 56 days in length. Study drug was titrated to the subject's assigned (target) dose or maximum tolerated dose in four 2-week intervals: during the first interval, the initial dose was 25 or 50 mg/day, based on weight and administered once in the evening; and, during subsequent intervals, the dosing interval was twice daily, titrated to maximum daily dosages of 125, 175, 225, and 400 mg/day based on weight (see Table 3 for dosing schedules). Target doses could be altered, depending on toleration; Table 22 lists treatment-emergent AEs necessitating dosage adjustments. Subjects then continued on this regimen for the 56 days of the stabilization period (see Table 19 for information about duration of the double-blind portion).

All patients completing the stabilization period were permitted to enter an open-label extension. Those who chose not to do so or discontinued prematurely had their study drug tapered off.

Three amendments to the original protocol were implemented:

(1) dated 10 November 1994, after enrollment had reached about 16%: the number of partial seizures required during baseline, for all but Lennox-Gastaut patients, was reduced from 8 to 6;
(2) dated 2 May 1995, after enrollment had reached about 39%: the use of centrally acting sympathomimetics and felbamate was added to the exclusion criteria;
(3) dated 13 July 1995, after enrollment had reached about 56%: the minimum eligibility age was modified from 4 years to 1, and the maximum age from 14 to 16 years; the sample size was decreased from 90 to 72 because of slow enrollment; and zonisamide was disallowed as a concomitant medication.

Another protocol change was implemented (though not as an amendment) when less than 10 subjects were enrolled, permitting subjects, who participated in the baseline period, to reduce

the duration of the baseline period if they were able to provide retrospective seizure information (based on a parent's or guardian's records) that totalled 56 days of seizure data when added to the prospective baseline experience.

INCLUSION/EXCLUSION CRITERIA: Males and females, aged 1-16; however, the youngest enrolled was 2 years old (two patients). Tables 1 and 2 delineate the inclusion/exclusion criteria.

POPULATION: Although the planned sample size was "approximately 72" subjects, 86 were eventually randomized (mean age: 10.6 years; age range: 2-16 years): 45 to placebo, 41 to topiramate. The sponsor explains (v 13, p 41) that there were already a number of potential subjects already screened for the study at the time the cohort approached 72 and the sponsor notified investigators to stop enrollment. "[I]t was considered unethical to disallow entry to those subjects" (v 13, p 41). All 86 subjects were included in the intent-to-treat analyses of safety and efficacy. Tables 6a and 6b display demographic and baseline characteristics.

With respect to demographic differences between treats and placebo, the mean was greater for the placebo group due to two patients with high baseline seizure rates, but the median baseline seizure rates were comparable: subject 45 (1,133/month) and subject 522 (271/month). Nevertheless, seizure types were similar in both groups. As for racial make-up, there were no blacks on placebo.

The profiles of concomitant medications appeared comparable between treatment groups. The most common non-anticonvulsants were analgesics, cough and cold preparations, vitamins, antibiotics, and nasal preparations (for a listing, see v 16, pp 1169-1234).

WITHDRAWALS: 83/86 subjects randomized to treatment completed double-blind therapy. The three withdrawals are shown on Table 7. Two patients were on placebo: one discontinued due to an adverse event (rash), and the second due to lack of patient cooperation. The single TOP dropout was a 5-year-old who failed two clinical visits during the trial but returned for his final appointment on Day 119, and who, moreover, was deemed noncompliant since he stopped taking study drug and had not maintained his seizure diary.

PROTOCOL DEVIATIONS: (1) 32 subjects (16 in each treatment group) were randomized to the double-blind phase before completing the protocol-specified 56-day baseline period; (2) 2 subjects (1 in each treatment group) weighed 15 kg and were allowed to enter baseline; (3) 6 placebo and 11 topiramate patients received more than 2 background AEDs at baseline; (4) 2 patients (1 in each treatment group) received a dosage of study drug exceeding the target daily dosage (the placebo patient, assigned to 125 mg/d, received 200 mg once during the study; the topiramate patient, assigned to 125 mg/d, received 250 mg once during the study; v 13, p 47).

DOSAGE FORM: TOP was supplied as 25-mg (Batches R4568, R5570) and 100-mg (Batches R5509, R5512) tablets. Maximum doses were based on subject weight: 125 mg/d (16-24.9 kg), 175 mg/d (25-33.9 kg), 225 mg/d (34-42.9 kg), and ≥400 mg/d (≥43 kg).

OUTCOME MEASURES:

PRIMARY: Percent reduction from baseline in the average monthly rate of partial-onset seizures during the double-blind portion of the trial. Seizures were coded by the International Classification of Epileptic Seizures (1981).

SECONDARY: (1) Percent reduction from baseline in the average monthly seizure rate for all seizures;
(2) percent reduction from baseline in the average monthly seizure rate for secondarily generalized seizures;
(3) percent treatment responders, defined as subjects with ≥50% reduction from baseline in the average months seizure rate;

(4) parental global evaluation of seizure severity.

PLANNED ANALYSES: The cohort was established at 72 (but see above). A sample size of 36 subjects in each treatment group was estimated to be adequate with 80% power to detect a between-group difference of 40% in percent reduction in the partial-onset seizure rate (see v 14, pp 36-7). This assumed a Type I error level of 5% and a population standard deviation of 60%.

According to the study protocol, "The primary efficacy parameter will be percent reduction from baseline seizure rate based on partial-onset seizures [for the double-blind phase of the study].

"Group differences in percent reduction from baseline partial-onset seizure rate will be analyzed using 2-way (with treatment and investigator as factors) analysis of variance. Group differences in responders will be analyzed using logistic regression methodology. Treatment by investigator interactions will be assessed and explored further if the p-value is ≤ 0.10. Parental/guardian global evaluation will be analyzed using Mantel-Haenszel methodology. Percent reduction from baseline seizure rate based on all seizures will be analyzed descriptively as a secondary parameter" (v 14, p 455).

PERFORMED ANALYSES: Primary analyses included all randomized subjects (ITT) during the double-blind phase (titration and stabilization periods) up to study drug discontinuation. Secondary analyses using only stabilization period data (beginning on Day 57 of the double-blind phase), employed identical statistical methods. Average monthly (28-day) seizure rates were computed for the baseline and double-blind phases. A 2-way analysis of variance on ranks (with treatment and center as factors), by means of SAS for general linear model, was chosen to analyze group differences in percent reduction from baseline seizure rate.

Centers with low enrollment ($n<6$) were pooled and included as single centers, not exceeding the size of the largest center ($n=12$). The algorithm ranked all centers in order of total sample size and then alphabetically within sample size.

For those subjects experiencing secondarily generalized seizures at baseline or during the double-blind phase, percent reduction from baseline *in generalized seizures only was computed.* However, if secondarily generalized seizures were absent during baseline but present during the double-blind phase, a baseline seizure rate of 0.001 per month was assigned to allow calculation of seizure-rate reduction.

Additionally, treatment groups were compared to derive the percent treatment responders for partial-onset and all seizures, using the Cochran-Mantel-Haenszel method stratified by center.

Parental global evaluation of improvement in seizure severity was analyzed by exact Wilcoxen rank-sum test unstratified and stratified by center (via StatXact).

All statistical tests were two-sided at alpha=0.05, except for interaction in the linear model, which was at the 0.10 level.

COMPLIANCE: Compliance appears to have been good, as determined by the maintenance of reasonably constant plasma concentrations of topiramate and concomitant AEDs throughout the stabilization period of the trial (see v 13, p 64; TOP concentrations are shown in v 16, pp 1095-1103, and concentrations of concomitant AEDs in v 16, pp 1125-60).

RESULTS: All 86 patients (45 placebo; 41 TOP) who entered the double-blind trial were included in the efficacy analyses (ITT). Seizure data for the three withdrawals were averaged for that portion of the double-blind phase completed up to the time study drug was discontinued; Table 19 shows the duration of the time spent in the double-blind phase for all randomized subjects. The ITT analyses included all seizure data for both partial-onset and all seizures (see Table 14). Note that two topiramate and no placebo patients were seizure free during the double-blind portion.

The primary outcome measure was the percent reduction from baseline in the average monthly partial-onset seizure rate during the double-blind phase. Table 8 shows a median percent reduction of 33.1% for the topiramate group versus 10.5% for the placebo group, yielding a statistically significant difference in favor of treatment (p=0.034).

With respect to secondary outcome measures, TOP patients demonstrated a median percent reduction in secondarily generalized seizures of 31.6% versus an increase of 10.6% in the placebo group. 21/24 (88%) TOP and 25/28 (89%) placebo patients who reported no secondarily generalized seizures at baseline did not exhibit this type of seizure activity during the double-blind phase. The median percent reduction from baseline for all seizures was 31.9% for TOP and 10.5% for placebo patients (p=0.077).

There were no statistically significant treatment-by-center interactions with respect to partial-onset seizures (p=0.159) or all seizures (p=0.252). Figure 3 displays the data graphically, illustrating results favorable to TOP in 7 of the 9 centers.

Treatment responders were defined as patients with ≥50% reduction from baseline seizure rates during the double-blind phase. Table 9 shows that (1) 39% TOP, as opposed to 20% placebo, subjects were treatment responders with respect to partial-onset seizure (p=0.080); (2) 39% TOP, compared to 22%, patients were treatment responders based on all seizures (p=0.127); and 45% TOP, versus 30% placebo, subjects were treatment responders for the category of secondarily generalized seizures. There were no statistically significant treatment-by-center interactions with respect to partial-onset seizures (p=0.120) or all seizures (p=0.206). In contrast (see Table 10), a statistically significant number of TOP, versus placebo, patients experienced ≥75% reduction in seizure rate with respect to both partial-onset seizures (17% to 2%; p=0.019) and all seizures (17% to 2%; p=0.019). For secondarily generalized seizures, the figures were 25% TOP vs 15% placebo patients.

Finally, for the parental global evaluation of improvement in seizure severity (Table 11), 59% TOP vs 33% placebo patients showed improvement (minimal, moderate, or marked). The figures for marked improvement were statistically significant (p=0.025) in favor of TOP (29%), compared to placebo (11%).

The review of Dr. Sue-Jane Wang (FDA Biostatistics) concurs with the above.

PHARMACOKINETIC DATA: The mean plasma concentration of TOP for the entire double-blind phase of the trial was 3.6 (±1.89 SD) ug/ml (v 13, p 47). Changes in plasma concentration for concomitant AEDs were insignificant (see Table 12). Of those who achieved their target dosage at some time during the trial, 38 (93%) were in the placebo and 42 (93%) in the TOP groups (Tables 15, 16, 17). 40 (89%) placebo and 31 (76%) TOP patients achieved their target dosage and completed the stabilization period at that dosage (Table 18).

Median percent reduction and percent treatment responders (≥50% reduction in seizure rate) were greatest in the mid-range plasma TOP concentration, 3.2-5.4 ug/ml, for both partial-onset and all seizures (see Table 13). No significant correlation (v 13, p 59) was observed between plasma TOP concentration and percent reduction in the average monthly partial-onset (p =0.536) or all seizure rates (p=0.452).

SUBGROUP ANALYSES: The ratio of male-to-female representation was relatively close (male:female::14:11 in both the drug-treated and placebo groups; see the demographics in Table 6b). the crude percentage rates shown in Attachment 2.1.4, which compares the two groups in terms of median seizure reduction, would lead to the conclusion that both did well on TOP. No differences with regard to effectiveness or safety issues were noted for gender, according to a phone conversation with the sponsor on 2/10/98 (Catherine Glenkowski , covering for Michael Kaufman, Joe Ward [medical writer], and Judy Smith [statistician]).

Racial representation was sparse, and no conclusions can therefore be reached about the effect of topiramate on groups other than whites. Only 4 (4/41) blacks and 1 (1/41) Oriental were randomized to study drug; in the placebo group, there were no blacks and 2 Orientals.

(b) Lennox-Gastaut Syndrome (Study YL)

TRIAL DESIGN: This Phase 3, multicenter (12 sites), randomized, double-blind, placebo-controlled study, conducted in the United States during the period 7/27/93-4/11/96, evaluated topiramate 6 mg/kg/d (≤600 mg/d) as adjunctive therapy in subjects with Lennox-Gastaut syndrome.

The trial was divided into two phases (see Table 3 and Figure 1): baseline (about 4 weeks) and double-blind (about 11 weeks). During the baseline period, subjects received a constant dose of one or two anticonvulsants (AEDs), and the number and type of seizures were monitored on this regimen. Subjects met eligibility requirements for the double-blind portion if they had at least 6 partial-onset seizures during the 56 days, with at least one seizure per 28-day period. Those who were eligible were randomized in equal proportions at each center to placebo or TOP arms while continuing their baseline AEDs.

The double-blind portion consisted of titration and maintenance phases. During titration, which lasted 3 weeks, study drug was administered the first week at 1 mg/kg/d, increasing to 3 mg/kg/d the second week, and 6 mg/kg/d the third; dosing was bid. Target doses could be altered, depending on toleration; Table 18 lists treatment-emergent AEs necessitating dosage adjustments. Subjects then continued on this regimen for the next 8 weeks of the maintenance period (see Table 15 for information about duration of the double-blind portion).

All patients completing the maintenance period were permitted to enter an open-label extension. Those who chose not to do so or discontinued prematurely had their study drug tapered off.

Efficacy was based on a statistically significant between-group difference (TOP vs placebo) with respect to either one of two variables: (1) percent reduction in the average monthly seizure rate for all seizure types or (2) a compound variable consisting of percent reduction in drop attacks (tonic-atonic seizures) and the parental global evaluation of improvement in seizure severity.

Three amendments to the original protocol were implemented:

(1) dated 10 August 1994, after enrollment had reached about 40%: the minimum eligibility age range was reduced from 4 to 3 years;
(2) dated 18 May 1995, after enrollment had reached about 50%:
   (a) the minimum age was dropped to 12 months and the maximum raised from 30 to "no upper age limit";
   (b) subjects who had discontinued a ketogenic diet 1 month prior to the study could now be enrolled (earlier subjects had to have discontinued 6 months prior to enrollment); and
   (c) centrally acting sympathomimetics and felbamate were disallowed;
(3) dated 16 September 1995: use of benzodiazepines (except as AEDs) was excluded.

INCLUSION/EXCLUSION CRITERIA: Males and females, ≥12 months, weight ≥11.5 kg,with a diagnosis of Lennox-Gastaut characterized by EEG tracings showing slow spike-and-wave patterns, atypical absence seizures and drop attacks (in addition to other types), and at least 60 seizures during the month before baseline. Tables 1 and 2 delineate the inclusion/exclusion criteria.

POPULATION: 112 subjects (mean age 10.5 years, age range: 2-42 years) were enrolled in the baseline phase at 12 US centers, 98 of whom were randomly assigned to treatment (n_{TOP}=48; $n_{placebo}$=50) and included in the ITT analysis. The 48 TOP patients included 40 pediatric (aged 2-16) and 8 adult; the placebo arm had 41 pediatric and 8 adult subjects.

For the 14 subjects who were enrolled but not randomized, explanations for not entering the double-blind phase include: incomplete seizure count (1), insufficient seizure count (1), parental decision not to enroll patient (4), patient moved out of state (1), seizures needing further clarification by video EEG (1), reasons not available (6); see v 21/168, p 90).

More subjects (98) were randomized than projected in the original estimate (80) provided in the protocol. The sponsor explains (v 21, p 40) that there were already a number of potential subjects already screened for the study at the time the cohort approached the planned enrollment size of 80 and investigators were notified to stop enrollment; "it was thought . . . unethical to

disallow entry to those subjects" (v 21, p 40).

