CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

Trade Name: Topamax

Generic Name: topiramate

Sponsor: Ortho-McNeil Pharmaceutical, Inc.

Approval Date: June 29, 2005

Purpose: Provides for the use of topiramate as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-505/S-018 & NDA 20-844/S-015
NDA 20-505/S-026 & NDA 20-844/S-022

Ortho-McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Catherine M. Glamkowski
Associate Director, Regulatory Affairs
920 Route 2020 South; P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Glamkowski:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Application	Drug Product	Submitted on:	Received on:	Provides for:
NDA 20-505/S-018	Topamax (topiramate) Tablets	October 29, 2002	October 30, 2002	Use of topiramate as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures.
NDA 20-844/S-015	Topamax (topiramate capsules) Sprinkle Capsules			
NDA 20-505/S-026	Topamax (topiramate) Tablets	April 9, 2004	April 12, 2004	Information regarding drug interactions between topiramate and hydrochlorothiazide and topiramate and pioglitazone.
NDA 20-844/S-022	Topamax (topiramate capsules) Sprinkle Capsules			

We also acknowledge receipt of your additional submissions to NDA 20-505/S-018 and NDA 20-844/S-015 dated January 18, 2005, January 26, 2005, April 21, 2005, May 10, 2005, and May 17, 2005.

Your submission of May 10, 2005 constituted a complete response to our January 19, 2005 action letter.

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed, agreed-upon labeling text. Accordingly, this application is approved, effective on the date of this letter.

Labeling

The final printed labeling (FPL) must be identical to the enclosed approved labeling text (text for the package insert). Marketing these products with FPL that is not identical to the approved labeling text may render these products misbranded.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplements NDA 20-505/S-018/S-026 and NDA 20-844/S-015/S-022**." Approval of these submissions by FDA is not required before the labeling is used.

Pediatrics

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for initial monotherapy in patients with partial seizures or primary generalized tonic clonic seizures ages birth up to 2 years.

We are deferring pediatric studies for initial monotherapy in patients with partial seizures or primary generalized tonic clonic seizures ages 2 years up to 10 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study(ies) under PREA for the treatment of initial monotherapy in pediatric patients with partial seizures or primary generalized tonic clonic seizures ages 2 years up to 10 years.

   Final Report Submission: June 30, 2010

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

Postmarketing Study Commitments

We remind you of your post-marketing study commitment in your submission dated May 27, 2004. This commitment is listed below, and we note that you submitted your draft protocol on November 24, 2004 as agreed.

1. A repeated-dose study in neonatal/juvenile rats to assess the effects of topiramate on growth and development

Submit draft protocol for review and discussion	November 2004
Start range-finding study	August 2005
Start definitive study	November 2005
Total time post-sNDA approval for submission of final report	September 2006

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Healthcare Professional Letters

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Reporting Requirements

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at 301-594-2850.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
6/29/05 10:07:35 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-505/S-018
NDA 20-844/S-015

Ortho-McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Catherine M. Glamkowski
Associate Director, Regulatory Affairs
920 Route 2020 South; P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Glamkowski:

Please refer to your supplemental new drug applications dated October 29, 2002, received October 30, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topamax (topiramate) Tablets and Topamax (topiramate capsules) Sprinkle Capsules.

We acknowledge receipt of your additional submissions dated December 4, 2003, January 27, 2004, March 23, 2004, May 27, 2004, June 18, 2004, July 19, 2004, November 24, 2004, and January 6, 2005.

Your submission of July 19, 2004 constituted a complete response to our November 26, 2003 action letter.

These supplemental new drug applications provide for the use of topiramate as monotherapy in adults and children 6 years of age and older with newly diagnosed epilepsy.

We have completed our review of these applications, as amended, and have determined that they are approvable. Before these applications may be approved, however, we ask that you respond to the following comments and requests.

The multiple imputations method and censoring bias function you have employed appear to be reasonable and thoughtful approaches to the fundamental questions raised in our November 26, 2003 Approvable letter. However, questions remain about each of these methods that preclude us from definitively concluding at this time that topiramate is effective as monotherapy.

With regard to the censoring bias function approach, we cannot be confident that this methodology is unambiguously interpretable. As you know, this method has not been validated, and the theory supporting this method is not well established. Further, and critically, we had discussed the necessity for clinical experts to choose the clinically relevant range of the parameters alpha and tau. However, as you acknowledge, the clinical interpretation of these parameters is so unclear that clinical experts are not likely to have a sufficient understanding of their meaning to make an informed choice of the relevant range of these values; indeed, as far as we can tell, you did not consult such experts in your

choice of the values you assigned to these parameters. For these reasons, although the approach is intriguing and suggestive, we cannot base a regulatory decision about effectiveness on its results.

However, we believe the multiple imputations method may permit us to reach such a conclusion.

Specifically, the range of p-values you present corresponding to the various imputed seizure rates in the discontinuation cohorts would be adequate to support a conclusion that topiramate is effective as monotherapy. In particular, the results as you present them support the conclusion that any reasonable imputed rates for these cohorts would result in statistically significant between-treatment differences.

However, as you know, the multiple imputations method uses a conditional exponential distribution and a chi-square test to produce p-values. Given this, we note that when seizure rates approach 100%, p-values from the multiple imputations method should approach those produced by the all-cause analysis, even though the patients' withdrawn times used are different in the two methods. However, we found that the p-value produced by the multiple imputations method when the assumed seizure rate is approaching 100% is less than half of that calculated in the all-cause analysis. Based on this finding, we are concerned about the appropriateness of your approach and the p-values it generated. Until we can understand this discrepancy and be confident that the p-values you have presented are appropriate, we cannot definitively decide the question of effectiveness.

If we were, ultimately, to conclude that topiramate is effective, other problems will need to be addressed.

In Study 106, the effective dose of 400 mg/day was reached in 6-7 weeks. In our view, this prolonged duration until an effective dose is reached raises serious questions about the propriety of approving topiramate as "initial" monotherapy (we recognize, of course, that you are proposing that topiramate be approved as monotherapy for "newly diagnosed patients"; we will have additional comments on this proposal below). That is, we would expect that a treatment to be used as monotherapy in epilepsy should be able to be titrated to an effective dose in a minimal amount of time, given that, at least as initial monotherapy, patients will not be receiving any other treatment. In order to support approval for initial monotherapy (or any similar claim), you must justify the safety of the long latency until an effective dose is achieved.

We note, of course, that you have presumably concluded, based on our reading of your proposed labeling, that doses of 100 mg and greater are effective doses. This conclusion is based on analyses you have done that have yielded nominally significant p-values at early weeks during the titration phase.

We disagree with your conclusion that the nominally significant comparisons at these earlier weeks establish that the doses attained at those time points are effective. Specifically, patients were treated with these lower doses for only one week; an effect seen at a dose given for only one week cannot reliably predict the effect at that same dose if patients were to stay on that dose for some longer, more reasonable, duration. It is theoretically possible that the data generated at these earlier weeks might be able to support a conclusion that, under this specific titration scheme (employed to reach the target dose of 400 mg/day), effectiveness appears to first be observed at a particular lower dose (or doses), but we do not consider this to be equivalent to concluding that these lower doses are, in themselves, effective. Further, we do not believe that we can even conclude, at this time, that effectiveness appears to be observed at doses lower than 400 mg/day, because we are unsure (given the difficulties

associated with potential informative censoring) how best to analyze the data at these earlier time points.

We could consider (all other things being equal) granting approval for conversion to monotherapy, despite the fact that you have not studied this setting. However, such a claim would be problematic for two reasons.

First, we cannot be certain that the patients who would be candidates for conversion to monotherapy are sufficiently similar to the patients you studied to permit us to conclude that it would be effective in that population. Specifically, it is our understanding that patients on multiple other drugs who are being considered for conversion to monotherapy typically have a more severe form of epilepsy than patients being treated initially with monotherapy. In this regard, not only did the patients enrolled in Study 106 have very few seizures prior to enrollment, but your re-analysis of Study 104 strongly suggests that it is just these patients (and not patients with more severe epilepsy) who benefit from topiramate monotherapy.

Second, before we could approve a treatment for a conversion to monotherapy claim, we would need to be able to provide dosing recommendations for the conversion. In the absence of empirical data supporting such a recommendation, it might be possible to provide dosing recommendations based on pharmacokinetic considerations (although this is less preferable than empirical data). In either case, you have not addressed this issue.

Although you have proposed that topiramate be approved as monotherapy for newly diagnosed patients, we believe that this indication is also potentially problematic.