Tables 5a and 5b display demographic and baseline characteristics. With respect to demographic differences between treats and placebo, the median baseline seizure rate were was higher for study drug, but the mean was greater for the placebo group. Nevertheless, seizure types were similar in both groups, particularly for drop attacks. As for racial make-up, there were insignificant numbers of blacks, American Indians, and other groups in either treatment arm.

The profiles of concomitant medications appeared fairly comparable between treatment arms. The most common non-anticonvulsants were analgesics (*eg*, acetaminophen, ibuprofen), vitamins, and nutritional supplements (v 21/168, pp 44).

WITHDRAWALS: 97 of 98 subjects randomized to treatment completed double-blind therapy. Subject 143, a 4-year-old male in the TOP arm who returned two months late for the final visit of the double-blind phase, was deemed a premature withdrawal by the investigator. The stated reason for the withdrawal was difficult family circumstances. Furthermore, there was uncertainty about dosing compliance and completeness of data. For analysis purposes, however, the subject was included as if he took study medication for the planned 77 days of the double-blind treatment phase, and seizure counts were estimated from the data provided in the final visit (v 21/168, p 44).

PROTOCOL DEVIATIONS: 3 subjects (numbers 28, 50, and 68) on placebo and 4 (numbers 14, 29, 32, and 85) on TOP received more than two AEDs during the baseline and double-blind phases of the study (v 21/168, p 45).

DOSAGE FORM: TOP was supplied as 25-mg (Batch R4568) and 100-mg (Batches R4561, R5509, R5512) tablets. The total daily (target) dosage was 6 mg/kg/d administered bid in equal doses.

OUTCOME MEASURES:

PRIMARY: *EITHER* (1) percent reduction in the average monthly seizure rate for all seizures
OR (2) a *compound variable* consisting of percent reduction in drop attacks (tonic-atonic seizures); only those subjects having drop attacks during the baseline phase were to be included
and
the parental global evaluation of improvement in seizure severity.

SECONDARY: (1) Percent treatment responders for all seizures
(2) Percent treatment responders for drop attacks (tonic-atonic seizures)

PLANNED ANALYSIS: Sample size was estimated by reference to percent reduction in seizure rates. The sample size needed in each group to detect a 30% difference in percent reduction in seizure rates from baseline between the two groups was calculated to be about 40, given a Type I error level of 5%, a power of 80%, and a standard deviation of 70%.

Group differences in percent reduction in seizure rates from baseline were, according to the plan in the protocol, to be examined by an analysis of variance on ranks, with treatment and investigator as factors. Treatment by investigator interactions were to be assessed further if the p-value were less than 0.10. Caregiver global evaluations were to be analyzed by means of Mantel-Haenszel methodology. Demographic, laboratory, vitals, EKG, and adverse event data were to be summarized descriptively (see v 22/168, p 346).

PERFORMED ANALYSIS: Primary efficacy analyses included the ITT population of all randomized subjects and used all data from both the baseline and double-blind (titration and maintenance) phases. Secondary analyses used only maintenance period data.

Average monthly (28-day) seizure rated were computed for both the baseline and double-

blind phases as 28 times the total number of seizures reported during the period divided by the number of days.

A two-way analysis of variance on ranks (with treatment and investigator as factors) was used to analyze treatment group differences in percent reduction from baseline seizure rate (SAS procedure for General Linear Model). The analysis of total seizures included all seizure types. However, as specified in the protocol, only those subjects having drop attacks during the baseline phase were included in the analysis of percent reduction in the drop-attack rate. Table 5b shows that 49/50 (98%) placebo, and 46/48 (96%) TOP, patients registered drop attacks during both the baseline and double-blind phases and so were included in the analysis.

The parental global evaluation of improvement in seizure severity was analyzed by exact Wilcoxen rank-sum tests with and without stratification by center. StatXact was used for this analysis, and all statistical tests were two-sided.

Not specified in the protocol was the comparison of treatment groups with respect to percent treatment-responders for all seizures and drop attacks. This analysis used the Cochran-Mantel-Haenszel method, stratified by center (v 21/168, pp 37-38).

COMPLIANCE: Plasma concentrations of TOP and concomitant AEDs were considered to be the most reliable indicators of compliance. According to the sponsor, these were "reasonably constant . . . throughout the maintenance period of the study" (v 21/168, p 44; for details, see v 23/168 pp 776-8 [Appendices 3.3.3] and pp 800-41 [Appendix 3.4.2]).

RESULTS: All 98 subjects (n_{TOP}=48; $n_{placebo}$=50) who entered the double-blind phase of the trial were included in the analysis of total seizure rate reduction. For the analysis of reduction in drop attacks (tonic-atonic seizures), only subjects who had tonic-atonic seizures during baseline were included, as described in the protocol.

There was only one premature withdrawal, subject 143 (TOP arm), who returned late for the final visit and about whom dosing compliance and completeness of data were uncertain. This subject was included as if he took study medication for the planned 77 days of the double-blind treatment phase, and seizure counts were estimated from data provided in the final visit.

With respect to the first primary efficacy variable, namely, percent reduction in the average monthly rate for all seizures (all types combined), the median percent reduction from baseline in the average seizure rate was 20.6% for TOP subjects and 8.8% for placebo, a difference that was not statistically significant.

When the compound efficacy variable is considered, however, both components demonstrated a statistically significant difference in favor of TOP (see Table 12). The median percent *reduction* in average monthly rate for drop attacks for the TOP group was 14.8%, as compared to an *increase* in average monthly seizure rate of 5.1% for placebo (p=0.041); see Figure 4. The analysis of drop attacks only included subjects who had drop attacks at baseline and during the double-blind phase. Table 5b shows that 49/50 (98%) of placebo, and 46/48 (96%) of TOP, patients registered drop attacks during both periods.

Additionally, Table 7 shows that the second component of the compound efficacy variable, or the parental global evaluation of improvement in seizure activity, also favored TOP over placebo: 52% to 28%, respectively, experienced an improvement in the severity of their seizures (p=0.037). Figure 2 shows no statistically significant treatment-by-center interaction ($p \geq 0.10$; according to the sponsor, results by center were more variable at centers with fewer subjects), but there was a trend in favor of TOP over placebo for reduction in drop attacks (8/12 centers; p=0.247); see v 21/168, p 48.

Although the statistically significant improvement in both components of the compound efficacy variable demonstrates drug effectiveness for the Lennox-Gastaut syndrome (see Table 6), the "either/or" endpoint design of the study provides no control over the possibility of a Type I error. The inflation depends upon the correlation between the three components of the primary efficacy endpoints, and there is at most a 10% chance for error.

Nine months (29 April 1998) after submitting the sNDAs, the sponsor forwarded a *post-*

hoc analysis (data dredging) which it feels further limits the Type I error. The argument centers on dividing the alpha in half, one-half for the first primary variable, one-half for the second compound variable -- a method not provided for by the protocol-defined analysis. To avoid "the need of having to interpret the significance of p-values using point estimates," the sponsor adopts "the overall one-sided significance level of 0.025 for superiority."

> The p-values for the percent reduction in seizure rates for all seizures, percent reduction in drop attacks, and parental global evaluation of severity are 0.2150, 0.0204, and 0.0298, respectively, all in favor of TOP. To determine if the results reach statistical significance at the overall significance level of 0.025, the Bonferroni adjustment states that the significance level for the percent reduction in seizure rate for all seizures or for the compound variable. . . is 0.0125. . . .
>
> To further determine the significance level for each individual component of the compound variable, the joint randomization of the p-values under the null for the percent reduction in drop attacks and parental global evaluation of seizure severity was obtained from a random sample of 20,000 re-randomizations. . . . The correlation between the p-value of the two individual components is 0.3036. The one-sided significance level for each individual component is 0.0721 such that the false positive rate for the significance for both components at level 0.0721 is 0.0125. The trial has therefore succeeded in the compound variable of percent reduction in drop attacks (p-value=0.0204 < 0.0721) and parental global evaluation of seizure severity (p-value=0.0298 < 0.0721). Note that the significance levels would be 0.1118 or 0.0125 if the two individual components were independent or 100-percent positively correlated, respectively.
>
> To assess the strength of evidence for the efficacy of TOP that the trial has demonstrated, different overall significance levels were used. The significance levels for the individual components of the compound variable were 0.0640, 0.512, and 0.040 for the overall significance level of 0.020, 0.015, and 0.010, respectively. Thus, the above findings that hold for the overall significance level of 0.0250 also hold for significance levels of 0.020, 0.015, and 0.010. The smallest overall significance level for which the above findings will still hold is 0.0065 where the corresponding significance level for the individual component of the compound variable is 0.0307.
>
> *In summary, the trial was successful at the overall one-sided significance level of 0.0065 for superiority. . . .*

This analysis is very problematic: from what percent of possible re-randomizations is the sponsor's random sample derived? The sponsor has performed a *post-hoc* analysis, selecting particular values that would corroborate his findings.

Finally, secondary outcome measures failed to reach statistical significance; see Table 8. For all seizures, the percentage of treatment responders (≥50% seizure rate reduction) was almost identical for TOP and placebo groups, 17% vs 16%, respectively. With regard to drop attacks, however, there was a trend in favor of TOP: 28% in the TOP group were responders, compared to 14% in the placebo (p=0.071).

PHARMACOKINETIC DATA: The median by-subject average TOP dose over the entire double-blind period (titration and maintenance) was 5.1 mg/kg/d (see Table 13). The median average TOP dose during maintenance was 5.8 mg/kg/d (see Table 14). 41 (85%)TOP, and 46 (92%)placebo, patients achieved their target dose at some time during the trial. 34 (71%)TOP , and 46 (92%) placebo, patients achieved their target dose and completed maintenance at that dose. The median per-protocol duration of the double-blind phase was 77 days; the median duration of double-blind therapy was 78.5 days for the TOP, and 79 days for the placebo, group (see Table 15).

Mean changes in plasma concentrations of each concomitant AED from the baseline to the double-blind phase were small and not statistically significant between TOP and placebo patients (see Table 10).

Furthermore, Table 11 reveals no consistent relationship between plasma TOP concentration and clinical efficacy endpoints (percent seizure rate reduction and percent treatment responders). No significant correlation was detected between plasma TOP concentrations and percent reduction in average monthly rate for all seizures or for drop attacks (see Table 11).

SUBGROUP ANALYSES: The ratio of male-to-female representation was relatively close in both the drug-treated and placebo groups; see the demographics in Table 5b. The crude percentage rates shown in Attachment 5.4 (v 21/168, pp 141-42), comparing the two groups in terms of median seizure reduction, would lead to the conclusion that both did well on TOP. No differences (v 21/168, p 50) with regard to effectiveness or safety issues were noted for gender or age (though only 8 adult treats vs 9 placebo were included in the study; see below).

The numbers of blacks and representatives of other racial groups were too few for any meaningful assessments and comparisons.

CONCLUSION FOR LENNOX-GASTAUT TRIAL: This study poses two problems which will now be summarized. The first is the failure to attain statistical significance on both efficacy components, providing no control over the possibility of a Type I error. Despite the lower standard of evidence (statistically borderline), I believe that the drug should be approved for this indication. Lennox-Gastaut Syndrome is a terrible disease, of which prognosis is guarded and seizures achieve, at best, poor-to-modest control with even the best regimen (see K. Ferrell, "Secondary Generalized Epilepsy and Lennox-Gastaut Syndrome," in E. Wylie, *The Treatment of Epilepsy: Principles and Practice* [Philadelphia: Lea & Febiger, 1993], pp 604-11). Only one anticonvulsant, Felbatol, has to date received FDA approval; a second, Lamictal, is in the approvable stage. Both are associated with serious toxicities -- aplastic anemia in the case of Felbatol, requiring special informed consent forms for its usage, and hospitalizable rash in the case of Lamictal. Furthermore, one must consider that TOP has been shown to be effective in other seizure types, such as partial-onset in adults and children. TOP could potentially be an important addition to the neurologist's limited armamentarium.

The second problem involves questions of efficacy for the affected adult population. Few adults (8 treats in all) were included in the trial. The actual clinical definition of the Lennox-Gastaut Syndrome is by EEG criteria: "EEG findings have been crucial in the individualization of the Lennox-Gastaut Syndrome as a clinical entity. The outstanding feature is the slow spike-wave complex ranging from 1 to 2.5/sec. . . ." (E. Niedermeyer, F. Lopes Da Silva, *Electroencephalography,* 3rd ed. [Philadelphia: Williams & Wilkins, 1993], p 497; see also K. Ferrell, "Generalized Tonic and Atonic Seizures," and "Secondary Generalized Epilepsy and Lennox-Gastaut Syndrome," in E. Wylie, *The Treatment of Epilepsy: Principles and Practice* [Philadelphia: Lea & Febiger, 1993], pp 443-49, 604-11). Similar EEG changes herald the onset of Lennox-Gastaut Syndrome in adolescence and adulthood (albeit rare at those stages) as in infancy and early childhood. Therefore, by the EEG definition of the clinical entity, the syndrome should be the same, no matter the age group, and TOP should be approved for both children and adults to treat drop attacks of the Lennox-Gastaut Syndrome.

(c) Generalized Tonic-Clonic Seizures

(1) Introduction

Two multicenter, randomized, double-blind, placebo-controlled studies (identical design) were conducted (YTC with 18 sites in the US and Costa Rica, YTCE with 16 sites in the US and Europe), to evaluate TOP in the treatment of uncontrolled primary generalized tonic-clonic seizures (tonic-clonic seizures considered to be generalized from the onset) with or without other generalized seizures subtypes (hereafter referred to as PGTC seizures).

(2) YTC

TRIAL DESIGN: This Phase 3, multicenter (18 centers, 18 investigators), randomized, double-blind, placebo-controlled study was conducted in the United States (17 sites) and Costa Rica (1 site) during the period 5/4/94-7/5/96. Its aim was to evaluate topiramate as adjunctive therapy in subjects with uncontrolled primary generalized tonic-clonic seizures with or without other generalized seizure subtypes. Maximum total daily (target) doses of TOP, based on subject weight, were 175 mg/day (25-33.9 kg), 225 mg/day (34-42.9 kg), and 400 mg/day (≥43 kg), to approximate 6 mg/kg/day (theoretical range: <9.3 mg/kg/d).

The trial was divided into two phases (see Figure 1): baseline (56 days) and double-blind (140 days). During the baseline period, subjects received a constant dose of one or two anticonvulsants (AEDs), and the number and type of seizures were monitored on this regimen. Subjects met eligibility requirements for the double-blind portion if they had ≥3 PGTC seizures during the 56 days (at least one during each 28-day period), with at least one seizure per 28-day period. Those who were eligible were randomized in equal proportions at each center to placebo or topiramate arms while continuing their baseline AEDs.

The double-blind portion consisted of two phases: titration (56 days) and stabilization (84 days). Study drug was titrated to the subject's assigned (target) dose or maximum tolerated dose as follows: during the first 28 days, TOP dosing was instituted as a single evening 50 mg dose, and thereafter increased to maximum daily dosages in two divided doses (see Table 3 for dosing schedules; Table 4 for a schedule of trial procedures). Target doses could be altered, depending on toleration; Tables 20 and 21 lists treatment-emergent AEs necessitating dosage adjustments. Subjects then continued on this regimen for the 84 days of the stabilization period (see Tables 15a, 15b, and 16 for dosage data during the double-blind and stabilization periods; Table 17 provides information about the duration of the double-blind portion).

All patients completing the stabilization period were permitted to enter an open-label extension. Those who chose not to do so or discontinued prematurely had their study drug tapered off.

No formal protocol amendments were made. However, a change in trial conduct was implemented to increase enrollment, permitting subjects to reduce the duration of the baseline phase if they could provide seizure information (based on personal records) that totaled 56 days of seizure information (*retrospective* seizure data) when added to their prospective baseline experience (*prospective* seizure data). This change affected 20 subjects (10 placebo, 10 TOP).

INCLUSION/EXCLUSION CRITERIA: Males and females, ≥4 years of age, weight >25 kg. Tables 1 and 2 delineate the inclusion/exclusion criteria.

POPULATION: 103 subjects were enrolled in the baseline phase, of whom 80 were randomly assigned to treatment (n_{TOP}=39; $n_{placebo}$=41). and included in the ITT analysis. Included among 39 TOP patients were 8, and among 41 placebo patients 13, pediatric subjects (aged 2-16).

With respect to the 23 subjects who were enrolled but not randomized, 9 were found ineligible during the baseline phase (8 due to an inadequate number of seizures; 1, AED medication change) and 13 were administrative exclusions (2 due to low body weight; 1, diagnosis of partial-onset seizures; 1, renal calculi history and unstable diabetes; 2, noncompliance; 1, history of brain abscess; 1, history of suicide attempt; 2 by subject choice; and 3 for reasons unspecified. See v 29/168, p 95).

Planned duration of the double-blind phase was 140 days, and the median duration for the two treatment groups was 142 days for TOP and 141 for placebo (see Table 17).

Tables 6a and 6b display demographic and baseline characteristics. Differences between treats and placebo included: (1) median body weight, according to which TOP patients were 10 kg heavier than placebo; and (2) the *mean/SD* and *range* for the category of all seizures, which show an imbalance between groups due to a single outlier with an average monthly seizure rate exceeding 79,000 (a figure difficult to believe), but the *medians* were very similar. Over 66% of randomized subjects had generalized tonic-clonic seizures, in addition to one or more other generalized seizures types. Rates for individual seizures types were similar between the two

groups.

Males and females were adequately represented, in terms of percentages, in both groups. As for racial make-up, there were small numbers of blacks (6 treats and 5 placebo) and only 1 representative from "other" racial groups (in the TOP arm).

The profiles of concomitant medications appeared fairly comparable between treatment arms. The most common non-anticonvulsants among placebo subjects were analgesics, antibiotics, nasal preparations, and vitamins; (v 33/168; pp 1180-1250).

WITHDRAWALS: Figure 2 provides a study completion and withdrawal summary for the randomized double-blind trial phase; Table 7 categorizes the dropouts. 72/80 randomized subjects completed double-blind therapy: 3 placebo and 5 TOP subjects prematurely dropped out (subject choice: 1 placebo, 2 TOP; limiting adverse event: 1 in each group; lost to follow-up: 1 placebo; and other: 2 TOP). Of these, 1 placebo and 2 TOP subjects completed all clinical visits and were therefore deemed to have completed the trial per protocol. Individual reasons for premature withdrawal are shown in Table 8.

PROTOCOL DEVIATIONS: 46 subjects (20 placebo, 24 TOP) had protocol deviations. 20 (10 placebo, 10 TOP) were randomized prior to completing the 56-day baseline phase. 21 (10 placebo, 11 TOP) were randomized, despite maintenance on more than two concomitant AEDs. In addition, 1 TOP subject was discontinued due to noncompliance with study drug and concomitant AED; 1 TOP subject prematurely advanced to the open-label extension because of a pharmacist's error in dispensing medication; and 1 TOP subject experienced complex partial seizures during the baseline phase and was subsequently randomized to the double-blind phase.

DOSAGE FORM: TOP was supplied as 25-mg (batch R5489) and 100-mg (batch R5509) tablets. Maximum doses, based on subject weight, were 175 mg/day (25-33.9 kg), 225 mg/day (34-42.9 kg), and 400 mg/day (≥43 kg), to achieve a total daily (target) dosage of 6 mg/kg/d, administered bid in equal doses.

OUTCOME MEASURES:

PRIMARY: "percent change in PGTC seizures during the double-blind phase as compare to the baseline phase. The study will be considered positive if the PGTC seizure rate has decreased significantly compared to placebo during the double-blind phase" (v 41/168, p 576).

SECONDARY: (1) Percent reduction from baseline in average monthly seizure rate during the double-blind phase for all seizures.

(2) Percent treatment responders for PGTC seizures, defined ≥50% reduction in baseline seizure rate during the double-blind phase.

(3) Global evaluation of seizure severity, completed by the subject or caregiver and assessing improvement in seizure severity at the end of the double-blind phase compared to the beginning of the titration period.

PLANNED ANALYSIS: Sample size was estimated by reference to percent reduction in seizure rates. The sample size needed in each group to detect a 30% difference in percent reduction in PGTC seizure rates from baseline between the two groups was calculated to be about 36 (total study population: 72), given a Type I error level of 5%, a power of 80%, two-sided test, and a population standard deviation of 45%.

Group differences in percent reduction in seizure rate from baseline, according to protocol, were to be examined using a two-way analysis of variance, with treatment and investigator as factors. Seizure rates, based on all seizures, were to be summarized by treatment groups. Group differences in responders, based on PGTC seizures, were to be analyzed using logistic regression methods. Treatment by investigator interactions were to be assessed further if the p-value were less than 0.10. Caregiver global evaluations were to be analyzed by means of Mantel-Haenszel

methodology. Demographic, laboratory, vitals, EKG, and adverse event data were to be summarized descriptively (see v 31/168, pp 27-28).

PERFORMED ANALYSIS: The primary efficacy analysis included the ITT population of all randomized subjects and used data from baseline and double-blind phases (both titration and stabilization periods) up to study drug discontinuation. Secondary analyses used data only from the stabilization period (beginning on Day 57 of the double-blind phase) but employed identical methodologies.

The average monthly (28-day) seizure rates were computed for both the baseline and double-blind phases and calculated as 28 times the total number of seizures reported during the period divided by the total number of days in the period. The double-blind phase seizure rate was defined, for each subject, as the average seizure rate over the entire double-blind phase. The percent reduction in PGTC seizure rate was defined as 100(B-D)/B, where B represents the baseline PGTC seizure rate and D the double-blind PGTC seizure rate. A two-way analysis of variance on ranks (with treatment and center as factors) was used to evaluate treatment group differences in percent reduction from baseline seizure rate. SAS procedure for General Linear Model was used in this analysis. Percent reduction in seizure rate was similarly analyzed for all seizures.

Centers with low enrollment ($\leq$6 subjects) were pooled and included as single analysis centers, with each analysis center not exceeding the size of the largest center (13). The algorithm ranked all centers in order of total sample size and then alphabetically within sample size.

An additional secondary efficacy assessment compared treatment groups with respect to percent of PGTC responders (defined as $\geq$50% reduction in PGTC seizures), stratified by center, using the Cochran-Mantel-Haenszel method. This analysis was also performed based on all seizures.

Global evaluation of improvement in seizure severity was analyzed by exact Wilcoxen rank-sum test, unstratified and stratified by center, employing StatXact.

All statistical tests were two-sided. The significance levels employed for evaluating the effects of the covariate and the interaction term were 0.05 and 0.10, respectively.

COMPLIANCE: Plasma concentrations of TOP and concomitant AEDs were considered to be the most reliable indicators of compliance. According to the sponsor, these were "reasonably constant . . . throughout the maintenance period of the study" (v 32/168, p 48; for details, see v 43/168 pp 1114-19 [Appendix 3.3.4 for TOP concentrations] and v 33/168 pp 1147-76 [Appendix 3.4.2 for concomitant AED concentrations]).

RESULTS: 103 subjects were enrolled in the baseline phase, of whom 80 were randomly assigned to treatment (n_{TOP}=39; $n_{placebo}$=41) and included in the ITT analysis. Planned sample size in the initial protocol had been 36 per treatment group, which was estimated to be adequate to detect a 30% between-group difference in PGTC seizure rate, given assumptions of a 5% Type I error level, 80% power, and 45% population standard deviation.

Of the 80 subjects entering the double-blind phase (41 randomized to placebo, 39 to TOP), one placebo subject (number 161) had no PGTC seizures during baseline or the double-blind phase and was therefore omitted in the intent-to-treat efficacy analysis for variables based on PGTC seizures; given the definition of percent reduction in PGTC seizure rate (100[B-D]/B, where in this case B=0; see above), he could not mathematically be assigned a value. For all other efficacy variables, however, all 80 subjects were included in the ITT analyses. With regard to the 8 premature withdrawals (see Table 8), seizure data were averaged for that portion of the double-blind phase completed up to the time study treatment was discontinued.

ITT analyses include PGTC seizures and all seizures from the prospective portion of the baseline phase (up to 8 weeks) and the entire double-blind phase of the study (or up to study drug discontinuation for premature withdrawals). Efficacy analyses were conducted using only data from the stabilization period. Additional efficacy analyses of the entire double-blind phase and

stabilization period were also conducted using all baseline seizure data (retrospective and prospective seizure data), and including seizures recorded after study treatment discontinuation. According to the sponsor, the results of all efficacy analyses for the stabilization period were similar overall to those for the double-blind phase; also similar were the results when seizures recorded after therapy discontinuation, as well as when retrospective baseline date, were included.

As to the primary efficacy variable (see Tables 9, 10b, and 14 for tabulated results; Figure 4, for Kaplan-Meier curves), the percent reduction from baseline in the average monthly PGTC seizure rate during the double-blind phase, TOP subject experienced a median percent reduction of 56.7%, vs 9.0% for placebo, a statistically significant result in favor of TOP ($p=0.019$).

Statistical significance favoring TOP was also seen for the secondary efficacy endpoint of median percent reduction from baseline for all seizures during the double-blind phase: TOP subjects experienced a median percent reduction of 42.1%, compared to 9.0% for placebo ($p=0.003$).

The relative treatment differences was consistent across all centers (see Figure 3). No treatment-by-center interactions were detected between placebo and TOP groups with respect to PGTC seizures ($p=0.796$) or all seizures ($p=0.584$).

Other secondary efficacy categories were treatment responders and the global evaluation of improvement in seizure severity. With respect to treatment responders, defined as $\geq$50% reduction from baseline in seizure rate during the double-blind phase, 56% TOP subjects vs 20% placebo could be classified as responders for PGTC seizures ($p=0.001$), and 46% TOP subjects vs 17% placebo as responders for all seizures ($p\leq0.003$). Both results were statistically significant in favor of treatment (see Table 10a). No treatment-by-center interactions were detected between placebo and TOP groups with respect to PGTC or all seizures ($p\geq0.677$). If treatment response is defined as $\geq$75% seizure rate reduction (not a protocol-defined secondary outcome measure), 33% TOP vs 13% placebo subjects were responders for PGTC seizures ($p=0.037$), and 26% TOP vs 7% placebo subjects were responders for all seizures ($p=0.026$). Again, both are statistically significant in favor of treatment.

With regard to the subject's global evaluation of seizure severity, 62% TOP vs 56% placebo subjects showed a subjective improvement (minimal, moderate, or marked), which was not statistically significant ($p=0.490$). Nevertheless, more TOP subjects classified their improvement as marked (21% vs 7% for placebo; see Table 11).

During the double-blind phase, 13% TOP vs 5% placebo remained free of PGTC seizures ($p=0.225$), and 5% TOP vs 0% placebo subjects free of all seizures ($p=0.173$) -- both categories (not protocol-defined endpoints), while not statistically significant, demonstrated a numerical trend in favor of TOP.

Although other seizure types -- except for absence and tonic -- were not adequately represented (see Table 6b), median percent reduction from baseline in average monthly seizure rate numerically favored TOP over placebo for absence (53% vs 4%), myoclonic (52% vs an increase of 40%), and tonic (28% vs an increase of 1%).

PHARMACOKINETIC DATA: Median average dosage during the double-blind phase (titration and stabilization) was 3.7 mg/kg/day for TOP subjects, and during the stabilization period 5.1 mg/kg/day. 36 (88%) placebo and 36 (92%) TOP subjects achieved their target dosage at some point in the study (see Tables 15a and 15b); 34 (83%) placebo and 30 (77%) TOP subjects completed stabilization at that dosage (see Table 16).

The mean TOP plasma concentration over the entire double-blind period (titration and stabilization) was 5.1 ug/ml (v 29/168, p 49). Efficacy results within the two higher concentration strata were similar and exceeded those in the lowest concentration stratum (see Table 13).

A mean decrease in the plasma concentration of carbamazepine (-1.4 ug/ml) was noted and is, according to the sponsor, "not in a direction that would be expected to favor TOP in treatment comparisons" (v 29/168, p 60). Mean changes from baseline in plasma concentrations of other concomitant AEDs were small and not statistically significant between TOP and placebo patients (see Table 12).

SUBGROUP ANALYSES: The ratio of male-to-female representation was relatively close in both the drug-treated and placebo groups; see the demographics in Table 6b. Crude percentage rates were not provided in the NDA comparing the two groups in terms of median seizure reduction. However, no differences with regard to effectiveness or safety issues were noted for gender, according to a phone conversation with the sponsor on 2/10/98 (Catherine Glenkowski, covering for Michael Kaufman, Joe Ward [medical writer], and Judy Smith [statistician]).

Racial representation was sparse, and no conclusions can therefore be reached about the effect of topiramate on groups other than whites.

When the pediatric populations of both YTC and YTCE were pooled, the number of patients provided a large enough subgroup to evaluate. The results are noted in the Summary below.

(3) YTCE

TRIAL DESIGN: This Phase 3, multicenter (16 centers, 16 investigators), randomized, double-blind, placebo-controlled study was conducted in the United States (six sites, 31 subjects) and Europe (10 sites, 49 subjects) during the period 9/15/94-11/12/96. Its aim was to evaluate TOP as adjunctive therapy in subjects with uncontrolled primary generalized tonic-clonic seizures with or without other generalized seizure subtypes. Maximum total daily (target) doses of TOP, based on subject weight, were 175 mg/day (25-33.9 kg), 225 mg/day (34-42.9 kg), and 400 mg/day (≥43 kg), to approximate 6 mg/kg/day (theoretical range: <9.3 mg/kg/d).

The trial was divided into two phases (see Figure 1 and Table 4): baseline (56 days) and double-blind (140 days). During the baseline period, subjects received a constant dose of one or two anticonvulsants (AEDs), and the number and type of seizures were monitored on this regimen. Subjects met eligibility requirements for the double-blind portion if they had ≥3 PGTC seizures during the 56 days (at least one during each 28-day period), with at least one seizure per 28-day period. Those who were eligible were randomized in equal proportions at each center to placebo or TOP arms while continuing their baseline AEDs.

The double-blind portion consisted of two phases: titration (56 days) and stabilization (84 days). Study drug was titrated to the subject's assigned (target) dose or maximum tolerated dose as follows: during the first 28 days, TOP dosing was instituted as a single 50 mg evening dose, and thereafter increased to maximum daily dosages in two divided doses (see Table 3 for dosing schedules). Target doses could be altered, depending on toleration; Table 21 lists treatment-emergent AEs necessitating dosage adjustments and Table 20 reasons for study drug discontinuation. Subjects then continued on this regimen for the 84 days of the stabilization period (see Table 17 for information about duration of the double-blind portion).