In our view, it would be difficult for prescribers to understand which patients would benefit from such a treatment. It is not clear which patients are subsumed under this designation. For example, patients with a history of many seizures might be "newly diagnosed" if they have not sought medical attention early in their course; as discussed above, we have questions about whether or not topiramate would be effective in these patients (assuming, of course, that we conclude it is effective at all as monotherapy). If we were to approve topiramate for patients with "mild" epilepsy, we are not confident that this designation is standard in this field; that is, each practitioner would presumably have his or her own definition of which patients meet this definition, and, again, we are not confident that topiramate would be effective in patients with more frequent seizures. Finally, if we were to approve this claim, this might support, legally, advertising that described such a drug as the first, or only, treatment specifically approved for newly diagnosed patients, when, in fact, this claim would represent a restricted claim, and we consider all previously approved treatments for monotherapy to subsume this use as well as use in other settings. We would like you to address these issues.

Finally, we note that wish to have the claim for monotherapy apply to children down to the age of 6 years. In your studies, you have enrolled a total of 20 patients below the age of 10 years. Given that the dose studied was 400 mg/day, a relatively high dose associated with significant risk of adverse events (including a high rate of metabolic acidosis), we question whether such minimal experience in these younger patients justifies approving the claim in these patients. Please address this issue.

Labeling
Because we still have not yet resolved what we consider fundamental issues related to a decision about the effectiveness of Topamax as monotherapy, we believe it would be premature to provide draft labeling with this letter at this time. However, in anticipation of eventual labeling discussions, we ask that you revise your proposed labeling in response to the following requests.

1. In your most recently proposed draft labeling, you have not updated the Cognitive/Neuropsychiatric Adverse Events section of the labeling with information for monotherapy in epilepsy. Specifically, you should draft language under the subheadings Cognitive-Related Dysfunction, Psychiatric/Behavioral Disturbances, and Somnolence/Fatigue based on the adult data from Study 106. The analyses should mirror those already described for adjunctive therapy in epilepsy and migraine.

2. Under the subheading Pediatric Patients, you should describe the discontinuations due to adverse events, if any, in Study 106.

3. In the Monotherapy Adverse Events Tables you provided, there are columns for daily doses of (b) (4) mg/day. Because these will not be recommended daily doses, we ask you to remove these columns. Further, because of differences in study design across the monotherapy studies, we believe that only the data from Study 106 should be described in the tables for both adult and pediatric patients.

4. In the pediatric Adverse Events Table, (b) (4) is listed with an incidence of (b) (4) in all but the (b) (4) mg/day dose column. Based on the analyses of lab data you provided, we believe this may be misleading. Please address this issue.

5. Please update the Metabolic Acidosis Warning section to include monotherapy data from Study 106.

We recognize that many of the issues we have identified in this letter could have been identified in our initial November 26, 2003 Approvable letter. However, in our initial review, the issues surrounding the fundamental question about the product's effectiveness were sufficiently complex that we primarily focused on trying to address that question. We regret any inconvenience that not identifying these issues earlier may have caused; we believe, however, that this application has raised significant and complex problems of data analysis and interpretation that have required unusually extensive efforts to try to solve. We do believe, however, that in this letter we have identified the major issues that are still pending at this time.

Acknowledgment of Post-marketing Commitment
We remind you of your post-marketing study commitment in your submission dated May 27, 2004. This commitment is listed below, and we note that you submitted your draft protocol on November 24, 2004 as agreed.

1. A repeated-dose study in neonatal/juvenile rats to assess the effects of topiramate on growth and development

Submit draft protocol for review and discussion	November 2004
Start range-finding study	sNDA Approval + 2 month
Start definitive study	sNDA Approval + 5 months
Total time post-sNDA approval for submission of final report	sNDA Approval + 15 months

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

Other
Within 10 days after the date of this letter, you are required to amend these applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change before approval of these supplemental applications.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-505/S-018
NDA 20-844/S-015

Ortho-McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Catherine M. Glamkowski
Associate Director, Regulatory Affairs
920 Route 2020 South; P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Glamkowski:

Please refer to your supplemental new drug applications dated October 29, 2003, received October 30, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topamax (topiramate) Tablets and Topamax (topiramate capsules) Sprinkle Capsules.

We acknowledge receipt of your additional submissions dated:

February 19, 2003	March 21, 2003	July 31, 2003
February 28, 2003	April 4, 2003	November 11, 2003
March 17, 2003	June 10, 2003	November 12, 2003

These supplemental new drug applications provide for the use of topiramate as monotherapy in adults and children 6 years of age and older with newly diagnosed epilepsy.

We have completed our review of these applications, as amended, and have determined that they are approvable. Before these applications may be approved, however, we ask that you respond to the following comments and requests.

As you know, we have been concerned about the effects of the large and differential number of patients who discontinued from Study TOPMAT-EPMN-106 before completing the trial or meeting exit criteria on the interpretability of the results of the primary analysis. Specifically we are concerned about whether these early discontinuations introduced a bias into the analysis.

We recognize that no analysis can definitively establish that the censoring was non-informative. However, we note that you have made several reasonable attempts to establish that the patients who discontinued the study early (and especially those who discontinued secondary to adverse events) were not fundamentally different in any relevant way from those who remained in the trial, and therefore would not be expected to have had a different intrinsic propensity to seizures. While these investigations have not identified any obvious reason to expect that an important bias has been introduced, we are concerned that additional work that may shed further light on this question has not been done. We are aware that various statistical methodologies have been proposed to deal with the question of informative censoring. In order to more definitively address this question, we ask you to propose additional statistical approaches to further evaluate this question.

In addition, we note that the large and differential number of discontinuations raise questions about what seizure rate to ascribe to these patients; these questions exist independent of whether or not the censoring is informative. In attempting to address this concern, you have performed simulations in which you assigned equal seizure rates to the discontinuation cohorts of both treatment groups, varying these rates from 1 to 99%. According to the analyses performed in which you accounted for all 114 early discontinuations (we believe that this is the more appropriate analysis, rather than the analysis that estimated varying seizure rates for only the 53 patients who discontinued due to adverse events), statistical significance of the between-treatment comparison is lost at seizure rates above 55%.

The interpretation of these simulations is problematic for several reasons.

First, we have questions about the p-values you have generated for each of these seizure rate strata. In particular, we note that you performed only a single run for each stratum; we believe that it would be more appropriate to perform repeated runs for each stratum. Further, when repeated runs are performed, you will need to address the question of how best to report (and interpret) the range of p-values generated.

Second, we are not confident that we can know how to reliably choose the particular seizure rate which should best inform our decision about the drug's effectiveness as monotherapy (we note that the cumulative risk of a next seizure in Study TOPMAT-EPMN-104 in the high dose group is about 50% and about 70% in the low dose group). Further, while we acknowledge and understand your choice of assigning equal seizure rates to both treatment groups, it is possible that performing simulations using a range of different absolute rates of seizures and different differences between the rates (i.e., varying the absolute rates yielding a given difference between the rates as well as varying the differences between different absolute rates) might provide additional insights into how to best make this decision. The purpose of these analyses would be to examine an increased range of outcomes possible under various assumptions about seizure rates, thereby hopefully providing better support for an informed decision about the effectiveness of the drug.

Finally, we must take note of the results of the primary analysis of Study TOPMAT-EPMN-104, the time to second seizure. As you know, this analysis revealed not only a non-significant between-treatment contrast, but the two Kaplan-Meier plots were nearly superimposable. We also note that the results of the analysis of time to first seizure (the primary outcome in Study TOPMAT-EPMN-106) in that study was nearly nominally significant, and similar to that seen in Study TOPMAT-EPMN-106. This, of course, raises the possibility that the time to second seizure in Study TOPMAT-EPMN-106, had it been collected, would have been similar to that seen in Study TOPMAT-EPMN-104. Were thissituation to represent the true state of affairs, it would raise serious concerns about the clinical meaning of time to first seizure as a measure of effectiveness of topiramate as monotherapy, even if we could be convinced that the result of the primary analysis of StudyTOPMAT- EPMN-106 was reliable. We are mindful that comparisons between studies can be misleading. Nonetheless, in this case the finding is of concern. We note that you had previously attempted to re-analyze Study TOPMAT-EPMN-104 (presented in a submission to IND 28,549 dated 7/20/98), and that we did not find your proposal acceptable. More to the point, however, we do not believe that you have ever adequately addressed this finding, and its clinical meaning, especially in the face of a nearly nominally significant finding on the time to the first seizure. Before we could approve this application, therefore, you will need to provide an explanation for this finding, and provide a convincing argument that it should not preclude a conclusion that the drug is effective as monotherapy.

For these reasons, we would like you to provide the above-described additional simulations and analyses, as well as the requested discussion about the outcome of Study TOPMAT-EPMN-104. We urge you to discuss with us your approach to these requests before you initiate any additional work.

Finally, because we have not yet resolved what we consider fundamental issues related to a decision about the effectiveness of Topamax as monotherapy, we believe it would be premature to provide draft labeling with this letter at this time.

Request for Post-Marketing Commitment
We note that topiramate has not yet been evaluated in a juvenile animal toxicology study. Therefore, we ask that you agree to conduct a repeated-dose study in neonatal/juvenile rats to assess the effects of topiramate on growth and development. Since there are no standard protocols in this area, we suggest that you design a study that would address long-term effects in animals of an age range analogous to that of the pediatric patient population. The protocol for such a study should be submitted for review prior to initiation.