All patients completing the stabilization period were permitted to enter an open-label extension. Those who chose not to do so or discontinued prematurely had their study drug tapered off.

No formal protocol amendments were made. However, a change in trial conduct was implemented to increase enrollment, permitting subjects to reduce the duration of the baseline phase if they could provide seizure information (based on personal records) that totaled 56 days of seizure information (*retrospective* seizure data) when added to their prospective baseline experience (*prospective* seizure data). This change affected 26 subjects (15 placebo, 11 TOP).

INCLUSION/EXCLUSION CRITERIA: Males and females, ≥4 years of age, weight >25 kg. Tables 1 and 2 delineate the inclusion/exclusion criteria.

POPULATION: 87 subjects were enrolled in the baseline phase, 80 of whom were randomly assigned to treatment (n_{TOP}=40; $n_{placebo}$=40). Included among the 40 TOP patients were 9, and among the 40 placebo patients 2, pediatric subjects (aged 2-16).

With respect to the 7 subjects who were enrolled but not randomized, 4 were found

ineligible during the baseline phase (less than 3 PGTC seizures) and 3 were administrative exclusions (1 screening failure (reason?); 1 failed to attend Visit 3 and did not take study treatments; 1 not randomized "due to some misunderstanding"; see v 39/168, p 111).

Planned duration of the double-blind phase was 140 days, and the median duration for each of the two treatment groups was 141 days. 77% of subjects had greater than 19 weeks (133 days) of double-blind treatment (see Table 17).

Tables 6a and 6b display demographic and baseline characteristics. There was one notable demographic imbalance between treats and placebo: the rate of baseline PGTC seizures and all seizures was higher in the TOP group. This problem is discussed at length in the Results section below. There were similar rates for most seizure types, except for atypical absence which was higher in the TOP group.

Males and females were adequately represented, in terms of percentages, in both groups. As for racial make-up, there were insignificant numbers of blacks (only 1 in the TOP group) and no representatives from other racial groups in either treatment arm.

The profiles of concomitant medications appeared fairly comparable between treatment arms. The most common non-anticonvulsants among placebo subjects were analgesics (acetaminophen [13 subjects], ibuprofen [4]); among TOP, analgesics (acetaminophen [5]), vitamins (5), and medroxyprogesterone acetate (4); (v 43/168, pp 1236-1306).

WITHDRAWALS: 60/80 subjects randomized to treatment completed the double-blind phase. Premature discontinuations numbered 11 in the placebo and 9 in the TOP group. Of these, 12 (7 placebo, 5 TOP) discontinued due to limiting adverse events, and 1 placebo subject died suddenly during the study (SUDEP). Table 8 delineates the reasons for withdrawal.

PROTOCOL DEVIATIONS: 31 subjects (16 placebo, 15 TOP) had deviations from the inclusion/exclusion criteria. 26 (15 placebo, 11 TOP) were randomized prior to completing the 56-day baseline phase. 8 (4 placebo, 4 TOP) were randomized, despite maintenance on more than two concomitant AEDs; and 2 in the TOP group, even though they had recently completed another experimental drug regimen (nitrazepam and clobazam). 1 TOP subject (number 39) was randomized to treatment even though he had no PGTC seizures during baseline; and 1 placebo subject, despite a history of attempted suicide. Incorrect dose treatments were found among 5 TOP subjects: 3 were assigned to a target dose of 400 mg/day, though their weights were 28.2, 41.4, and 28.2 kg; 2 took an overdosage (800 mg/day for 84.2 kg body weight, 1,200 mg/day for 84.9 kg).

DOSAGE FORM: TOP was supplied as 25-mg (US: batch R4993; Europe: batches 911 301, 913 410) and 100-mg (US: batch R6147; Europe: batches 909 301, 916 410, 917 410) tablets. Maximum doses, based on subject weight, were 175 mg/day (25-33.9 kg), 225 mg/day (34-42.9 kg), and 400 mg/day (≥43 kg), to achieve a total daily (target) dosage of 6 mg/kg/d, administered bid in equal doses.

OUTCOME MEASURES:

PRIMARY: "Percent change in PGTC seizures during the double-blind phase as compared to the baseline phase. The study will be considered positive if the PGTC seizure rate has decreased significantly compared to placebo during the double-blind phase" (v 41/168, p 576).

SECONDARY: (1) Percent reduction from baseline in average monthly seizure rate during the double-blind phase for all seizures.

(2) Percent treatment responders for PGTC seizures, defined as ≥50% reduction in baseline seizure rate during the double-blind phase.

(3) Global evaluation of seizure severity, completed by the subject or caregiver and assessing improvement in seizure severity at the end of the double-blind phase compared to the beginning of the titration period.

PLANNED ANALYSIS: Sample size was estimated by reference to percent reduction in seizure rates. The sample size needed in each group to detect a 30% difference in percent reduction in PGTC seizure rates from baseline between the two groups was calculated to be about 36 (total study population: 72), given a Type I error level of 5%, a power of 80%, two-sided test, and a population standard deviation of 45%.

Group differences in percent reduction in seizure rate from baseline, according to protocol, were to be examined using a two-way analysis of variance, with treatment and investigator as factors. Seizure rates, based on all seizures, were to be summarized by treatment groups. Group differences in responders, based on PGTC seizures, were to be analyzed using logistic regression methods. Treatment by investigator interactions were to be assessed further if the p-value were less than 0.10. Caregiver global evaluations were to be analyzed by means of Mantel-Haenszel methodology. Demographic, laboratory, vitals, EKG, and adverse event data were to be summarized descriptively (see v 41/168, p 584).

PERFORMED ANALYSIS: The primary efficacy analysis included the ITT population of all randomized subjects and used data from baseline and double-blind phases (both titration and stabilization periods) up to study drug discontinuation. Secondary analyses used data only from the stabilization period (beginning on Day 57 of the double-blind phase) but employed identical statistical methodologies.

The average monthly (28-day) seizure rates were computed for both the baseline and double-blind phases and calculated as 28 times the total number of seizures reported during the period divided by the total number of days in the period. The double-blind phase seizure rate was defined, for each subject, as the average seizure rate over the entire double-blind phase. The percent reduction in PGTC seizure rate was defined as 100(B-D)/B, where B represents the baseline PGTC seizure rate and D the double-blind PGTC seizure rate. A two-way analysis of variance on ranks (with treatment, center, and baseline PGTC seizure rate as factors) was used to evaluate treatment group differences in percent reduction from baseline seizure rate. SAS procedure for General Linear Model was used in this analysis. Percent reduction in seizure rate was similarly analyzed for all seizures.

Centers with low enrollment ($\leq$6 subjects) were pooled and included as single analysis centers, with each analysis center not exceeding the size of the largest center (13). The algorithm ranked all centers in order of total sample size and then alphabetically within sample size.

An additional secondary efficacy assessment compared treatment groups with respect to percent PGTC responders (defined as $\geq$50% reduction in PGTC seizures), stratified by center and using the Cochran-Mantel-Haenszel method. This analysis was also performed based on all seizures.

Global evaluation of improvement in seizure severity was analyzed by exact Wilcoxen rank-sum test, unstratified and stratified by center, employing StatXact.

All statistical tests were two-sided. The significance levels employed for evaluating the effects of the covariate and the interaction term were 0.05 and 0.10, respectively.

COMPLIANCE: Plasma concentrations of TOP and concomitant AEDs were considered to be the most reliable indicators of compliance. According to the sponsor, these were "reasonably constant . . . throughout the maintenance period of the study" (v 39/168, p 51; for details, see v 43/168 pp 1194-98 [Appendix 3.3.4 for TOP concentrations] and pp 1212-32 [Appendix 3.4.2 for concomitant AED concentrations]).

RESULTS: 80 subjects entered the double-blind phase, 40 randomized to placebo and 40 to TOP. The ITT population, accepted for the purpose of analysis for variables based on PGTC seizures, consisted of 40 placebo and 39 TOP subjects. One TOP subject (number 39) had no PGTC seizures during baseline or the double-blind phase and was therefore omitted; given the definition of percent reduction in PGTC seizure rate (100[B-D]/B, where in this case B=0; see above), he

could not mathematically be assigned a value. For all other efficacy variables, however, all 80 subjects were included in the ITT analyses. With regard to the 20 premature withdrawals, seizure data were averaged for that portion of the double-blind phase completed up to the time study treatment was discontinued.

ITT analyses include PGTC seizures and all seizures from the prospective portion of the baseline phase (up to 8 weeks) and the entire double-blind phase of the study (or up to study drug discontinuation for premature withdrawals). Efficacy analyses were conducted using only data from the stabilization period. Additional efficacy analyses of the entire double-blind phase and stabilization period were also conducted using all baseline seizure data (retrospective and prospective seizure data), and including seizures recorded after study treatment discontinuation. According to the sponsor, the results of all efficacy analyses for the stabilization period were similar overall to those for the double-blind phase; also similar were the results when seizures recorded after therapy discontinuation, as well as when retrospective baseline date, were included.

With regard to the primary efficacy variable (percent reduction from baseline in average monthly PGTC seizure rate during the double-blind phase), TOP subjects experienced a 57.1% median percent reduction, compared to 33.2% for the placebo group (see Tables 9 and 10a, as well as Figure 4 for Kaplan-Meier graphs). Although the difference numerically favored TOP, the result was not statistically significant (p=0.124). The TOP group also had a greater median percent reduction from baseline for all seizures, 26% compared to 12.1% for placebo subjects, but the results were again not statistically significant (p=0.212).

Treatment-by-center interactions failed to achieve statistical significance for either percent reduction from baseline in PGTC seizures (p=0.250) or all seizures (p=0.781). The relative differences favoring TOP over placebo appeared consistent across centers (see Figure 3).

Efficacy summaries for each seizure type experienced during the double-blind phase favored TOP over placebo for myoclonic seizures (15.2% vs 5.5%) and absence seizures (-6.6% vs -16.1%). The number of subjects experiencing atypical absence, clonic, drop attack (including atonic), tonic, and other generalized seizures was too small (<8 in each treatment group) for meaningful comparisons (see Table 6b).

An analysis of treatment responders, defined as ≥50% reduction from baseline in seizure rate during the double-blind period, showed 54% responders in the TOP group vs 35% in the placebo (p=0.102) for PGTC seizures, and 40% of TOP subjects vs 20% for all seizures (p=0.061; see Table 10a). Treatment-by-center interactions were not statistically significant with respect to PGTC seizures (p=0.285) or all seizures (p=0.671). If, however, treatment response is defined as ≥75% reduction in PGTC seizure rate (*post-hoc* analysis), the difference between groups is statistically significant for both PGTC seizures (36% TOP subjects vs 15% placebo; p=0.040) and all seizures (30% TOP subjects vs 5% placebo; p=0.0005).

Another secondary efficacy measure, the global evaluation of seizure severity, did show statistical significance: 48% TOP subjects, compared to 33% placebo, reported subjective improvement (minimal, moderate, or marked) in seizure severity (p=0.026; see Table 11). Marked improvement was reported by 33% TOP subjects, but by none in the placebo group.

The reasons proposed by the sponsor to explain the lack of statistical significance in efficacy include (1) the imbalance in baseline PGTC seizure rate in favor of placebo (3 seizures/month for placebo vs 5 seizures/month for TOP); and (2) the higher number of placebo patients, compared to TOP, who reported efficacy-related results as safety assessments (3 placebo vs 1 TOP subject prematurely discontinued study medication because of aggravated convulsions). "Because of these efficacy-related discontinuations, the last-observation-carried-forward approach, which implicitly assumes uninformative censoring, becomes a more conservative approach as it may be somewhat biased against TOP" (v 39/168, p 103). However, the latter point would seem rather to favor the treatment arm.

Because of the imbalance in baseline PGTC seizure rate for the two groups, an additional analysis was conducted that included baseline PGTC seizure rate as a covariate. Efficacy variables considered included the percent reduction from baseline in PGTC seizure rate during the double-blind phase and percent responders based on ≥50% reduction in PGTC seizure rate. For percent reduction in PGTC seizure rate, the rank-based analysis method was employed with baseline

PGTC seizure rate as a covariate. The analysis of responders used logistic regression, with treatment, center, and baseline PGTC seizure rate as terms. Though not imbalanced at baseline, additional covariates, such as age and sex, were also considered, but had no important effect on the treatment comparisons.

The only covariate found to be statistically significant ($p<0.05$) for either analysis was baseline seizure rate: for PGTC responders, $p=0.016$, indicating TOP was superior to placebo, while the covariate (baseline seizure rate) was significantly associated with response ($p=0.002$) but the interaction between treatment and covariate was not ($p=0.693$). With regard to percent reduction from baseline in PGTC seizure rate, the baseline PGTC seizure rate had a weaker relationship with response ($p=0.078$); neither the covariate nor the interaction was statistically significant (v 39/168, p 63).

Finally, patient mental status was assessed by means of a questionnaire, "Global Evaluation of Mental Status," completed by subjects or their legal guardian at the first and final visits of the double-blind phase, with responses scored on a scale from 0 (worsening of mental status) to 4 (marked improvement). Comparison of the two questionnaires shows that most patients in either treatment group recognized no change (see Table 22).

PHARMACOKINETIC DATA: Median average dosage during the double-blind phase (titration and stabilization) was 3.6 mg/kg/day for TOP subjects, and during the stabilization period 5.1 mg/kg/day. 30 (75%) placebo and 29 (73%) TOP subjects achieved their target dosage at some point in the study (see Tables 15a and 15b); 24 (60%) placebo and 25 (63%) TOP subjects completed stabilization at that dosage (see Table 16).

The mean TOP plasma concentration over the entire double-blind period (titration and stabilization) was 5.3 ug/ml (c 39/168, p 53). The greatest reduction in PGTC seizures and in all seizures was seen in the middle plasma TOP concentration stratus (5.01-<9.67 ug/ml); see Table 13. No significant correlation was detected between TOP plasma concentration and percent reduction in average monthly PGTC seizure rate ($p=0.382$) or in the total seizure rate ($p=0.263$).

A *mean* decrease in the plasma concentration of valproic acid (-26.4 ug/ml) was noted and, according to the sponsor, was "consistent with previous pharmacokinetic data" ($p=0.189$) and "not in a direction that would be expected to favor TOP in efficacy comparisons" (v 39/168, p 65). This decrease, however, was effected by values from a single patient (discussed with Dr. Iftekar Mahmood, FDA Biopharm). Current labeling states that concomitant VPA concentration show no change. Mean changes from baseline in plasma concentrations of other concomitant AEDs were small and not statistically significant between TOP and placebo patients (see Table 12).

SUBGROUP ANALYSES: The ratio of male-to-female subjects was relatively close in both the drug-treated and placebo groups; see the demographics in Table 6b. Crude percentage rates were not provided in the NDA comparing the two groups in terms of median seizure reduction. However, no differences with regard to effectiveness or safety issues were noted for gender or age, according to a phone conversation with the sponsor on 2/10/98 (Catherine Glenkowski , covering for Michael Kaufman, Joe Ward [medical writer], and Judy Smith [statistician]).

Racial representation was sparse, and no conclusions can therefore be reached about the effect of TOP on groups other than Caucasian. There was only 1 black and, aside from whites, no other racial groups were represented.

Even pooling the pediatric populations of both YTC and YTCE would not yield an evaluable subgroup sufficiently large, by FDA traditional standards, to assess TOP's efficacy . However, case can be made to support such an indication, but on a much lower standard of evidence. See the summary below.

(4) Summary of PGTC Trials

There are two trials for primary generalized epilepsy, one highly significant (YTC) and the

other a washout (YTCE). Figure 2 shows that the combined population for both trials consisted of 190 subjects who were initially enrolled in the baseline phase; of these, 160 (mean age 27.2 years; age range 3-60 years) were randomized to the double-blind phase (81 placebo, 79 TOP). However, the actual intent-to-treat analysis of primary efficacy variables based on PGTC seizures encompassed 158 subjects (80 placebo, 78 TOP), since one placebo YTC subject (#161) and one YTCE TOP subject (#39) failed to experience PGTC seizures during baseline or the double-blind phase. All 160 subjects were included in the intent-to-treat analyses for all other efficacy variables.

Table 1 (v 53/168) summarizes features of the two trials, tables 2a and 2b review demographics, and Table 4 provides data on therapy discontinuation and study completion. 83 (52%) were male, 147 (92%) were white, and 32 (20%) were ≤16 years old (age range: 3-60). All subjects were required to have PGTC seizures. Most received treatment with at least 2 concomitant AEDs during the double-blind phase: 26% of YTC, and 19% of YTCE, subjects had >2 background AEDs. Valproate VPA), carbamazepine (CBZ), phenytoin (PHT), and lamotrigine (LTG) were the most commonly used background AEDs in both trials (VPA, PHT, and CBZ in YTC; VPA, CBZ, and LTG in YTCE). The median by-subject average TOP dosage over the entire double-blind treatment phase (titration and stabilization periods) was 3.7 mg/kg/day for YTC and 3.6 mg/kg/day for YTCE; the median average dosage during the stabilization period was 5.1 mg/kg/day for each trial. The median duration of double-blind therapy was within 2 days of the planned duration (140 days) for each trial; however, the mean duration was 10 days longer for YTC than YTCE (v 53/168, p 48).

Although both trials had identical designs, eligibility criteria, and total sample sizes, there were some differences, which, the sponsor claims, "may have reduced the power in Protocol YTCE, relative to that of Protocol YTC, especially when analyzed by standard, unadjusted, last-observation-carried-forward methods" (v 53/168, p 103). First, the mean duration of therapy in YTCE was about 10 days shorter than YTC, the result, according to the sponsor, of the larger percentage of patient withdrawals in the former (YTCE, 25%; YTC, 10%); the median duration was, however, identical for the two studies (see Table 7). Second, more subjects had seizure-related limiting adverse events (4 in YTCE, 3 in the placebo group; none in YTC): "Because of these efficacy-related discontinuations, predominantly in the placebo group, the last-observation-carried-forward approach, which implicitly assumes uninformative censoring, may be biased against TOP" (v 53/168, p 105). However, this scenario should, on the contrary, favor the placebo group, as pointed out by FDA statistician Dr. Sue-Jane Wang. Finally, there is the baseline PGTC seizure imbalance in favor of the placebo group in YTCE (as noted above), and baseline seizure rate was the only covariate that was found statistically significant ($p<0.05$) for the analysis of PGTC seizures in study YTCE (it had no important impact on the results of analyses based on YTC -- the positive study -- or the combined trials [v 53/168, p 49]). To emphasis his point, the sponsor cites a post hoc completer analysis, according to which the TOP vs placebo baseline PGTC seizure-rate imbalances even more pronounced, median of 6.2 PGTC seizures/month vs 3.0 PGTC seizures/month. Nevertheless, even analyses that compensated for the baseline imbalance were not statistically significant. A similar baseline imbalance can be found in the positive YTC study between TOP (median of 6.4 PGTC seizures/month) and placebo (4.0 PGTC seizures/month) subjects who experienced PGTC seizures and at least one other generalized seizure type; but this imbalance did not negatively affect the outcome. Additionally, for the pooled population (combined studies), the treatment effect based on percent seizure-rate reduction and treatment responders -- for the categories of PGTC seizures and all seizures -- showed no significant differences between subjects experiencing <4 seizures/months and those with ≥4 (or <17 and ≥17) seizures/month (see Table 22). According to the sponsor, "the results for the intent-to-treat population were generally consistent with those for subjects who completed the trials" (v 53/168, p 80).

In study YTC, TOP subjects had a median percent reduction from baseline in their average monthly PGTC seizure rate of 56.7%, compared to 9.0% in the placebo group ($p=0.019$; baseline PGTC seizure rate-adjusted p-value=0.020). TOP subjects in YTCE experienced a similar median percent reduction of 57.1%, but placebo subjects enjoyed a 33.2% reduction, or three times the amount the placebo cohort in YTC; the results were not statistically significant ($p=0.124$).

Nonetheless, the baseline PGTC seizure rate-adjusted analysis showed a statistical trend in favor of TOP (p=0.078); see Table 8. If both protocols are considered collectively, the median percent reduction was 56.9% for TOP subjects vs 27.1% for placebo, a statistically significant between-group comparison for both unadjusted (p=0.004) and baseline seizure rate-adjusted (p=0.003) analyses.

With respect to PGTC responder rates (≥50% reduction from baseline seizure rate), results from study YTC were statistically significant in favor of TOP, 56% TOP responders vs 20% placebo (p=0.001); this was not the case for YTCE, with 54% TOP responders vs 35% placebo (p=0.102). However, when adjusted for the baseline PGTC seizure rate imbalance, YTCE results were also statistically significant in favor of TOP (p=0.002). Collectively, for both protocols (see Table 9), 55% TOP vs 28% placebo subjects were treatment responders, a significant result in favor of TOP (p=0.001). If treatment response were defined as ≥75% median PGTC seizure-rate reduction (v 53/168, p 57), the results would be statistically significant in favor of TOP: 33% TOP vs 13% placebo in YTC (p=0.037), 36% TOP vs 15% placebo in YTCE (p=0.04), and, collectively, 35% TOP vs 14% placebo (p=0.003).

For all seizures, the intent-to-treat analysis showed a median percent seizure reduction from baseline during the double-blind phase of 42.1% TOP vs 0.9% placebo for YTC (p=0.003), 26.0% TOP vs 12.1% placebo for YTCE (p=0.212), and collectively for the combined trials 36.7% TOP vs 7.3% placebo (p=0.003). Treatment responders (≥50% seizure reduction) for all seizures showed percentages of 46% TOP vs 17% placebo for YTC (p=0.003), 43% TOP vs 19% placebo for YTCE (p=0.061), and overall, for the combined studies, 43% TOP vs 19% placebo (p=0.001). When treatment response is defined as ≥75% reduction, the percentages are 26% TOP vs 7% placebo for YTC (p=0.026), 30% TOP vs 5% placebo for YTCE (p=0.005), and overall, for the combined trials, 28% TOP vs 6% placebo (p<0.001).

Subgroup population analyses (age or gender) failed to demonstrate a statistically significant treatment difference with respect to PGTC seizures. There were too few non-white patients for definite conclusions TOP's effect in different racial subgroups. Table 20 reviews the data for the pooled population, grouped by PGTC seizures and all seizures. Median percent reduction and percent responders (≥50% seizure reduction) were reviewed by geographical location (see Table 21).

FDA biostatistician, Dr. Sue-Jane Wang, was asked to explore the possibility of differences between trials conducted in the US and Europe. YTC, the positive study, was an essentially US study (with a single center in Costa Rica), whereas YTCE contained centers in the US (39% of the patient population) and Europe (61%). Baseline seizure rates were similar between TOP and placebo arms in European centers (3.5 seizures/month vs 3.2), but not US ((8.8 vs 2.5). Nonetheless, when country subgroup data was submitted to protocol-defined primary efficacy analyses, percent reduction in PGTC seizures were not statistically significant (p >0.09) for TOP in either the US (48% TOP vs 37.9% placebo) or Europe (60% vs 31.4%); see p 8 of Dr. Wang's review.

The sponsor conducted several additional *post hoc* analyses to examine potential differences in treatment effect for PGTC and all seizures:

(1) *COMPLETERS*

CATEGORY OF PGTC SEIZURES: Table 11 reviews PGTC seizure data on subjects who completed the trials. Median percent reduction from baseline in average monthly PGTC seizure rates were 64.2% TOP vs 9.3% placebo in YTC (p=0.005), 60% TOP vs 33.8% placebo for YTCE (p=0.094), and, collectively, 60.7% TOP vs 27.1% placebo (p=0.002). Dr. Wang also found a numerical trend -- albeit not statistical significance -- in favor of TOP for percent reduction in PGTC seizures (60% TOP vs 33.8% placebo for study YTCE (see her review, p 9). In terms of *treatment response* for completers, results generally favor TOP for the categories of (a) ≥50% (a similar pattern showing statistical significance in favor of TOP for YTC and collective (combined study) analyses, and a numerical trend for YTCE; see Table 12), and (b) ≥75% (for YTC, 35% TOP vs 11% placebo [p=0.02], YTCE 39% TOP vs 10%

placebo [p=0.003], and, collectively (combined analysis), 37% TOP vs 11% placebo [p<0.001]); see Table 13 and Figure 5.

CATEGORY OF ALL SEIZURES: the percentages for completers were similar to the intent-to-treat population. Study YTC saw 50.8% TOP vs 5.2% placebo ($p \leq 0.001$); YTCE, 25.3% vs 12.6% (p=0.192); and the pooled population, 40.1% vs 11.5% ($p \leq 0.001$). In terms of *treatment response,* the percentages were again consistent with the intent-to-treat population. For ≥50% seizure reduction, study YTC had 50% TOP vs 18% placebo responders (p=0.001); YTCE, 35% TOP vs 17% responders (p=0.131); and, for the pooled population, 43% TOP vs 18% responders (p=0.001). When treatment response was defined as ≥75% seizure reduction, all groups demonstrated statistical significance in favor of TOP: 29% TOP vs 8% placebo for YTC ($p \leq 0.017$), 23% TOP vs 0% placebo for YTCE ($p \leq 0.017$), and 26% TOP vs 4% placebo for the combined studies ($p \leq 0.017$).

(2) *"SUBJECTS WHO EXPERIENCED PGTC SEIZURES WITH OTHER GENERALIZED SEIZURE TYPES":*

CATEGORY OF PGTC SEIZURES: In general, 82% of the combined populations of the two trials had PGTC seizures; the remainder "were believed to have PGTC seizures of unclear etiology" (v 53/168, p 61). (Data on subjects with only PGTC seizures were summarized, but the numbers were too few to conduct meaningful statistical analyses.) For subjects who experienced PGTC seizures with other generalized seizure types, the median percent reduction in baseline average monthly seizure rate trended in favor of TOP for YTC (56.7% vs 6.4%; p=0.066) and YTCE (48.5% vs 27.3%; p=0.065), but collectively was statistically significant (50.9% vs 21.4%; p=0.011). For subjects with only PGTC seizures, there was trend in favor of TOP (v 53/168, p 62). In term of *treatment response* for subjects who experienced PGTC seizures with other generalized seizure types was similar to results for the intent-to-treat population. In YTC, 52% TOP, compared to 21% placebo, subjects realized a ≥50% seizure reduction in their seizures (p=0.011). For YTCE, the percentages were 50% TOP vs 26% placebo (p=0.0004); and collectively, 51% TOP vs 23% placebo (p=0.002). For the category of ≥75% seizure reduction, the percentages were 31% TOP vs 12% placebo for YTC (p=0.060), 31% TOP vs 11% placebo for YTCE (p=0.063), and collectively 31% TOP vs 12% placebo (p=0.008); see 53/168, p 63.

CATEGORY OF ALL SEIZURES: statistical significance was shown for study YTC (40.1% TOP vs -3.3% placebo; p=0.005), but not for YTCE (17.3% vs -2.3%; p=0.368). No percentages were provided for the pooled population. With respect to treatment response for ≥50% seizure reduction, all groups demonstrated statistical significance: YTC (38% vs 18%; p<0.033), YTCE (31% vs 9%; p<0.033), and the pooled population (34% vs 13%; p<0.033). For ≥75% seizure reduction, all groups favored TOP: YTC (21% vs 6%; p=0.062), YTCE (22% vs 0%; $p \leq 0.006$), and the pooled population (21% vs 3%; $p \leq 0.006$).

Summaries of other seizure types, also classified as generalized, favor TOP, as shown by Table 17. Representative numbers were adequate for absence, myoclonic, and tonic seizures.

The subject's Global Evaluation of Improvement in Seizure Severity was a secondary efficacy parameter; see Table 18. In YTC, 62% TOP subjects vs 56% placebo patients (p=0.490) showed an improvement (minimal, moderate, or marked), though more TOP patients saw themselves as markedly improved (21% TOP vs 7% placebo). In YTCE, the percentages were statistically significant (48% TOP vs 33% placebo; p=0.026); and 33% TOP subjects registered as markedly improved vs 0% placebo (p=0.024). Overall, for the pooled population, the percentages were statistically significant (54% TOP vs 44% placebo; p=0.020); and more TOP patients described themselves as markedly improved (27% vs 4%; p=0.017). A similar pattern of results was seen when global evaluation scores were analyzed for completers (see Table 19): for YTC,

24% TOP vs 8% placebo (p=0.259); for YTCE, 39% vs 0% placebo (p=0.009); and, for the combined trial population, 62% TOP vs 49% placebo (p=0.005).

Despite the disparate results of studies YTC and YTCE, a case can nonetheless be made in support of TOP as adjunctive treatment for PGTC seizures. However, the reasoning to support this indication is based on a much lower standard of evidence than is traditionally offered:

(1) New FDAMA guidance document allows for proof of efficacy on the basis of a single study plus supportive data. In the case at hand, there is a positive trial, YTC, which is supported by corroborative data showing efficacy in partial-onset seizures in adults (an already approved indication) and children (see above).

(2) TOP efficacy was similar in both trials, 56.7% in YTC (which was strongly positive) and 57.1% in YTCE.

(3) TOP appears effective in the treatment of other generalized seizure types, such as tonic seizures and drop attacks. In study YTC, the median percent reduction from baseline in the average monthly tonic seizure rate numerically favored TOP over placebo (28% vs an increase of 1% in placebo) and, in the Lennox-Gastaut study (primarily pediatric subjects), the between-group difference with respect to drop attacks was statistically significant (14.8% median percent reduction in average monthly rate, as compared to an increase of 5.1% for placebo; p=0.041).

(4) Study YTCE's placebo rate of 33% was remarkably high. In most other trials, including epilepsy trials, the placebo rate hovers around 10-12%. The reason for the high placebo rate is unclear, although the sponsor suggests as possible causes (a) the high dropout rate of >20% (in YTC: 7% placebo vs 13%; in YTCE: 28% placebo vs 22% TOP), and (b) the imbalance in baseline seizure rate favoring the placebo group.

(5) In study YTC, 13% of TOP vs 5% placebo remained free of PGTC seizures (p=0.225), and 5% of TOP vs 0% placebo subjects free of all seizures (p=0.173) during the double-blind phase -- both categories (not protocol-defined endpoints), while not statistically significant, demonstrated a numerical trend in favor of TOP. Additionally, in YTCE,there is a statistically significant difference between groups for treatment response defined as ≥75% reduction in baseline seizure rate (p=0.04), unadjusted for baseline PGTC seizure rate.

(6) For study YTCE, *post-hoc* analyses by the sponsor, which adjusted for the substantial imbalance in baseline PGTC seizure rates, favor TOP more strongly, resulting in a p-value (0.078) for the primary variable (percent reduction from baseline in PGTC seizure rate), and a highly significant difference (p=0.016) for the comparison of treatment response based on PGTC seizures (p=0.002).