When you respond to this post-marketing commitment study request, please include the following projected dates (month and year) for (1) submission of protocol, (2) start of study, and (3) submission of final study report.

Other
Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change before approval of these supplemental applications.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz

11/26/03 04:44:43 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

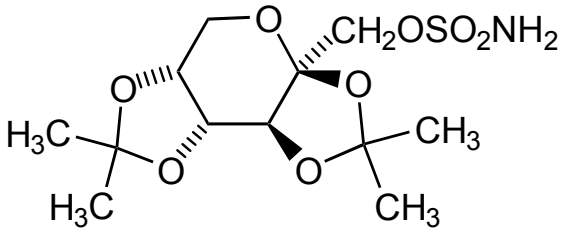
LABELING

TOPAMAX®
(topiramate)
Tablets
TOPAMAX®
(topiramate capsules)
Sprinkle Capsules

DESCRIPTION

Topiramate is a sulfamate-substituted monosaccharide. TOPAMAX® (topiramate) Tablets are available as 25 mg, 50 mg, 100 mg, and 200 mg round tablets for oral administration. TOPAMAX® (topiramate capsules) Sprinkle Capsules are available as 15 mg and 25 mg sprinkle capsules for oral administration as whole capsules or opened and sprinkled onto soft food.

Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.37. Topiramate is designated chemically as 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate and has the following structural formula:



TOPAMAX® (topiramate) Tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, titanium dioxide, polyethylene glycol, synthetic iron oxide (50, 100 and 200 mg tablets) and polysorbate 80.

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain topiramate coated beads in a hard gelatin capsule. The inactive ingredients are: sugar spheres (sucrose

and starch), povidone, cellulose acetate, gelatin, silicone dioxide, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

CLINICAL PHARMACOLOGY

Mechanism of Action:

The precise mechanisms by which topiramate exerts its anticonvulsant and migraine prophylaxis effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and migraine prophylaxis. Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant concentrations, blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

Pharmacodynamics:

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole. Topiramate is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia.

Pharmacokinetics:

The sprinkle formulation is bioequivalent to the immediate release tablet formulation and, therefore, may be substituted as a therapeutic equivalent.

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady state is thus reached in about 4 days in patients with normal renal function. Topiramate is 15-41% bound to human plasma proteins over the blood concentration range of 0.5 - 250 μg/mL. The fraction bound decreased as blood concentration increased.

Carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 ug/mL (a concentration 5-10 times higher than considered therapeutic for valproate) decreased the protein binding of topiramate from 23% to 13%. Topiramate does not influence the binding of sodium valproate.

Metabolism and Excretion:

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

Pharmacokinetic Interactions (see also Drug Interactions):

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized under **PRECAUTIONS (Table 3).**

Special Populations:

Renal Impairment:

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30-69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment (see **PRECAUTIONS: Adjustment of Dose in Renal Failure** and **DOSAGE AND ADMINISTRATION**).

Hemodialysis:

Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20-30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may be required (see **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment:

In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood.

Age, Gender, and Race:

The pharmacokinetics of topiramate in elderly subjects (65-85 years of age, N=16) were evaluated in a controlled clinical study. The elderly subject population had reduced renal function [creatinine clearance (-20%)] compared to young adults. Following a single oral 100 mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1-2 hours. Reflecting the primary renal elimination of topiramate, topiramate plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced. As recommended for all patients, dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate $\leq$70 mL/min/1.73 m^2) is evident. It may be useful to monitor renal function in the elderly patient (see **Special Populations: Renal Impairment, PRECAUTIONS: Adjustment of Dose in Renal Failure** and **DOSAGE AND ADMINISTRATION**).

Clearance of topiramate in adults was not affected by gender or race.

Pediatric Pharmacokinetics:

Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose.

Pediatric patients have a 50% higher clearance and consequently shorter elimination half-life than adults. Consequently, the plasma concentration for the same mg/kg dose may be lower in pediatric patients compared to adults. As in adults, hepatic enzyme-inducing antiepileptic drugs decrease the steady state plasma concentrations of topiramate.

CLINICAL STUDIES

The studies described in the following sections were conducted using TOPAMAX® (topiramate) Tablets.

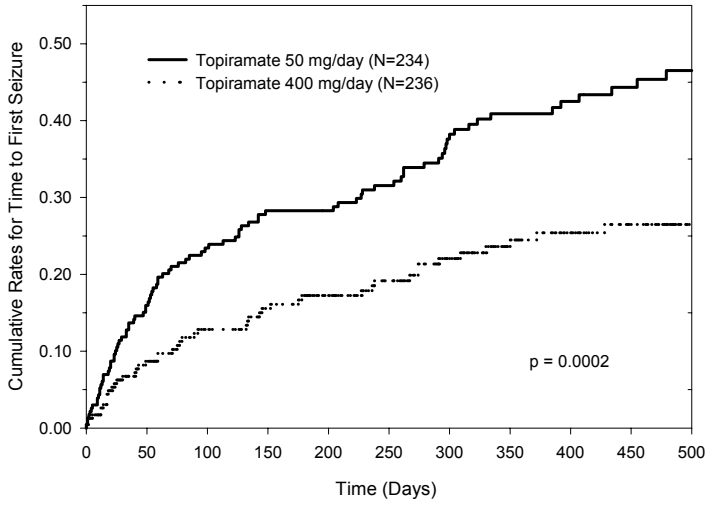
Epilepsy

Monotherapy Controlled Trial

The effectiveness of topiramate as initial monotherapy in adults and children 10 years of age and older with partial onset or primary generalized seizures was established in a multicenter, randomized, double-blind, parallel-group trial.

The trial was conducted in 487 patients diagnosed with epilepsy (6 to 83 years of age) who had 1 or 2 well-documented seizures during the 3-month retrospective baseline phase who then entered the study and received topiramate 25 mg/day for 7 days in an open-label fashion. Forty-nine percent of subjects had no prior AED treatment and 17% had a diagnosis of epilepsy for greater than 24 months. Any AED therapy used for temporary or emergency purposes was discontinued prior to randomization. In the double-blind phase, 470 patients were randomized to titrate up to 50 mg/day or 400 mg/day. If the target dose could not be achieved, patients were maintained on the maximum tolerated dose. Fifty eight percent of patients achieved the maximal dose of 400 mg/day for $\geq$ 2 weeks, and patients who did not tolerate 150 mg/day were discontinued. The primary efficacy assessment was a between group comparison of time to first seizure during the double-blind phase. Comparison of the Kaplan-Meier survival curves of time to first seizure favored the topiramate 400 mg/day group over the topiramate 50 mg/day group (p=0.0002, log rank test; Figure 1). The treatment effects with respect to time to first seizure were consistent across various patient subgroups defined by age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use.

Figure 1: Kaplan-Meier Estimates of Cumulative Rates for Time to First Seizure



Adjunctive Therapy Controlled Trials in Adult Patients With Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for adults with partial onset seizures was established in six multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo and four comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalized seizures.

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® Tablets or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during baseline phase lasting between 4 and 12 weeks. Patients who experienced a prespecified minimum number of partial onset seizures, with or without secondary generalization, during the baseline phase (12 seizures for 12-week baseline, 8 for 8-week baseline, or 3 for 4-week baseline) were randomly assigned to placebo or a specified dose of TOPAMAX® Tablets in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. In five of the six studies, patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. In the sixth study (119), the 25 or 50 mg/day initial doses of topiramate were followed by respective weekly increments of 25 or 50 mg/day until the target dose of 200 mg/day was reached. After titration, patients entered a 4, 8, or 12-week stabilization period.

The numbers of patients randomized to each dose, and the actual mean and median doses in the stabilization period are shown in Table 1.

Adjunctive Therapy Controlled Trial in Pediatric Patients Ages 2 - 16 Years With Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for pediatric patients ages 2 - 16 years with partial onset seizures was established in a multicenter, randomized, double-blind, placebo-controlled trial, comparing topiramate and placebo in patients with a history of partial onset seizures, with or without secondarily generalized seizures.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® Tablets or placebo. In this study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8 week baseline phase. Patients who experienced at least six partial onset seizures, with or without secondarily generalized seizures, during the baseline phase were randomly assigned to placebo or TOPAMAX® Tablets in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 25 or 50 mg per day; the dose was then increased by 25 mg to 150 mg/day increments every other week until the assigned dosage of 125, 175, 225, or 400 mg/day based on patients' weight to approximate a dosage of 6 mg/kg per day was reached, unless intolerance prevented increases. After titration, patients entered an 8-week stabilization period.