(7) In study YTCE, fewer patients in the TOP group (7 placebo vs 1 TOP) reported serious or limiting adverse events directly related to an increase in PGTC seizure rate or severity.

The serious reservations and weaknesses attached to data from unblinded trials notwithstanding, information derived from results of the unblinded extensions to YTC and YTCE are at least *suggestive* of -- that is, point in the direction of -- drug efficacy in the treatment of PGTC seizures. Table 9 in the Four-Month Safety Update (v 3/45, p 32) shows that rates for median percent seizure reduction from baseline for PGTC and all seizures jump dramatically once placebo patients are placed on drug and are consistent with rates obtained for treats in the controlled trials and unblinded extensions.

Table 9: Overall Summary of Topiramate's Efficacy in Protocols YTC/YTCE (All Subjects Who Entered the Open-Label Extension Phase)

Variable	Double-Blind Placebo Subjects		Double-Blind Topiramate Subjects	
	Double-Blind Phase (N=66)	Open-Label Extension (N=66)	Double-Blind Phase (N=65)	Open-Label Extension (N=65)
Median Average Daily Dose, mg/kg/day	4.1	6.2	4.0	6.4
PGTC Seizures				
N	65[a]	65[a]	65	65
Median % reduction from baseline[b]	27.0	63.3	62.0	58.1
% treatment responders[c]	23	62	57	58
All Seizures				
N	66	66	65	65
Median % reduction from baseline[b]	9.4	42.1	40.1	32.6
% treatment responders[c]	17	45	43	42

[a] One of the 66 subjects did not experience a PGTC seizure.
[b] Monthly seizure rate = 28 x (no. seizures during period)/(no. days during period).
[c] Subjects with 50% or greater reduction from baseline seizure rate.

(According to the sponsor, most of the TOP subjects who completed the controlled segments of YTC and YTCE had their dosage slightly increased when they entered the unblinded extensions [see Table 3, Four-Month Safety Update, v 3/45, p 24]).

In order to provide additional support for the PGTC indication, the sponsor submitted a very late sNDA addition, dated 4/28/98 (nine months after the date of the original sNDA), in the form of a response to a March 1998 talk given by Dr. Russell Katz (Deputy Director, Neuropharmacological Drug Products, FDA) about the problems of approving a drug with two contradictory trials, one negative and one positive. The sponsor performed a subgroup analysis, using tonic-clonic seizure data from the Lennox-Gastaut trial. 38 (39%) of the 98 subjects (age range: 2-42; mean TOP age 11.9, mean placebo 13.8) in the trial had tonic-clonic seizures during baseline: 21 placebo and 17 TOP. Of these, 14 (37%) were $\leq$7 years old, 4 (11%) were 8-11, 9 (24%) were 12-16, and 11 (29%) were $\geq$17. TOP subjects realized a 34.8% median percent reduction from baseline in the average monthly seizure rate for tonic-clonic seizures, whereas placebo subjects experienced an increase of 4%, a between-group difference favoring TOP (p=0.034):

Percent Reduction From Baseline in Average Monthly Tonic-Clonic Seizure Rate (All Randomized Subjects With Tonic-Clonic Seizures During Baseline in Study YL)

	Percent Seizure Rate Reduction[a]	
	Median	25th to 75th Percentile
Placebo (N = 21)	-4.0	-108.3 to 23.5
Topiramate (N = 17)	34.8	16.1 to 74.1
p - value[b]	0.034	

[a] A negative number denotes an increase in seizure rate.
[b] Topiramate vs placebo; two factor (treatment and center) ANOVA on ranks.

There are, however, several problems with the analysis. First, the data were derived from a small subgroup of the larger study population. Second, the primary efficacy measure for the PGTC trials was different from study YL. Third, "tonic-clonic seizures" may be generalized or of partial-onset in origin; the true nature of these seizures can only be determined on the basis of an EEG. Moreover, because of the complicated seizure pattern that makes up the Lennox-Gastaut Syndrome, it can never be clear whether the tonic-clonic seizures are truly primarily generalized at onset unless an EEG is running continuously. At least one expert feels that many be of partial onset (K. Ferrell, "Generalized Tonic and Atonic Seizures," and "Secondary Generalized Epilepsy and Lennox-Gastaut Syndrome," in E. Wylie, *The Treatment of Epilepsy: Principles and Practice* [Philadelphia: Lea & Febiger, 1993], pp 443-49, 604-11). Finally, the vast majority of the Lennox-Gastaut subgroup used in this analysis fall into the pediatric age group. The PGTC studies mainly enrolled adults. While the FDA Advisory Committee for Tegretol found that

pediatric partial-onset seizures share the same mechanism of action as those in adults, there is no evidence to date that this is also true of PGTC seizures.

Lastly, there remains the question of TOP efficacy for PGTC seizures in the pediatric age group. Subgroup analyses detected no statistical difference between the response in pediatric and adult patients. The NDA PGTC pediatric population (YTC + YTCE) consisted of 17 TOP and 15 placebo subjects; and, of these, there were only 8 TOP patients in YTC, the positive study. On the basis of so small a sample, it would be very difficult to justify approval of TOP for PGTC seizures in the pediatric age group. Because of the associated neuropsychiatric side effects, TOP s not a benign drug. If other supposed generalized seizures types are considered, such as drop attacks, adding the TOP population in the Lennox-Gastaut study (40) yields 57 as the number of pediatric subjects involved in the controlled clinical trials who experienced at least one generalized seizure type. However, unless an EEG is running at the time of an event, it is not possible to determine whether the event is generalized (see E. Niedermeyer, F. Lopes Da Silva, *Electroencephalography,* 3rd ed. [Philadelphia: Williams & Wilkins, 1993], p 497). Adequate evidence is therefore lacking to approve the use of TOP, as adjunctive treatment, for PGTC seizures in children.

In sum, TOP should be approved as an adjunctive agent to treat PGTC seizures in adults, but not children.

III. SAFETY

DATA BASE: The safety data base is comprised of:

(1) the three supplemental NDAs (with ISS centering on the pediatric experience new to the drug), which examine information from blinded, controlled trials plus some on-going open-label experience through 30 June 1996;

(2) the Four-Month Safety Update (through 2 April 1997); and

(3) additional more recent information through 11 March 1998, submitted 20 March 1998 by FDA request (this medical reviewer).

Safety parameters used in all studies included vitals, weight, EKG, physical and neurological examination, labs (hematology, chemistries, urinalysis), adverse events, and patient/caregiver global evaluations of mental status (compared to baseline and scored at the last double-blind visit as worse [0], no change [1], minimally improved [2], moderately improved [3], or markedly improved [4]; see v 13, p 33).

Adverse events were coded in accordance with the sponsor's "modified" WHOART dictionary ("an included term is the description most closely related to the investigator's terminology, the preferred term in a group of closely related included terms, and the body system is a broad category including related preferred terms" [v 13, p 39]). The Kaplan-Meier method was used to examine the relationship between time on study medication and occurrence of treatment-emergent adverse events. Other results, such as the patient/caregiver global evaluations of mental status, were summarized.

Table 1 (20 March 1998 submission) provides a breakdown of the adult and pediatric patients by study and seizure type (128, *partial-onset seizures;* 140, *Lennox-Gastaut Syndrome;* 32, PGTC seizures; 10, other seizures types). The table in Appendix 2 shows the average and maximum daily dosage of duration of treatment, and Appendix 3 the distribution of subjects by duration of treatment.

The adult cohort consists of subjects (both treats and placebo) from studies YL, YTC, and YTCE who completed the controlled trials, as well as those who elected to continue on to the open-label extensions after the completion of the controlled segment; a few additional subjects were recruited during the open-label extension. TOP has been approved as adjunctive treatment for partial-onset seizures in adults, and the safety profile in adults has been studied extensively and the

results can be found in labeling.

Unlike the adult indication, evidence to support safety in the pediatric population is new. The pediatric cohort (310 subjects in all) consists of subjects from the controlled trials, the open-label extensions, and nine additional open-label trials (EPPD-001, YOL, YOLE, YEP, YLT, YI, YJ, YK, YKE). Table 2 from the sNDA ISS (v 56/168) displays the patient population through 30 June 1996 and Table 1 (20 March 1998 submission), adding 7 patients, updates this information through 11 March 1998. The double-blind group contained 98 TOP pediatric subjects (YP, YL, YTC, and YTCE); of the 101 placebo subjects, 96 entered the open-label extension, receiving study drug. Moreover, there were 116 pediatric subjects from other open-label trials (109 subjects as of the cut-off date of the sNDA + 7 additional subjects who enrolled subsequently in those trials and were included in the Four-Month Safety Update). There were nine additional open-label trials. (EPPD-001, YOL, YOLE, YEP, YLT, YI, YJ, YK, YKE). YI and YJ were double-blind, placebo-controlled monotherapy trials in subjects ≥14 years with partial-onset seizures that also included open-label extensions (from which the safety-base subjects were taken); TOP was administered at one of two target dosages (100 or 1,000 mg/day) after gradual withdrawal of background AEDs. YEP and YLT were long-term open-label extensions for subjects with partial-onset seizures who completed open-label protocols (YKP/YKT and YCO2) or drug interaction protocols (M-215, M-216, M-218). EPPD-001 was an open-label pharmacokinetic study in which subjects (with any seizure type), aged 4-17, received TOP at four successive, increasing dosages (1, 3, 6, and 9 mg/kg/day; each for 7 days), after which they could enter a long-term extension (if <14 years, the dose could be increased to a maximum of 30 mg/kg/day, or ≤1600 mg/day; if ≥14, the dose could be increased to a maximum of 2,400 mg/day). YK and YKE were pilot, open-label, adjunctive therapy trials specifically evaluating subjects with Lennox-Gastaut Syndrome; see sNDA Table 4 (v 56/168, p 39).

DEATHS: TOP labeling provides a SUDEP incidence of 0.0035 death per patient-year for the exposed adult population. The safety review for the original TOP NDA (partial-onset seizures in adults) consisted of 1446 individuals, of whom 20 were in the age 4-12, and 68 in the age 13-18, group. There were no pediatric deaths (the youngest was a 20 year old).

In the sNDA, Four-Month Safety Update, and recent 20 March 1998 submission, the combined safety base lists a total of 8 deaths, 6 of them in pediatric subjects. Three deaths form part of the clinical data base (1 adult, 2 children), another 3 are the result of voluntary spontaneous reports (all pediatric); 2 come from voluntary spontaneous European reports (1 adult, 1 pediatric). Following is a summary of available information (from the Four-Month Safety Update v 13/45, p 304, and v 21/45, p 337; 20 March 1998 submission, p 12; and clarification of the information via personal communication, 5/13/98, with Michael Kaufman and Catherine Glenkowski, RW Johnson):

(1) STUDY YTCE: 49-year-old, 75.9-kg female, with PGTC seizures, irregular menses, and depression, who died suddenly as a result of a seizure disorder after 152 days of double-blind placebo treatment in study YTCE. Concomitant AEDs included lamotrigine 300 mg/day, valproate 500 mg/day, sertraline, and estrogen/medroxyprogesterone as hormone replacement. Based on information available through day 126, she experienced two tonic-clonic seizures (one during the third trial week, or the titration period; and a second during the 17th, or the stabilization period). On day 152 she was found dead at home. An autopsy report concluded that the death was "as a result of a seizure disorder." The investigator assessed the relation of the death to study treatment as "unlikely."

(2) STUDY YL: 8-year-old boy, with past medical history of acute gastroenteritis and failure to thrive,was randomized to TOP at a dose of 7.76 mg/kg/day. Concomitant AEDs included clonazepam and valproate. One month after entry into the double-blind phase (day 30), he experienced GE reflux and was hospitalized for fundoplication and gastrostomy tube. Pneumonia was diagnosed 5 days later, for which he was treated with gentamicin, ampicillin, metronidazole, ceftazidine, piperacillin, and albuterol inhalers. The GE reflux resolved in 4 days, the pneumonia in 6; both events were considered unrelated to TOP

therapy. The subject continued the trial, completing the double-blind phase and entering the open-label extension. After receiving TOP for 18 months, he was found unresponsive and resuscitation attempts were unsuccessful; the death was deemed "unlikely to be related to TOP."

(3) STUDY YP: 10-year-old girl, with partial-onset seizures who had been randomized to TOP in study YP at 9.4 mg/kg/day, dropped out of the trial after 441 days for lack of efficacy. More than 5 months after withdrawal, she was found dead. No autopsy was performed, and the cause of death is unknown; the relation to TOP was felt "to be doubtful" (SUDEP, per the sponsor).

(4) SPONTANEOUS REPORT (UK): 13-year-old boy with intractable epilepsy, associated with a hypothalamic hamartoma, congenital hydrocephalus, hypopituitarism, on nasogastric nutrition, was receiving TOP 600 mg/day adjunctive therapy. Concomitant AEDs were primidone 500 mg/day and CBZ 400 mg/day. On TOP for about 2 months, he was hospitalized "slightly dehydrated and severely constipated" and "essentially unconscious, flexing to pain, and vocalizing incoherently." The patient died suddenly; the cause of death was unknown.

(5) SPONTANEOUS REPORT (US): 9-year-old male, with undefined epilepsy, was receiving TOP 150 mg/day, along with PHT 275 mg/day and vigabatrin 1,500 mg/day. "He had a seizure, choked, and died in his sleep."

(6) SPONTANEOUS REPORT (US): 4-year-old male, receiving TOP 225 mg/day for 6 days was "found dead at home, face down on a pillow. Death was attributed to asphyxiation following a seizure and was considered unrelated to TOP therapy."

(7) SPONTANEOUS REPORT (AUSTRIA): 25-year-old female "with sudden death." No dosing information provided.

It is difficult to derive a suitable denominator for the experience encompassing the 6 pediatric patients described above. The most reliable information comes of course from the clinical data base, which consists of 310 children and represents an estimated 459 subject-years of exposure. There were two pediatric deaths in this population, yielding a SUDEP rate of 2/459, or 0.00436 deaths per patient-year; because one of the patients had been off medication for >5 months, this rate might therefore be construed as the worst-case scenario. Nevertheless, the rate appears to fall within the expected range, described in current labeling, for the incidence of SUDEP in epilepsy patients in general (from 0.0005 for the general epilepsy population, to 0.003 for a clinical trial population, to 0.005 for patients with refractory epilepsy).

SERIOUS ADVERSE EVENTS: A list of all serious adverse events in adults and children, and their incidence rates, can be found in the two tables in Appendix 4c. Similarities shared by many of these patients are (1) other concomitant serious medical problems, and (2) the severity of their underlying seizure disorder. Following are brief narratives of cases during the double-blind trials and selected cases from open-label extensions, which the sponsor provided in the 20 March 1998 submission:

KEY: db= double-blind phase op=open-label phase

Study	*Pt*	*Age/Sex/Group*	*Adverse Event*	*Onset*	*Resolved*	*Tx Related*
YP - db	13	5 F - placebo 25 mg/d	CONVULSIONS AGGRAVATED. Hosp on day 26 for prolonged postictal state; discharged day 27 and completed study. Concomitant drugs: VPA 1,125 mg/d, ethotoin 1,125 mg/d.	Day 26	Day 27	Possible

YP - db	74	9 M - placebo 175 mg/d	INFECTION VIRAL. Hosp with cough, sore throat, fever, vomiting (probably flu) day 66, given IV antibx. LP negative. Resolved 7 days later. Concomitant drugs: CBZ 600 mg/day.	Day 66	About Day 73	Unlikely
YP - db	116	5 M - placebo 100 mg/d	CONVULSIONS AGGRAVATED. Concomitant drugs: DPT 125 mg/d. Had 55-min seizure and elevated temp on day 104 after discontinuing AEDs x 2 days. Seizure cluster on day 105 led to hosp. PHT level 8.6. Loaded with IV PHT to give level 15.5 on day 106, at which time seizures stopped; temp reached 102.	104	Not available	Unlikely
YP - db	2	11 M - TOP 125 mg/d (5.2 mg/kg/d)	CONSTIPATION. PMH: Hydrocephalus, quadriparetic CP, constipation. Had sinusitis day 49, tx sulfa; then constipation day 50. Hosp on day 58 for fever, dehydration, anorexia, abd pain; was rehydrated and placed on antibx, laxatives. Prolonged PT treated with vit K. Discharged day 64. Still on TOP x 580 days.	49	64	Unlikely
YL - db	29	10 M - TOP 175 mg/d (5.1 mg/kg/d)	PNEUMONIA, OTITIS MEDIA, SINUSITIS, VOMITING. Concomitant drugs: ethotoin, VPA. On day 29 developed anorexia, persisting through end of trial. Day 79 had flu-like sxs with fever and vomiting. Hosp on day 82 with mod severe pneumonia, sinusitis, otitis, resolving in 13 days on antibx. Completed trial; mild vomiting persisted to end of trial. Still on TOP x 606 days.	29 79	 95	Unrelated Unrelated

YL -db	49	8 M - TOP 125 mg/d (6.5 mg/kg/d)	GASTROESOPHAGEAL REFLUX. PMH: acute gastroenteritis, failure to thrive. Concomitant AEDs: clonazepam, VPA. During baseline, experienced mild vomiting that resoled in 3 days. Hosp on day 30 for GE reflux; had fundoplication and gastrostomy insertion. Received H2 blockers, analgesics, anesthetics. 5 days later, dx with pneumonia; given antibx, and albuterol inhaler. GE reflux resolved in 4 day; pneumonia in 6. Completed trial. Still on TOP x 351 days.	30	40	Unrelated
YL - db	126	8 M - TOP 150 mg/d (5.3 mg/kg/d)	CONVULSIONS AGGRAVATED, ASTHMA. Nonverbal; concomitant drugs: CBZ 600 mg/d,lamotrigine 300 mg/d. Hosp on day 71 for prolonged seizure x 35 min, which stopped after IV diazepam 5 mg; CBZ increased to 700 mg/d. Discharged 24 hr later. Hosp day 162 with acute asthma; resolved in 16 days. Still on TOP x 244 days.	71 162	72 178	Remotely related Unrelated
YTC - db	146	6 M - TOP 100 mg/d (3.9 mg/kg/d)	PNEUMONIA. PMH: MR, bowel/bladder incontinence, hypotonia, nonketotic hyperglycemia. Concomitant drugs: gabapentin 800 mg/d, phenobarb 120 mg/d, lorazepam 0.5 mg/d. Hosp on day 40 (during titration period, TOP dose 100 mg/d) for markedly severe pneumonia; discharged day 44, full resolution day 54.	40	54	Unlikely

YP - op	4	4 M - TOP open-label x 1 yr + pt's 22-month-old F cousin	OVERDOSE. Hosp after found asleep and difficult to arouse; found to have shallow resp, unresponsive except to pain. Tx lavage, charcoal, intubated, and hydrated. Discharged 2 days later; OD sxs resolved 3 days later, and TOP restarted. He received his last TOP dose 7 months later (8.7 mg/k/g/d). His TOP supply had run out, and his gave extra CBZ. As a result, his seizure activity increased; 3 days later, he became ataxic, fell, and blacked out -- sxs felt to be due to CBZ toxicity. The sxs resolved within 3 days, and he was withdrawn from the study due to noncompliance. The 22-month-old F was found "with a wild look in her eyes," then became unresponsive. On admission, she was irritable, combative when touched, had an arched back, extended legs, and questionable dystonic neck posture. Tx lavage, charcoal, and normal saline IV. 2 days post overdose, she was unresponsive, staring, and posturing bizarrely. The next day, she was asymptomatic and discharged.	~365	~367	Remotely related Likely
YP - op	45	2 M - TOP 29.3 mg/kg/d x 7 months	SEPSIS AND GASTROENTERITIS. PMH: frequent RSV infections, pneumonia, otitis. Concomitant AEDs: phenobarb 112.5 mg/d, lamotrigine 250 mg/d, diazepam. Hosp about 7 months into op extension when developed fever to 104, despite tx with ibuprofen and diazepam, and increased seizures. WBC 23,000; +blood cx. Tx antibx and discharged 11 days later. Then, 10 weeks later, hosp for gastroenteritis, tx with lorazepam; discharged 4 days later. Continued TOP.	~7 months	In 11 days	Remotely related

YP - op	47	3 M - placebo arm of the db trial, then on TOP 26.4 mg/kg/d during op x 8 months	AGGRAVATED CONVULSION AND VIRAL INFECTION. Concomitant AED: VPA 750 mg/d. Hosp after ~8 months on TOP for 2 prolonged episodes (5 hrs) of altered mental status and walking in circles. Dx: otitis, sinusitis, pneumonia, viral syndrome. Tx antibx. Continued TOP.	~8 months		Remotely related
YP - op	530	14 F - TOP 5.96 mg/kg/d	AGGRAVATED CONVULSION, DYSPHAGIA. Concomitant AEDs: clonazepam 0.525 mg/d, lamotrigine 50 mg/d. Hosp on day 82 after increased seizure activity, becoming "heavily sedated leading to difficulty swallowing. Events resolved (date unknown) and the pt was continued on TOP. Per sponsor: "This represents the first case of difficulty swallowing (dysphagia) submitted as an expedited report."	82	?	Definitely related
EPPD-001 - op	8	10 F - TOP 950 mg/d (23.1 mg/kg/d)	CONVULSIONS GRAND MAL. Concomitant AEDs: phenobarb 180 mg/d (Felbatol has just been discontinued). Day 2, and persisting throughout study, slowed mentation was observed. Erythema was noted after ~7 months (not TOP related). Hosp after 1 yr with partial complex status x 1 day; previously had up to 5 simple partial seizures/week. Still on TOP x 620 days.	2 ~210 ~365	Persist-ing	(Probably related) Not related Remotely related
YOL - op	22	13 M - TOP 1100 mg/d (10.1 mg/kg/d)	CONVULSIONS AGGRAVATED. PMH: multiple seizure types, encephalitis age 10, obesity, MR, multiple neurological abnormalities. Concomitant AEDs: CBZ 1200 mg/d, PHT 400 mg/d, chlorazepate 37.5 mg/d. Hosp on day 164 after "large seizure,'" for which received diazepam 5 mg, and increased seizure frequency over next 4 weeks. TOP was increased to 1300 mg/d and PHT discontinued. 4 weeks post discharge, again had serious aggravated convulsions; TOP increased to 1900 mg/d (17.5 mg/kg/d), before tapering due to ineffectiveness (off day 686).	164	686	Not related

YOL - op	181	14 M - TOP 300 mg/d (3.8 mg/kg/d) increasing to 1200 mg/d (15.2 mg/kg/d)	CONVULSIONS GRAND MAL, CONVULSIONS AGGRAVATED, EEG ABNORMAL. PMH: partial complex seizures 180/month + simple partial seizures 3/month. Concomitant AEDs: ethotoin, PHT 350 mg/d. Day 22, after discontinuation of ethotoin, had status; day 27 had serial seizures, resolving with IV PHT and lorazepam. ~5 months into enrollment had seizure surgery; TOP increased to 1300 mg/d, but then tapered because considered ineffective, eventually off on day 226.	22	226	Remotely related
YOLE - op	230	15 M - TOP 200 mg/d (3 mg/kg/d)	HALLUCINATIONS, APATHY, FATIGUE. PMH: gelastic seizures. Concomitant AEDs: CBZ, VPA, clonazepam. Hosp on day 59 with visual hallucinations and apathy (loss of contact with his environment). Tx diazepam with resolution. EEG showed no seizures. Also noted fatigue from day 57 to 68, when TOP discontinued. Follow-up 3 yrs later: fatigue resolved.	57	68	Probably related
YOLE - op	967	15 M - 200 mg/d (4.5 mg/kg/d)	CONVULSIONS AGGRAVATED. Concomitant AEDs: CBZ 1200 mg/d and VPA 1500 mg/d, reduced 1 month, then discontinued 4 months, after TOP began. ~6 months into study, breakthrough seizures occurred on 3 days, ~1 week apart. Hosp, tx diazepam; CBZ and VPA resumed with resolution of seizures. TOP continued.	~250		Probably related
YL - op	7	4 F - TOP 350 mg/d (24.4 mg/kg/d), db and op	CONVULSIONS AGGRAVATED. Concomitant AED: lamotrigine 125 mg/d. Hosp on day 392 with "prolonged seizures"; given benzodiazepine, lamotrigine increased to 200 mg, with resolution in 8 days. TOP tapering begun. After 423 days, ketogenic diet discontinued.	392	400	Possibly related

YL - op	16	11 F - TOP 425 mg/d (6.9 mg/kg/d); randomized to TOP during db stage	RASH, PERIORBITAL EDEMA. Concomitant AEDs: VPA, clonazepam. After ~6 months, lamotrigine 25 mg/d was added to regimen. 13 days later, developed fever, overall body rash, periorbital swelling (all "markedly severe"). Tx Benadryl with resolution 12 days later. Still on TOP x 704 days, at maximum dosage (1000 mg/d; 16.2 mg/kg/d).	~180	~192	Remotely related; probably due to lamotrigine
YL - op	21	15 M - TOP 800 mg/d (16.2 mg/kg/d); randomized to TOP during db stage	FATIGUE (450 mg/d; 9.1 mg/kg/d); CONVULSIONS GRAND MAL (800 mg/d; 16.2 mg/kg/d). PMH: MR, corpus callosotomy in '88. Concomitant AEDs: ethotoin 3750 mg/d, methsuximide 900 mg/d. After 4 months on TOP, fatigue noted, resolving two months later. Then, after 8 months, fatigue, slurred speech, motor slowness noted. Had left temp lobectomy and frontal topectomy; sxs resolved. Seizure free x 14 months post surgery; ethotoin tapered and TOP increased to 800 mg/d (16.2 mg/kg/d). At month 29, 2 weeks post surgery for hernia repair, had increased seizures and status on day 800. Concomitant AEDS: phenobarb 1200 mg and PHT 500 mg/d. Ethotoin 2500 mg/d restarted, with decreased seizures. Still on TOP x 950 days.	~120 ~240	? ?	Remotely related Not related
YL - op	22	15 F - TOP 400 mg/d (9 mg/kg/d); randomized to placebo during db phase	CONVULSIONS AGGRAVATED. PMH: MR, autism, mixed seizure types. Concomitant AEDs: felbamazte 4200 mg/d, ethotoin 1375 mg/d. After 3 months (TOP 275 mg/d; 8.3 mg/kg/d), noted decreased seizures, following directions better, playing with toys more appropriately. Hosp on day 183 for increased seizures, decreased responsiveness, lethargy. Felbamate tapered with worsening seizures. Then TOP tapered over 2 months (last dose on day 244), with resolution of seizures.	183	244	Possibly related

YL - op	23	16 M - TOP 400 mg/d (6.4 mg/kg/d); randomized to TOP during db phase	CONVULSIONS AGGRAVATED. PMH: MR. Concomitant AEDs: felbamate 4200 mg/d, phenytoin 150 mg/d. Drooling, poor fluency, cognitive problems worsened during study. After 5 months, felbamate tapered (weight decrease), methsuximide started. Hosp day 225 (one month later) for increased seizures, for which given lorazepam and diazepam. Methsuximide and phenytoin stopped, VPA started. Sx resolved in 16 days, though continued to have frequent seizures. Still on TOP x 865 days.	225	241	Remotely related
YL - op	66	13 M - TOP 1500 mg/d (52.4 mg/kg/d); randomized to placebo during db stage	LACTIC ACIDOSIS. Concomitant AED: phenytoin 250 mg/d. During db placebo treatment, CO_2 20-21 mmol/l. After starting TOP, CO_2 decreased between days 88 and 918 to 13-18. Hosp on day 984 with seizure cluster, fever (102.7), lactic acidosis (due to sepsis?). Tx antibx, discharged 3 days later. On day 1002, 54 days after onset of lactic acidosis, had markedly low $C0_2$ (17). Per sponsor, this is first reported serious case of lactic acidosis in association with TOP.	88	Persis-tent	Probably related
YL - op	96	5 M - TOP 200 mg/d; randomized to TOP during db stage	DEHYDRATION, VIRAL INFECTION. Concomitant AED: primidone 500 mg/d. Hosp day 541 with dehydration, viral illness, abnormal LFTs; at screening, SGOT 49, SGPT 67, but week prior to hosp SGOT 81, SGPT 118. Discharged day 546; virus resolved in 6 days, dehydration in 27 days, but LFTs remained abnormal (SGOT 59, SGPT 84 on day 567, pt's last visit). TOP continuing.	541	Persis-tent	Possibly related

YL - op	106	8 F - TOP 375 mg/d (14.7 mg/kg/d); randomized to TOP during db stage	CONVULSIONS GRAND MAL (375 mg/d; 14.7 mg/kg/d); CONVULSIONS AGGRAVATED + SOMNOLENCE (225 mg/d; 8.8 mg/kg/d); DYSTONIA, SALIVA INCREASED, CONVULSIONS GRAND MAL (375 mg/d; 14.7 mg/kg/d). Concomitant AEDs: VPA 875 mg/d, ethosuximide 750 mg/d. Increased seizures and somnolence noted day 107 (on TOP 225 mg/d; 8.8 mg/kg/d), culminating in slurred speech, unsteadiness, decreased alertness, and status on day 127 (375 mg/d; 14.7 mg/kg/d). TOP stopped with resolution of all sxs in 2 days. Exam 3 weeks later showed increased responsiveness, steadiness, "without lip movement," and no seizures that day.	107	130	Definitely related
YL - op	126	8 M - TOP 175 mg/d; randomized to TOP during db stage	OSTEOMALACIA, PNEUMONIA, SINUSITIS, URI, AGGRAVATED CONVULSIONS. PMH: asthma, splenectomy, pneumothoraces, kerosene ingestion. Concomitant AEDs: lamotrigine 425 mg/d and CBZ 600 mg/d. Hosp after about 1 yr on TOP with 5-6 T-C seizures and fever 38.7C; received diazepam. CXR: LLL pneumonia; received antibx, lamotrigine decreased to 450 mg/d. Discharged 3 days later; pneumonia resolved 15 days later. CBZ was reduced to 500 mg/d due to antibx interaction. Hosp next month for sinusitis, URI , increased seizures. CXR showed osteomalacia; received oral calcium.	~365	~395	Unrelated
YK	2	4 F - TOP 550 mg/d	PNEUMONIA, AGGRAVATED CONVULSIONS. Concomitant AEDs: VPA 375 mg/d, diazepam 2 mg/d. Hosp after 2 days T-C seizures, pneumonia, tx antibx; resolved in 11 days.	?	?	Convulsion possibly related