Adjunctive Therapy Controlled Trial in Patients With Primary Generalized Tonic-Clonic Seizures

The effectiveness of topiramate as an adjunctive treatment for primary generalized tonic-clonic seizures in patients 2 years old and older was established in a multicenter randomized, double-blind, placebo-controlled trial, comparing a single dosage of topiramate and placebo.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. Patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least three primary generalized tonic-clonic seizures during the baseline phase were randomly assigned to placebo or TOPAMAX® in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 50 mg per day for four weeks; the dose was then increased by 50 mg to 150 mg/day increments every other week until the assigned dose of 175, 225, or 400 mg/day based on patients' body weight to approximate a dosage of 6 mg/kg per day was reached, unless intolerance prevented increases. After titration, patients entered a 12-week stabilization period.

Adjunctive Therapy Controlled Trial in Patients With Lennox-Gastaut Syndrome

The effectiveness of topiramate as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome was established in a multicenter, randomized, double-blind, placebo-controlled trial comparing a single dosage of topiramate with placebo in patients 2 years of age and older.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. Patients who were experiencing at least 60 seizures per month before study entry were stabilized on optimum dosages of their concomitant AEDs during a 4-week baseline phase. Following baseline, patients were randomly assigned to placebo or TOPAMAX® in addition to their other AEDs. Active drug was titrated beginning at 1 mg/kg per day for a week; the dose was then increased to 3 mg/kg per day for one week then to 6 mg/kg per day. After titration, patients entered an 8-week stabilization period. The primary measures of effectiveness were the percent reduction in drop attacks and a parental global rating of seizure severity.

Table 1: Topiramate Dose Summary During the Stabilization Periods of Each of Six Double-Blind, Placebo-Controlled, Add-On Trials in Adults with Partial Onset Seizures[b]

Protocol Stabilization Dose		Target Topiramate Dosage (mg/day)					
		Placebo[a]	200	400	600	800	1,000
YD	N	42	42	40	41	--	--
	Mean Dose	5.9	200	390	556	--	--
	Median Dose	6.0	200	400	600	--	--
YE	N	44	--	--	40	45	40
	Mean Dose	9.7	--	--	544	739	796
	Median Dose	10.0	--	--	600	800	1,000
Y1	N	23	--	19	--	--	--
	Mean Dose	3.8	--	395	--	--	--
	Median Dose	4.0	--	400	--	--	--
Y2	N	30	--	--	28	--	--
	Mean Dose	5.7	--	--	522	--	--
	Median Dose	6.0	--	--	600	--	--
Y3	N	28	--	--	--	25	--
	Mean Dose	7.9	--	--	--	568	--
	Median Dose	8.0	--	--	--	600	--
119	N	90	157	--	--	--	--
	Mean Dose	8	200	--	--	--	--
	Median Dose	8	200	--	--	--	--

[a] Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocols YD and Y2, 6 tablets/day; Protocol Y3 and 119, 8 tablets/day; Protocol YE, 10 tablets/day.

[b] Dose-response studies were not conducted for other indications or pediatric partial onset seizures.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reductions in seizure rates and the responder rates (fraction of patients with at least a 50% reduction) by treatment group for each study are shown below in Table 2. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

Table 2: Efficacy Results in Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Efficacy Results	Placebo	Target Topiramate Dosage (mg/day) 200	400	600	800	1,000	≈6 mg/kg/day*
Partial Onset Seizures								
Studies in Adults								
YD	N	45	45	45	46	--	--	--
	Median % Reduction	11.6	27.2[a]	47.5[b]	44.7[c]	--	--	--
	% Responders	18	24	44[d]	46[d]	--	--	--
YE	N	47	--	--	48	48	47	--
	Median % Reduction	1.7	--	--	40.8[c]	41.0[c]	36.0[c]	--
	% Responders	9	--	--	40[c]	41[c]	36[d]	--
Y1	N	24	--	23	--	--	--	--
	Median % Reduction	1.1	--	40.7[e]	--	--	--	--
	% Responders	8	--	35[d]	--	--	--	--
Y2	N	30	--	--	30	--	--	--
	Median % Reduction	-12.2	--	--	46.4[f]	--	--	--
	% Responders	10	--	--	47[c]	--	--	--
Y3	N	28	--	--	--	28	--	--
	Median % Reduction	-20.6	--	--	--	24.3[c]	--	--
	% Responders	0	--	--	--	43[c]	--	--
119	N	91	168	--	--	--	--	--
	Median % Reduction	20.0	44.2[c]	--	--	--	--	--
	% Responders	24	45[c]	--	--	--	--	--
Studies in Pediatric Patients								
YP	N	45	--	--	--	--	--	41
	Median % Reduction	10.5	--	--	--	--	--	33.1[d]
	% Responders	20	--	--	--	--	--	39
Primary Generalized Tonic-Clonic[h]								
YTC	N	40	--	--	--	--	--	39
	Median % Reduction	9.0	--	--	--	--	--	56.7[d]
	% Responders	20	--	--	--	--	--	56[c]
Lennox-Gastaut Syndrome[i]								
YL	N	49	--	--	--	--	--	46
	Median % Reduction	-5.1	--	--	--	--	--	14.8[d]
	% Responders	14	--	--	--	--	--	28[g]
	Improvement in Seizure Severity[j]	28	--	--	--	--	--	52[d]

Comparisons with placebo: [a] p=0.080; [b] p≤0.010; [c] p≤0.001; [d] p≤0.050; [e] p=0.065; [f] p≤0.005; [g] p=0.071;
[h] Median % reduction and % responders are reported for PGTC Seizures;
[i] Median % reduction and % responders for drop attacks, i.e., tonic or atonic seizures;
[j] Percent of subjects who were minimally, much, or very much improved from baseline

* For Protocols YP and YTC, protocol-specified target dosages (<9.3 mg/kg/day) were assigned based on subject's weight to approximate a dosage of 6 mg/kg per day; these dosages corresponded to mg/day dosages of 125, 175, 225, and 400 mg/day.

Subset analyses of the antiepileptic efficacy of TOPAMAX® Tablets in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

Migraine

The results of 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials established the effectiveness of TOPAMAX® in the prophylactic treatment of migraine headache. The design of both trials (one study was conducted in the U.S. and one study was conducted in the U.S. and Canada) was identical, enrolling patients with a history of migraine, with or without aura, for at least 6 months, according to the International Headache Society diagnostic criteria. Patients with a history of cluster headaches or basilar, ophthalmoplegic, hemiplegic, or transformed migraine headaches were excluded from the trials. Patients were required to have completed up to a 2 week washout of any prior migraine preventive medications before starting the baseline phase.

Patients who experienced 3 to 12 migraine headaches over the 4-weeks in the baseline phase were equally randomized to either TOPAMAX® 50 mg/day, 100 mg/day, 200 mg/day, or placebo and treated for a total of 26 weeks (8-week titration period and 18-week maintenance period). Treatment was initiated at 25 mg/day for one week, and then the daily dosage was increased by 25-mg increments each week until reaching the assigned target dose or maximum tolerated dose (administered twice daily).

Effectiveness of treatment was assessed by the reduction in migraine headache frequency, as measured by the change in 4-week migraine rate from the baseline phase to double-blind treatment period in each TOPAMAX® treatment group compared to placebo in the intent to treat (ITT) population.

In the first study a total of 469 patients (416 females, 53 males), ranging in age from 13 to 70 years, were randomized and provided efficacy data. Two hundred sixty five patients completed the entire 26-week double-blind phase. The median average daily dosages were 47.8 mg/day, 88.3 mg/day, and 132.1 mg/day in the target dose groups of TOPAMAX® 50, 100, and 200 mg/day, respectively.

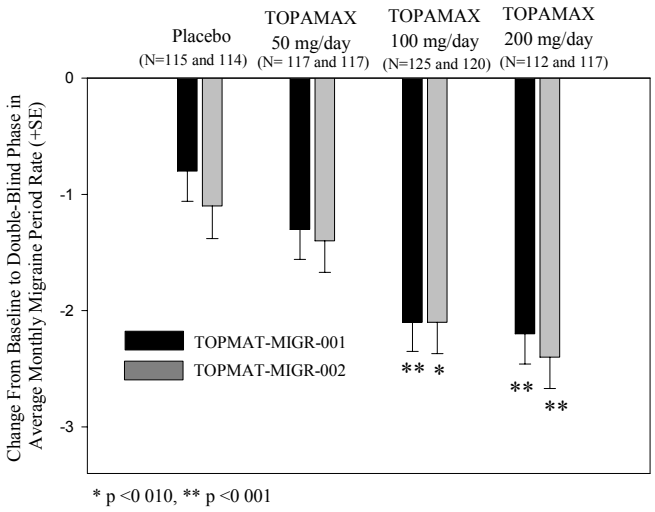
The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches/28 days and was similar across treatment groups. The change in the mean 4-week migraine headache frequency from baseline to the double-blind phase was -1.3, -2.1, and -2.2 in the TOPAMAX® 50, 100, and 200 mg/day groups, respectively, versus -0.8 in the placebo group (see Figure 2). The differences between the TOPAMAX® 100 and 200 mg/day groups versus placebo were statistically significant ($p<0.001$ for both comparisons).

In the second study a total of 468 patients (406 females, 62 males), ranging in age from 12 to 65 years, were randomized and provided efficacy data. Two hundred fifty five patients completed the entire 26-week double-blind phase. The median average daily dosages were 46.5 mg/day, 85.6 mg/day, and 150.2 mg/day in the target dose groups of TOPAMAX® 50, 100, and 200 mg/day, respectively.

The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches/28 days and was similar across treatment groups. The change in the mean 4-week migraine headache period frequency from baseline to the double-blind phase was -1.4, -2.1, and -2.4 in the TOPAMAX® 50, 100, and 200 mg/day groups, respectively, versus –1.1 in the placebo group (see Figure 2). The differences between the TOPAMAX® 100 and 200 mg/day groups versus placebo were statistically significant (p=0.008 and <0.001, respectively).

In both studies, there were no apparent differences in treatment effect within age, or gender, subgroups. Because most patients were Caucasian, there were insufficient numbers of patients from different races to make a meaningful comparison of race.

Figure 2: Reduction in 4-Week Migraine Headache Frequency (Studies TOPMAT-MIGR-001 and TOPMAT-MIGR-002)



* p <0 010, ** p <0 001

INDICATIONS AND USAGE

Monotherapy Epilepsy

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures.

Effectiveness was demonstrated in a controlled trial in patients with epilepsy who had no more than 2 seizures in the 3 months prior to enrollment. Safety and effectiveness in patients who were converted to monotherapy from a previous regimen of other anticonvulsant drugs have not been established in controlled trials.

Adjunctive Therapy Epilepsy

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2 - 16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

Migraine

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated for adults for the prophylaxis of migraine headache. The usefulness of TOPAMAX® in the acute treatment of migraine headache has not been studied.

CONTRAINDICATIONS

TOPAMAX® is contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS

Metabolic Acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can

occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may be additive to the bicarbonate lowering effects of topiramate.

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mEq/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence of persistent treatment-emergent decreases in serum bicarbonate in adults in the epilepsy controlled clinical trial for monotherapy was 15% for 50 mg/day and 25% for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in the adjunctive therapy trials was 3% for 400 mg/day, and 0% for placebo and in the monotherapy trial was 1% for 50 mg/day and 7% for 400 mg/day. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

In pediatric patients (<16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures was 67% for TOPAMAX (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for TOPAMAX and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

In pediatric patients (10 years up to 16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in the epilepsy controlled clinical trial for monotherapy was 7% for 50 mg/day and 20% for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in this trial was 4% for 50 mg/day and 4% for 400 mg/day.

The incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44% for 200 mg/day, 39% for 100 mg/day, 23% for 50 mg/day, and 7% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for 200 mg/day, 9% for 100 mg/day, 2% for 50 mg/day, and <1% for placebo.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

Acute Myopia and Secondary Angle Closure Glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX®. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating TOPAMAX® therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible, according to the judgment of the treating

physician. Other measures, in conjunction with discontinuation of TOPAMAX®, may be helpful.

Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.

Oligohidrosis and Hyperthermia

Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with TOPAMAX® use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures.

The majority of the reports have been in children. Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TOPAMAX® is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

Withdrawal of AEDs

Antiepileptic drugs, including TOPAMAX®, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Cognitive/Neuropsychiatric Adverse Events

Adults

Adverse events most often associated with the use of TOPAMAX® were related to the central nervous system and were observed in both the epilepsy and migraine populations. In adults, the most frequent of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g. confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g. depression or mood problems); and 3) Somnolence or fatigue.

Cognitive-Related Dysfunction

The majority of cognitive-related adverse events were mild to moderate in severity, and they frequently occurred in isolation. Rapid titration rate and higher initial dose were associated with higher incidences of these events. Many of these events contributed to withdrawal from treatment [see **ADVERSE REACTIONS, Table 4, Table 6, and Table 10**].

In the original add-on epilepsy controlled trials (using rapid titration such as 100-200 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse events was 42% for 200 mg/day, 41% for 400 mg/day, 52% for 600 mg/day, 56% for 800 and 1000 mg/day, and 14% for placebo. These dose-related adverse reactions began with a similar frequency in the titration or in the maintenance phase, although in some patients the events began during titration and persisted into the maintenance phase. Some patients who experienced one or more cognitive-related adverse events in the titration phase had a dose-related recurrence of these events in the maintenance phase.

In the monotherapy epilepsy controlled trial, the proportion of patients who experienced one or more cognitive-related adverse events was 19% for TOPAMAX® 50 mg/day and 26% for 400 mg/day.

In the 6-month migraine prophylaxis controlled trials using a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse events was 19% for TOPAMAX® 50 mg/day, 22% for 100 mg/day, 28% for 200 mg/day, and 10% for placebo. These dose-related adverse reactions typically began in the titration phase and often persisted into the maintenance phase, but infrequently began in the maintenance phase. Some patients experienced a recurrence of one or more of these cognitive adverse events and this recurrence was typically in the titration phase. A relatively small proportion of topiramate-treated patients experienced more than one concurrent cognitive adverse event. The most common cognitive adverse events occurring together included difficulty with memory along with difficulty with concentration/attention, difficulty with memory along with language problems, and difficulty with concentration/attention along with language problems. Rarely, topiramate-treated patients experienced three concurrent cognitive events.

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (depression or mood problems) were dose-related for both the epilepsy and migraine populations.

Somnolence/Fatigue

Somnolence and fatigue were the adverse events most frequently reported during clinical trials of TOPAMAX® for adjunctive epilepsy. For the adjunctive epilepsy population, the incidence of somnolence did not differ substantially between 200 mg/day and 1000 mg/day, but the incidence of fatigue was dose-related and increased

at dosages above 400 mg/day. For the monotherapy epilepsy population in the 50 mg/day and 400 mg/day groups, the incidence of somnolence was dose-related (9% for the 50 mg/day group and 15% for the 400 mg/day group) and the incidence of fatigue was comparable in both treatment groups (14% each). For the migraine population, fatigue and somnolence were dose-related and more common in the titration phase.

Additional nonspecific CNS events commonly observed with topiramate in the add-on epilepsy population include dizziness or ataxia.

Pediatric Patients

In double-blind adjunctive therapy and monotherapy epilepsy clinical studies, the incidences of cognitive/neuropsychiatric adverse events in pediatric patients were generally lower than observed in adults. These events included psychomotor slowing, difficulty with concentration/attention, speech disorders/related speech problems and language problems. The most frequently reported neuropsychiatric events in pediatric patients during adjunctive therapy double-blind studies were somnolence and fatigue. The most frequently reported neuropsychiatric events in pediatric patients in the 50 mg/day and 400 mg/day groups during the monotherapy double-blind study were headache, dizziness anorexia, and somnolence.

No patients discontinued treatment due to any adverse events in the adjunctive epilepsy double-blind trials. In the monotherapy epilepsy double-blind trial, 1 pediatric patient (2%) in the 50 mg/day group and 7 pediatric patients (12%) in the 400 mg/day group discontinued treatment due to any adverse events. The most common adverse event associated with discontinuation of therapy was difficulty with concentration/attention; all occurred in the 400 mg/day group.

Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of TOPAMAX® (topiramate) Tablets, 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject years of exposure). This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX® (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX® program, to 0.005 for patients with refractory epilepsy).

PRECAUTIONS

Hyperammonemia and Encephalopathy Associated with Concomitant Valproic Acid Use

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction.

It is not known if topiramate monotherapy is associated with hyperammonemia.

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons.

In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured.

Kidney Stones

A total of 32/2,086 (1.5%) of adults exposed to topiramate during its adjunctive epilepsy therapy development reported the occurrence of kidney stones, an incidence about 2-4 times greater than expected in a similar, untreated population. In the double-blind monotherapy epilepsy study, a total of 4/319 (1.3%) of adults exposed to topiramate reported the occurrence of kidney stones. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men. Kidney stones have also been reported in pediatric patients.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors or potentially in patients on a ketogenic diet may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

Paresthesia

Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®. Paresthesia was more frequently reported in the monotherapy epilepsy trials and migraine prophylaxis trials versus the adjunctive therapy epilepsy trials. In the majority of instances, paresthesia did not lead to treatment discontinuation.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required in patients with reduced renal function (see **DOSAGE AND ADMINISTRATION**).

Decreased Hepatic Function

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

Information for Patients

Patients taking TOPAMAX® should be told to seek immediate medical attention if they experience blurred vision or periorbital pain.

Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather.

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation [see **PRECAUTIONS: Kidney Stones**, for support regarding hydration as a preventative measure].

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Additional food intake may be considered if the patient is losing weight while on this medication.

Please refer to the end of the product labeling for important information on how to take TOPAMAX® (topiramate capsules) Sprinkle Capsules.

Laboratory Tests:

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended (see **WARNINGS**).

Drug Interactions:

In vitro studies indicate that topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 isozymes.