YK	9	6 M - TOP 150 mg/d (5.8 mg/kg/d)	CONVULSIONS GRAND MAL (100 mg/d; 3.9 mg/kg/d); CONFUSION, CONVULSIONS GRAND MAL (150 mg/d; 5.8 mg/kg/d). Concomitant AEDs: PHT, VPA, chlorazepate. After 2 weeks, mood problems, somnolence, deterioration in daily functioning noted, progressing over next 3 days to decreased orientation, memory difficulties, unclear thinking, increased ataxia, dysarthria. Toxic free PHT level was noted; dosage decreased to 100 mg/d. On day 55 (TOP 150 mg/d; 5.8 mg/kg/d) had status and confusion x 1 day; TOP decreased to 100 mg/d (3.9 mg/kg/d), and on day 57 had prolonged atypical absence seizures lasting 29 days. TOP tapered over 2 weeks (last dose day 70) due to confusion and grand mal convulsion. Hosp 6 days later for absence status, stabilized and discharged in 11 days.	55	70	Possibly related
YK	50	6 M - TOP 350 mg/d (18.2 mg/kg/d)	SOMNOLENCE. PMH: multiple seizure types, ADD, hyperactivity, MR. Concomitant AEDs: lamotrigine (reduced as study began), phenytoin, clonazepam. After 5 weeks on study, somnolence noted due to increased seizures, lasting 23 days. Clonazepam reduced. After 4 months, somnolence, ataxia noted, resolving in 12 days. VPA added. Intermittent somnolence persisted. Still on TOP x 180 days (400 mg/d; 20.8 mg/kg/d).	~35	Persis-tent	Possibly related
YK	807	7 M - TOP 225 mg/d	DEHYDRATION. PMH: mixed seizure types, MR, chronic sinusitis, cystic fibrosis with chronic pneumonias, decreased appetite, malabsorption, GI reflux, decreased IgA, hypotonia. Concomitant AEDs: VPA, diazepam. On first study day, developed dehydration, diarrhea x 12 days, vomiting x 19 days; dx rotavirus. These conditions resulted I, gastric tube/Nissen fundoplication on day 19.	1	?	Remotely related

YKE	2	14 F - TOP 500 mg/d (9.5 mg/kg/d)	CONVULSIONS GRAND MAL. Concomitant AEDs: PHT 325 mg/d, vigabatrin 2500 mg/d, clobazam 40 mg/d. After 3 weeks on study, vigabatrin tapered, and on day 42 (1 week after discontinuation), hosp for status and fever, tx diazepam; vigabatrin restarted. Grand mal convulsions stopped 3 days alter. Still on TOP x 952 days.	42	?	Not related
YTC - op	65	11 F - TOP 175 mg/d (5.3 mg/kg/d); randomized to TOP during db stage	FEVER, RASH, RESPIRATORY DISORDER, CONVULSIONS GRAND MAL,HALLUCINATIONS. Concomitant AED: VPA. Hosp day 163 with fever (103), rash, GTC seizure x 20 min; tx antibx, intubated x 1 day. Fever and rash resolved in 3 days. On day 165 had auditory (lasting 1 day) and visual (lasting 2 days) hallucination. Till on TOP x 663 days.	163	167	Possibly related: rash and hallucina-tions; remotely related: convulsions grand mal; not related: fever and respiratory disorder
YTC - db and op	146	6 M - 6.7 mg/kg/d; randomized to TOP during db stage	PNEUMONIA. PMH: gastrostomy tube, MR, nonketotic hyperglycemia. Concomitant AEDs: gabapentin 800 mg/d, phenobarb 120 mg/d, lorazepam 0.5 mg/d. Hosp on day 40 (titration phase) with pneumonia, tx antibx, discharged day 44, pneumonia resolved day 54. During op, on TOP 17.2 mg/kg/d (concomitant AED: phenobarb), hosp on day 303 due to increased seizure frequency, mild to moderate respiratory distress, fever; dx pneumonia, resolving in 7 days on antibx. Lamotrigine added, still on TOP.	40 303	54 310	Remotely related Remotely related
YTCE - op	218	15 M - TOP 4.6 mg/kg/d (db stage), increasing to 8.7 mg/kg/d (op stage)	PANCREATITIS. Concomitant AED: phenobarb 90 mg/d, PHT 500 mg/d, lorazepam 3-4 mg/d. Hosp on day 230 for bronchitis, hypovolemia, suspected pancreatitis (amylase 389, ref range <310; lipase 3566, ref range <208). Had cholecystectomy. TOP resumed.	310	?	Remotely related.

An examination of the table in Appendix 4a generally shows a comparable or lower percentage of similar complaints listed in current labeling. The side effect profiles for the pediatric and adult populations are compared below.

The adult experience with TOP has been examined in detail in the original NDA. More

extensive postmarketing experience has not turned up any additional serious problems with the drug to date (personal communication, April 1998, with Mary Mease, FDA Epidemiology, who provided a computer printout of the entire postmarketing experience to date).

The major side effects -- listed in current labeling with incidences >5% (in the order placebo, 200-400 mg, 600-1000 mg) -- have been disorders of the following systems:

neuropsychiatric (somnolence 10%, 30%, 26%; psychomotor slowing 2%, 17%, 25%; nervousness 7%, 16%, 21%; difficulty with memory 3%, 12%, 13%); confusion 5%, 10%, 15%; depression 6%, 8%, 13%; difficulty with concentration/attention 1%, 8%, 15%; anorexia 4%, 5%, 11%; mood problems 2,%, 4%, 10%)

GI (nausea 6%, 12%, 14%; dyspepsia 5%, 8%, 6%; abdominal pain 3%, 5%, 7%; constipation <1%, 5%, 3%)

central and peripheral nervous system (dizziness 14%, 28%, 32%; ataxia 7%, 21% 17%; speech disorders/related speech problems 3%, 17%, 14%; nystagmus 12%, 15%, 15%; paresthesia 3%, 15%, 15%; tremor 6%, 11%, 14%; language problems <1%, 6%, 12%; coordination abnormal 2%, 5%, 4%)

respiratory (URI 12%, 12%, 12%)

vision (diplopia 6%, 14%, 15%; vision abnormal 3%, 14%, 11%).

A comparison with figures in Appendix 4a generally shows lower percentages among the adult population of the sNDA.

WITHDRAWALS DUE TO ADVERSE EVENTS: There were relatively few withdrawals for adverse events in the controlled trials: none in YP and YL, 2 in YTC (1 in each arm; see Table 8 YTC), and 12 in YTCE (5 TOP, 7 placebo; see Table 8 YTCE). There were no real differences between the side effects experienced by the TOP and placebo patients.

OVERALL ADVERSE EVENT PROFILE: By request (20 March 1998 submission), the sponsor compared the incidence of adverse events in adults, occurring with a frequently ≥1%, from the original NDA (6 trials for partial-onset seizures in adults) with the profile obtained in the sNDAs and Four-Month Safety Update (adults with PGTC seizures and Lennox-Gastaut Syndrome). The results can be seen in Table 2 of that submission. No significant change in the overall adverse event profile was seen in adults.

In pediatric subjects, 7 neuropsychiatric events, along with weight decrease, occurred more frequently (≥5% difference) in TOP subjects than placebo, as follows:

--somnolence (26% vs 16%)
--anorexia (24% vs 15%)
--fatigue (16% vs 5%)
--nervousness (14% vs 7%)
--difficulty with concentration/attention (10% vs 2%)
--aggressive reaction (9% vs 4%)
--difficulty with memory (5% vs 0%)
--weight decrease (9% vs 1%).

With the exception of anorexia, mood problems, aggressive reaction, and personality disorder (behavior problems), neuropsychiatric adverse events were less often reported in pediatric than in adult patients. It may be true, as the sponsor suggests, that children are less likely to report adverse events: they may be less able to articulate their complaints or may be less willing to do so. But the incidence of mood problems and personality disorder (behavior problems) were similar between TOP and placebo groups. On the other hand, such adverse events as headache, vomiting, and diarrhea occurred more frequently among placebo subjects.

Furthermore, the incidence of common neuropsychiatric events reported in the sNDA ISS for the 303 pediatric subjects that formed its cohort did not increase appreciably (<5% increase for individual adverse events) in the total TOP group of 310 pediatric subjects in the Four-Month Safety Update over the sNDA population (303 subjects), despite a longer duration of exposure to study drug (12.5 months to 18 months). Somnolence (41%) and anorexia (38%) were the most frequently reported, followed by fatigue (25%), nervousness (21%), headache (20%), insomnia

(15%), mood problems (11%), difficulty with concentration/attention (11%), and personality disorder (11%).

The studies for all three indications each contained an assessment of patient mental status by means of a questionnaire completed by the subjects or caregiver at the first and final visits of the double-blind phase. In YP responses were scored on a scale from 0 (worsened) to 7 (marked improvement); in YL and YTC/YTCE, a 4-point scale was employed (from 0, or worsening of mental status, to 4, or marked improvement). For YP, comparison of the two questionnaires (before and after) showed that most subjects in both groups (the TOP and placebo) recognized no change from baseline, though numerically more TOP patients were seen as improved on each of the four scales (see YP Table 23). For YL and YTC/YTCE, comparison of the two questionnaires showed similar results for TOP and placebo groups (see YL Table 19, YTC Table 22, and YTCE Table 22).

Weight loss occurred in 22% adult vs 11% pediatric subjects. According to the sponsor, anorexia is related to weight loss in both children and adults: subjects with weight loss reported as an adverse event were more likely to have also reported anorexia (26/34; 76%) compared with those who did not exhibit weight loss (84/274; 30%). The sponsor suggests that the slower titration rates and lower dosages in the sNDA studies may explain the differences in the adverse event profile, as well as the fact that children may not report certain types of subjective symptoms (depression) as readily as adults. The rate of discontinuation due to adverse events was also lower among children (0% in the double-blind trials among TOP subjects, 11% overall among TOP subjects) than adults (11% and >20%, respectively).

Another commonly reported adverse event in the original NDA adult population was paresthesia (15% for dosages of 200-400 mg/day, 18% for dosages up to 1000 mg/day), attributed by the sponsor to the drug's similarity to the carbonic anhydrase inhibitor group; the side effect led to drug discontinuation in 2% of the patients. In contrast, only 6% of the children and 8% of the adults in the sNDA or Four-Month Safety Update reported paresthesias, and none in either age group discontinued therapy due to the complaint.

As a result of its activity as a carbonic anhydrase inhibitor, TOP increased the incidence of kidney stones in adults in the original NDA population by 2-4 times that of a similar, untreated population (1.9% confirmed kidney stones). Three cases were found in the pediatric group:

(1) STUDY YL: 18-year-old male, with Lennox-Gastaut and history of multiple fractures ("weak bones"), completed the double-blind phase and had entered the open-label extension, receiving TOP 275 mg/day and lamotrigine 50 mg/day. Hospitalized "due to retching and crying," he was found to have left tibia and right hip fractures as a result of osteomalacia, in turn felt to be caused by discontinuation of calcium supplements. A kidney stone was passed 6 days later, which was felt initially to be "related to TOP," but "based on the subject's history of calcium imbalance. . .; The investigator remained unsure. . . ."

(2) SPONTANEOUS REPORT: 23-month-old female, on TOP 50 mg/day for about 3 months, passed a kidney stone, considered "probably related to TOP." Concomitant medications included lamotrigine 200 mg/day and CBZ 300 mg/day; the patient was also on a ketogenic diet. The diet was stopped, but TOP was continued.

(3) SPONTANEOUS REPORT: 5-year-old male, with Menke's syndrome, passed a kidney stone while on TOP 25 mg/day, lamotrigine (dose unknown), and primidone (dose unknown). "The reporting physician felt that the patient's free water was decreased by 300 ml." Concomitant medications included ascorbic acid and antacids. No other information is available.

SAFETY LABS AND OTHER DATA: There were no abnormalities in adult or pediatric subjects not already mentioned in current labeling, and there were no significant differences between the two age groups. There were no noteworthy treatment-related changes from baseline at the start of the double-blind phase to the final visit at the end of the double-blind phase in mean vital-sign measurements in YP, YL, or YTC/YTCE. Data in the sNDAs, Four Month Safety Update, and 20 March 1998 submission do not differ significantly from information found in current labeling.

There were no additional safety concerns or precautions.

IV. Dosing Recommendations

Based on the current package insert, the recommended dose in adults, as adjunctive treatment for partial-onset seizures, is 400 mg/day in 2 divided doses. In studies YTC and YTCE, which included pediatric as well as adult subjects, the daily target doses of 175, 225, and 400 mg were based on weight and intended to approximate 6 mg/kg/day (maximum: 9.3 mg/kg/day) for pediatric patients and 6 mg/kg/day for adults. The titration schedule as add-on for adults with PGTC seizures is identical to the regimen recommended in the labeling for partial-onset seizures: 50 mg/day as starting dose, with weekly increments of 50 mg/kg until the target dose of 400 mg/day is reached. Among pediatric subjects (98 total in the 4 double-blinded studies, YTC, YL, and YP), most received a target dose of 5-9 mg/kg/day (median: 6.1 mg/kg/day). The recommended titration schedule, reflecting the 4 double-blind trials, begins with a dose of 25 mg/kg/day (or less, based on a range of 1-3 mg/kg/day), with increases every 1-2 weeks, as tolerated, in increments of 1-3 mg/kg/day. Titration should be guided by response and side effects. In study YP, the starting dose for subjects <43 kg was 25-50 mg/day, increasing by 25, 50, or 75 mg/day every 1-2 weeks over a 6-week period until the target dose was reached. In studies YTC and YTCE (17 pediatric subjects total), subjects <43 kg started at 50 mg/day for the first 28 days, increasing the dose in increments of 25 to 75 mg/day every 2 weeks over an 8-week period, until the target dose was reached. In YL, a more rapid titration was employed, increasing the daily dosage by 2-3 mg/kg/day every week over a 3 week period. The sponsor, however, recommends a slower rate of titration for better tolerability. The sponsor states that maximum doses of 30 mg/kg/day (specified in the pediatric protocols) may be administered in adults and children, as tolerated, for optimal seizure control, but it should be noted that there is very little experience with such high doses (see Appendix 2 of the 20 March 1998 submission).

In subjects with renal impairment (creatinine clearance <70 ml/min/1.73 m^2), the dose should be halved. No dosage adjustment is suggested for patients with moderate hepatic impairment (about 30%). In both subsets of patients, titration should be guided by response and side effects, and a longer time period is required to reach steady state. (See v 53/198, pp 101-2.)

V. Conclusion

Topamax (TOP) was approved as adjunctive therapy for the treatment of partial seizures in adults with epilepsy on December 24, 1997. The sponsor has submitted three supplemental NDAs to support its use as an adjunctive agent in the treatment of (1) pediatric partial-onset seizures, (2) Lennox-Gastaut syndrome, and (3) primary generalized tonic-clonic seizures in adults.

The sponsor has provided adequate proof of efficacy and safety to support all three indications at the recommended doses.

VI. RECOMMENDATIONS

I recommend approval of topiramate, as an adjunctive agent, for the treatment of (1) pediatric partial-onset seizures, (2) Lennox-Gastaut syndrome (in children>2 years of age and adults), and (3) primary generalized tonic-clonic seizures in adults.

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NDA 20,505 (1) Supplements (Topamax: [a] pediatric partial-onset seizures, [b] Lennox-Gastaut, [c] generalized tonic-clonic seizures); (2) Four-Month Safety Update; (3) 20 March 1998 (ISE update); (4) 28 April 1998 (additional analyses) div file/Katz R/Ware J/Tresley R/9 May 1998