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on mean plasma AUCs are summarized in Table 3.

In Table 3, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added.

The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 3: Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400 mg/day	15% increase

[a] = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.
[b] = Is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration.
AED = Antiepileptic drug.
NE = Not Evaluated.
TPM - Topiramate

In addition to the pharmacokinetic interaction described in the above table, concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (see **PRECAUTIONS**, Hyperammonemia and Encephalopathy Associated with Concomitant Valproic Acid Use).

Other Drug Interactions

Digoxin: In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

CNS Depressants: Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX® given in the absence of other medications at doses of 50 to 200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX® (50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200-800 mg/day, there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

Hydrochlorothiazide (HCTZ): A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Pioglitazone: A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the $AUC_{\tau,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known. When TOPAMAX® is added to pioglitazone therapy or pioglitazone is added to TOPAMAX® therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Lithium: Multiple dosing of topiramate 100 mg every 12 hrs decreased the AUC and C_{max} of Lithium (300 mg every 8 hrs) by 20% (N=12, 6 M; 6 F).

Haloperidol: The pharmacokinetics of a single dose of haloperidol (5 mg) were not affected following multiple dosing of topiramate (100 mg every 12 hr) in 13 healthy adults (6 M, 7 F).

Amitriptyline: There was a 12% increase in AUC and C_{max} for amitriptyline (25 mg per day) in 18 normal subjects (9 male; 9 female) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose

should be made according to the patient's clinical response and not on the basis of plasma levels.

Sumatriptan: Multiple dosing of topiramate (100 mg every 12 hrs) in 24 healthy volunteers (14 M, 10 F) did not affect the pharmacokinetics of single dose sumatriptan either orally (100 mg) or subcutaneously (6 mg).

Risperidone: There was a 25% decrease in exposure to risperidone (2 mg single dose) in 12 healthy volunteers (6 M, 6 F) receiving 200 mg/day of topiramate. Therefore, patients receiving risperidone in combination with topiramate should be closely monitored for clinical response.

Propranolol: Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 M, 17 F) did not affect the pharmacokinetics of propranolol following daily 160 mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27M, 12F) had no effect on the exposure to topiramate at a dose of 200 mg/day of topiramate.

Dihydroergotamine: Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 M, 12 F) did not affect the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergotamine. Similarly, a 1 mg subcutaneous dose of dihydroergotamine did not affect the pharmacokinetics of a 200 mg/day dose of topiramate in the same study.

Others: Concomitant use of TOPAMAX®, a carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided.

Drug/Laboratory Test Interactions There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady-state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400

mg, and 1.5 to 2 times steady- state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a mg/m^2 basis).

Topiramate did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Topiramate was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro*; and it did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo*.

No adverse effects on male or female fertility were observed in rats at doses up to 100 mg/kg (2.5 times the RHD on a mg/m^2 basis).

Pregnancy: Pregnancy Category C.

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD=400 mg/day) on a mg/m^2 basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30 and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m^2 basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m^2 basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m^2 basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m^2 basis).

Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above.

When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m^2 basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m^2 basis) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30 or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m^2 basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m^2 basis) and higher.

There are no studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established.

Labor and Delivery:

In studies of rats where dams were allowed to deliver pups naturally, no drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg/day.

The effect of TOPAMAX® on labor and delivery in humans is unknown.

Nursing Mothers:

Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive secretion of topiramate into breast milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to TOPAMAX® is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing.

Pediatric Use:

Safety and effectiveness in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. Safety and effectiveness in patients below the age of 10 years have not been established for the monotherapy treatment of epilepsy. Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia/rickets and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated (see **WARNINGS**).

Safety and effectiveness in pediatric patients have not been established for the prophylaxis treatment of migraine headache.

Geriatric Use:

In clinical trials, 3% of patients were over 60. No age related difference in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with impaired renal function (creatinine clearance rate $\leq$70 mL/min/1.73 m^2) due to reduced clearance of topiramate (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Race and Gender Effects:

Evaluation of effectiveness and safety in clinical trials has shown no race or gender related effects.

ADVERSE REACTIONS

The data described in the following section were obtained using TOPAMAX® (topiramate) Tablets.

Monotherapy Epilepsy

The adverse events in the controlled trial that occurred most commonly in adults in the 400 mg/day group and at a rate higher than the 50 mg/day group were: paresthesia, weight decrease, somnolence, anorexia, dizziness, and difficulty with memory NOS [see Table 4].

The adverse events in the controlled trial that occurred most commonly in children (10 years up to 16 years of age) in the 400 mg/day group and at a rate higher than the 50 mg/day group were: weight decrease, upper respiratory tract infection, paresthesia, anorexia, diarrhea, and mood problems [see Table 5].

Approximately 21% of the 159 adult patients in the 400 mg/day group who received topiramate as monotherapy in the controlled clinical trial discontinued therapy due to adverse events. Adverse events associated with discontinuing therapy (≥2%) included depression, insomnia, difficulty with memory (NOS), somnolence, paresthesia, psychomotor slowing, dizziness, and nausea.

Approximately 12% of the 57 pediatric patients in the 400 mg/day group who received topiramate as monotherapy in the controlled clinical trial discontinued therapy due to adverse events. Adverse events associated with discontinuing therapy (≥5%) included difficulty with concentration/attention.

The prescriber should be aware that these data cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during the clinical study. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

Table 4: Incidence of Treatment-Emergent Adverse Events in the Monotherapy Epilepsy Trial in Adults[a] Where Rate Was at Least 2% in the 400 mg/day Topiramate Group and Greater Than the Rate in the 50 mg/day Topiramate Group

	TOPAMAX® Dosage (mg/day)	
Body System/ Adverse Event	50 (N= 160)	400 (N=159)
Body as a Whole-General Disorders		
Asthenia	4	6
Leg Pain	2	3
Chest Pain	1	2
Central & Peripheral Nervous System Disorders		
Paresthesia	21	40
Dizziness	13	14
Hypoaesthesia	4	5
Ataxia	3	4
Hypertonia	0	3
Gastro-Intestinal System Disorders		
Diarrhea	5	6
Constipation	1	4
Gastritis	0	3
Dry Mouth	1	3
Gastroesophageal Reflux	1	2
Liver and Biliary System Disorders		
Gamma-GT Increased	1	3
Metabolic and Nutritional Disorders		
Weight Decrease	6	16
Psychiatric Disorders		
Somnolence	9	15
Anorexia	4	14
Difficulty with Memory NOS	5	10
Insomnia	8	9
Depression	7	9
Difficulty with Concentration/Attention	7	8
Anxiety	4	6
Psychomotor Slowing	3	5
Mood Problems	2	5
Confusion	3	4
Cognitive Problem NOS	1	4
Libido Decreased	0	3
Reproductive Disorders, Female		
Vaginal Hemorrhage	0	3
Red Blood Cell Disorders		
Anemia	1	2
Resistance Mechanism Disorders		
Infection Viral	6	8
Infection	2	3
Respiratory System Disorders		
Bronchitis	3	4
Rhinitis	2	4
Dyspnea	1	2
Skin and Appendages Disorders		
Rash	1	4
Pruritus	1	4
Acne	2	3
Special Senses Other, Disorders		
Taste Perversion	3	5
Urinary System Disorders		
Cystitis	1	3
Renal Calculus	0	3
Urinary Tract Infection	1	2
Dysuria	0	2
Micturition Frequency	0	2

[a] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Table 5: Incidence of Treatment-Emergent Adverse Events in the Monotherapy Epilepsy Trial in Children Ages 10 up to 16 Years[a] Where Rate Was at Least 5% in the 400 mg/day Topiramate Group and Greater Than the Rate in the 50 mg/day Topiramate Group

	TOPAMAX® Dosage (mg/day)[b]	
Body System/ Adverse Event	50 (N=57)	400 (N=57)
Body as a Whole-General Disorders		
Fever	0	9
Central & Peripheral Nervous System Disorders		
Paresthesia	2	16
Gastro-Intestinal System Disorders		
Diarrhea	5	11
Metabolic and Nutritional Disorders		
Weight Decrease	7	21
Psychiatric Disorders		
Anorexia	11	14
Mood Problems	2	11
Difficulty with Concentration/Attention	4	9
Cognitive Problems NOS	0	7
Nervousness	4	5
Resistance Mechanism Disorders		
Infection Viral	4	9
Infection	2	7
Respiratory System Disorders		
Upper Respiratory Tract Infection	16	18
Rhinitis	2	7
Bronchitis	2	7
Sinusitis	2	5
Skin and Appendages Disorders		
Alopecia	2	5

[a] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Adjunctive Therapy Epilepsy

The most commonly observed adverse events associated with the use of topiramate at dosages of 200 to 400 mg/day in controlled trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater frequency in topiramate-treated patients and did not appear to be dose-related were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia and diplopia [see Table 6]. The most common dose-related adverse events at dosages of 200 to 1,000 mg/day were: fatigue, nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, anxiety, mood problems, and weight decrease [see Table 8].

Adverse events associated with the use of topiramate at dosages of 5 to 9 mg/kg/day in controlled trials in pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater frequency in topiramate-treated patients were: fatigue, somnolence, anorexia,

nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease [see Table 9].

In controlled clinical trials in adults, 11% of patients receiving topiramate 200 to 400 mg/day as adjunctive therapy discontinued due to adverse events. This rate appeared to increase at dosages above 400 mg/day. Adverse events associated with discontinuing therapy included somnolence, dizziness, anxiety, difficulty with concentration or attention, fatigue, and paresthesia and increased at dosages above 400 mg/day. None of the pediatric patients who received topiramate adjunctive therapy at 5 to 9 mg/kg/day in controlled clinical trials discontinued due to adverse events.

Approximately 28% of the 1,757 adults with epilepsy who received topiramate at dosages of 200 to 1,600 mg/day in clinical studies discontinued treatment because of adverse events; an individual patient could have reported more than one adverse event. These adverse events were: psychomotor slowing (4.0%), difficulty with memory (3.2%), fatigue (3.2%), confusion (3.1%), somnolence (3.2%), difficulty with concentration/attention (2.9%), anorexia (2.7%), depression (2.6%), dizziness (2.5%), weight decrease (2.5%), nervousness (2.3%), ataxia (2.1%), and paresthesia (2.0%). Approximately 11% of the 310 pediatric patients who received topiramate at dosages up to 30 mg/kg/day discontinued due to adverse events. Adverse events associated with discontinuing therapy included aggravated convulsions (2.3%), difficulty with concentration/attention (1.6%), language problems (1.3%), personality disorder (1.3%), and somnolence (1.3%).

Incidence in Epilepsy Controlled Clinical Trials Adjunctive Therapy– Partial Onset Seizures, Primary Generalized Tonic-Clonic Seizures, and Lennox-Gastaut Syndrome

Table 6 lists treatment-emergent adverse events that occurred in at least 1% of adults treated with 200 to 400 mg/day topiramate in controlled trials that were numerically more common at this dose than in the patients treated with placebo. In general, most patients who experienced adverse events during the first eight weeks of these trials no longer experienced them by their last visit. Table 9 lists treatment-emergent adverse events that occurred in at least 1% of pediatric patients treated with 5 to 9 mg/kg topiramate in controlled trials that were numerically more common than in patients treated with placebo.

The prescriber should be aware that these data were obtained when TOPAMAX® was added to concurrent antiepileptic drug therapy and cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

Other Adverse Events Observed During Double-Blind Adjunctive Therapy Epilepsy Trials

Other events that occurred in more than 1% of adults treated with 200 to 400 mg of topiramate in placebo-controlled epilepsy trials but with equal or greater frequency in the placebo group were: headache, injury, anxiety, rash, pain, convulsions aggravated, coughing, fever, diarrhea, vomiting, muscle weakness, insomnia, personality disorder, dysmenorrhea, upper respiratory tract infection, and eye pain.

Table 6 : Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Epilepsy Trials in Adults[a,b] Where Rate Was > 1% in Any Topiramate Group and Greater Than the Rate in Placebo-Treated Patients

	TOPAMAX® Dosage (mg/day)		
Body System/ Adverse Event[c]	Placebo (N=291)	200-400 (N=183)	600-1,000 (N=414)
Body as a Whole-General Disorders			
Fatigue	13	15	30
Asthenia	1	6	3
Back Pain	4	5	3
Chest Pain	3	4	2
Influenza-Like Symptoms	2	3	4
Leg Pain	2	2	4
Hot Flushes	1	2	1
Allergy	1	2	3
Edema	1	2	1
Body Odor	0	1	0
Rigors	0	1	<1
Central & Peripheral Nervous System Disorders			
Dizziness	15	25	32
Ataxia	7	16	14
Speech Disorders/Related Speech Problems	2	13	11
Paresthesia	4	11	19
Nystagmus	7	10	11
Tremor	6	9	9
Language Problems	1	6	10
Coordination Abnormal	2	4	4
Hypoaesthesia	1	2	1
Gait Abnormal	1	3	2
Muscle Contractions Involuntary	1	2	2
Stupor	0	2	1
Vertigo	1	1	2
Gastro-Intestinal System Disorders			
Nausea	8	10	12
Dyspepsia	6	7	6
Abdominal Pain	4	6	7
Constipation	2	4	3
Gastroenteritis	1	2	1
Dry Mouth	1	2	4
Gingivitis	<1	1	1
GI Disorder	<1	1	0
Hearing and Vestibular Disorders			
Hearing Decreased	1	2	1
Metabolic and Nutritional Disorders			
Weight Decrease	3	9	13
Muscle-Skeletal System Disorders			
Myalgia	1	2	2
Skeletal Pain	0	1	0
Platelet, Bleeding, & Clotting Disorders			
Epistaxis	1	2	1
Psychiatric Disorders			
Somnolence	12	29	28
Nervousness	6	16	19
Psychomotor Slowing	2	13	21
Difficulty with Memory	3	12	14
Anorexia	4	10	12
Confusion	5	11	14
Depression	5	5	13
Difficulty with Concentration/Attention	2	6	14
Mood Problems	2	4	9
Agitation	2	3	3
Aggressive Reaction	2	3	3
Emotional Lability	1	3	3
Cognitive Problems	1	3	3
Libido Decreased	1	2	<1

Apathy	1	1	3
Depersonalization	1	1	2

(Continued)

Table 6: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Epilepsy Trials in Adults[a,b] Where Rate Was > 1% in Any Topiramate Group and Greater Than the Rate in Placebo-Treated Patients (Continued)

	TOPAMAX® Dosage (mg/day)		
Body System/ Adverse Event[c]	Placebo (N=291)	200-400 (N=183)	600-1,000 (N=414)
Reproductive Disorders, Female			
Breast Pain	2	4	0
Amenorrhea	1	2	2
Menorrhagia	0	2	1
Menstrual Disorder	1	2	1
Reproductive Disorders, Male			
Prostatic Disorder	<1	2	0
Resistance Mechanism Disorders			
Infection	1	2	1
Infection Viral	1	2	<1
Moniliasis	<1	1	0
Respiratory System Disorders			
Pharyngitis	2	6	3
Rhinitis	6	7	6
Sinusitis	4	5	6
Dyspnea	1	1	2
Skin and Appendages Disorders			
Skin Disorder	<1	2	1
Sweating Increased	<1	1	<1
Rash Erythematous	<1	1	<1
Special Sense Other, Disorders			
Taste Perversion	0	2	4
Urinary System Disorders			
Hematuria	1	2	<1
Urinary Tract Infection	1	2	3
Micturition Frequency	1	1	2
Urinary Incontinence	<1	2	1
Urine Abnormal	0	1	<1
Vision Disorders			
Vision Abnormal	2	13	10
Diplopia	5	10	10
White Cell and RES Disorders			
Leukopenia	1	2	1

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.
[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.
[c] Adverse events reported by at least 1% of patients in the TOPAMAX® 200-400 mg/day group and more common than in the placebo group are listed in this table.

Incidence in Study 119 – Add-On Therapy– Adults with Partial Onset Seizures

Study 119 was a randomized, double-blind, placebo-controlled, parallel group study with 3 treatment arms: 1) placebo; 2) topiramate 200 mg/day with a 25 mg/day starting dose, increased by 25 mg/day each week for 8 weeks until the 200 mg/day maintenance dose was reached; and 3) topiramate 200 mg/day with a 50 mg/day starting dose, increased by 50 mg/day each week for 4 weeks until the 200 mg/day maintenance dose was reached. All patients were maintained on concomitant carbamazepine with or without another concomitant antiepileptic drug.

The incidence of adverse events (Table 7) did not differ significantly between the 2 topiramate regimens. Because the frequencies of adverse events reported in this study were markedly lower than those reported in the previous epilepsy studies, they cannot be directly compared with data obtained in other studies.

Table 7: Incidence of Treatment-Emergent Adverse Events in Study 119[a,b] Where Rate Was ≥ 2% in the Topiramate Group and Greater Than the Rate in Placebo-Treated Patients

		TOPAMAX® Dosage (mg/day)
Body System/ Adverse Event[c]	Placebo (N=92)	200 (N=171)
Body as a Whole-General Disorders		
Fatigue	4	9
Chest Pain	1	2
Cardiovascular Disorders, General		
Hypertension	0	2
Central & Peripheral Nervous System Disorders		
Paresthesia	2	9
Dizziness	4	7
Tremor	2	3
Hypoasthesia	0	2
Leg Cramps	0	2
Language Problems	0	2
Gastro-Intestinal System Disorders		
Abdominal Pain	3	5
Constipation	0	4
Diarrhea	1	2
Dyspepsia	0	2
Dry Mouth	0	2
Hearing and Vestibular Disorders		
Tinnitus	0	2
Metabolic and Nutritional Disorders		
Weight Decrease	4	8
Psychiatric Disorders		
Somnolence	9	15
Anorexia	7	9
Nervousness	2	9
Difficulty with Concentration/Attention	0	5
Insomnia	3	4
Difficulty with Memory	1	2
Aggressive Reaction	0	2
Respiratory System Disorders		
Rhinitis	0	4
Urinary System Disorders		
Cystitis	0	2
Vision Disorders		
Diplopia	0	2
Vision Abnormal	0	2

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

[c] Adverse events reported by at least 2% of patients in the TOPAMAX® 200 mg/day group and more common than in the placebo group are listed in this table.

Table 8: Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Add-On Trials in Adults with Partial Onset Seizures[a]

		TOPAMAX® Dosage (mg/day)		
Adverse Event	Placebo (N =216)	200 (N = 45)	400 (N = 68)	600 - 1,000 (N = 414)
Fatigue	13	11	12	30
Nervousness	7	13	18	19
Difficulty with Concentration/Attention	1	7	9	14
Confusion	4	9	10	14
Depression	6	9	7	13
Anorexia	4	4	6	12
Language problems	<1	2	9	10
Anxiety	6	2	3	10
Mood problems	2	0	6	9
Weight decrease	3	4	9	13

[a] Dose-response studies were not conducted for other adult indications or for pediatric indications.

Table 9: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Epilepsy Trials in Pediatric Patients Ages 2 -16 Years[a,b] (Events that Occurred in at Least 1% of Topiramate-Treated Patients and Occurred More Frequently in Topiramate-Treated Than Placebo-Treated Patients)

Body System/ Adverse Event	Placebo (N=101)	Topiramate (N=98)
Body as a Whole - General Disorders		
Fatigue	5	16
Injury	13	14
Allergic Reaction	1	2
Back Pain	0	1
Pallor	0	1
Cardiovascular Disorders, General		
Hypertension	0	1
Central & Peripheral Nervous System Disorders		
Gait Abnormal	5	8
Ataxia	2	6
Hyperkinesia	4	5
Dizziness	2	4
Speech Disorders/Related Speech Problems	2	4
Hyporeflexia	0	2
Convulsions Grand Mal	0	1
Fecal Incontinence	0	1
Paresthesia	0	1
Gastro-Intestinal System Disorders		
Nausea	5	6
Saliva Increased	4	6
Constipation	4	5
Gastroenteritis	2	3
Dysphagia	0	1
Flatulence	0	1
Gastroesophageal Reflux	0	1
Glossitis	0	1
Gum Hyperplasia	0	1
Heart Rate and Rhythm Disorders		
Bradycardia	0	1
Metabolic and Nutritional Disorders		
Weight Decrease	1	9
Thirst	1	2
Hypoglycemia	0	1
Weight Increase	0	1
Platelet, Bleeding, & Clotting Disorders		
Purpura	4	8
Epistaxis	1	4
Hematoma	0	1
Prothrombin Increased	0	1
Thrombocytopenia	0	1
Psychiatric Disorders		
Somnolence	16	26
Anorexia	15	24
Nervousness	7	14
Personality Disorder (Behavior Problems)	9	11
Difficulty with Concentration/Attention	2	10
Aggressive Reaction	4	9
Insomnia	7	8
Difficulty with Memory NOS	0	5
Confusion	3	4
Psychomotor Slowing	2	3
Appetite Increased	0	1
Neurosis	0	1

(Continued)

Table 9: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Epilepsy Trials in Pediatric Patients Ages 2 -16 Years[a,b] (Events that Occurred in at Least 1% of Topiramate-Treated Patients and Occurred More Frequently in Topiramate-Treated Than Placebo-Treated Patients) (Continued)

Body System/ Adverse Event	Placebo (N=101)	Topiramate (N=98)
Reproductive Disorders, Female		
Leukorrhoea	0	2
Resistance Mechanism Disorders		
Infection Viral	3	7
Respiratory System Disorders		
Pneumonia	1	5
Respiratory Disorder	0	1
Skin and Appendages Disorders		
Skin Disorder	2	3
Alopecia	1	2
Dermatitis	0	2
Hypertrichosis	1	2
Rash Erythematous	0	2
Eczema	0	1
Seborrhoea	0	1
Skin Discoloration	0	1
Urinary System Disorders		
Urinary Incontinence	2	4
Nocturia	0	1
Vision Disorders		
Eye Abnormality	1	2
Vision Abnormal	1	2
Diplopia	0	1
Lacrimation Abnormal	0	1
Myopia	0	1
White Cell and RES Disorders		
Leukopenia	0	2

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Other Adverse Events Observed During All Epilepsy Clinical Trials

Topiramate has been administered to 2,246 adults and 427 pediatric patients with epilepsy during all clinical studies, only some of which were placebo controlled. During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The frequencies presented represent the proportion of patients who experienced an event of the type cited on at least one occasion while receiving topiramate. Reported events are included except those already listed in the previous tables or text, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* occurring in at least 1/100 patients; *infrequent* occurring in 1/100 to 1/1000 patients; *rare* occurring in fewer than 1/1000 patients.

Autonomic Nervous System Disorders: *Infrequent:* vasodilation.

Body as a Whole: *Frequent:* syncope. *Infrequent:* abdomen enlarged. *Rare:* alcohol intolerance.

Cardiovascular Disorders, General: *Infrequent:* hypotension, postural hypotension, angina pectoris.

Central & Peripheral Nervous System Disorders: *Infrequent*: neuropathy, apraxia, hyperaesthesia, dyskinesia, dysphonia, scotoma, ptosis, dystonia, visual field defect, encephalopathy, EEG abnormal. *Rare:* upper motor neuron lesion, cerebellar syndrome, tongue paralysis.

Gastrointestinal System Disorders: *Infrequent:* hemorrhoids, stomatitis, melena, gastritis, esophagitis. *Rare:* tongue edema.

Heart Rate and Rhythm Disorders: *Infrequent:* AV block.

Liver and Biliary System Disorders: *Infrequent:* SGPT increased, SGOT increased.

Metabolic and Nutritional Disorders: *Infrequent:* dehydration, hypokalemia, alkaline phosphatase increased, hypocalcemia, hyperlipemia, hyperglycemia, xerophthalmia, diabetes mellitus. *Rare:* hyperchloremia, hypernatremia, hyponatremia, hypocholesterolemia, hypophosphatemia, creatinine increased.

Musculoskeletal System Disorders: *Frequent:* Arthralgia. *Infrequent:* arthrosis.

Neoplasms: *Infrequent:* thrombocythemia. *Rare:* polycythemia.

Platelet, Bleeding, and Clotting Disorders: *Infrequent:* gingival bleeding, pulmonary embolism.

Psychiatric Disorders: *Frequent:* impotence, hallucination, psychosis, suicide attempt. *Infrequent:* euphoria, paranoid reaction, delusion, paranoia, delirium, abnormal dreaming. *Rare:* libido increased, manic reaction.

Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.

Reproductive Disorders, Male: *Infrequent:* ejaculation disorder, breast discharge.

Skin and Appendages Disorders: *Infrequent:* urticaria, photosensitivity reaction, abnormal hair texture. *Rare:* chloasma.

Special Senses Other, Disorders: *Infrequent:* taste loss, parosmia.

Urinary System Disorders: *Infrequent:* urinary retention, face edema, renal pain, albuminuria, polyuria, oliguria.

Vascular (Extracardiac) Disorders: *Infrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.

Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, strabismus. *Rare:* mydriasis, iritis.

White Cell and Reticuloendothelial System Disorders: *Infrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia. *Rare:* lymphocytosis.

Migraine

In the four multicenter, randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials, most of the adverse events with topiramate were mild or moderate in severity. Most adverse events occurred more frequently during the titration period than during the maintenance period.

Table 10 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in any topiramate treatment group was at least 2% and was greater than that for placebo patients.

Table 10: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Migraine Trials Where Rate Was ≥2 % in Any Topiramate Group and Greater than the Rate in Placebo-Treated Patients [a]

	TOPAMAX® Dosage (mg/day)			
Body System/ Adverse Event	Placebo (N=445)	50 (N=235)	100 (N=386)	200 (N=514)
Body as a Whole-General Disorders				
Fatigue	11	14	15	19
Injury	7	9	6	6
Asthenia	1	<1	2	2
Fever	1	1	1	2
Influenza-Like Symptoms	<1	<1	<1	2
Allergy	<1	2	<1	<1
Central & Peripheral Nervous System Disorders				
Paresthesia	6	35	51	49
Dizziness	10	8	9	12
Hypoaesthesia	2	6	7	8
Language Problems	2	7	6	7
Involuntary Muscle Contractions	1	2	2	4
Ataxia	<1	1	2	1
Speech Disorders/Related Speech Problems	<1	1	<1	2
Gastro-Intestinal System Disorders				
Nausea	8	9	13	14
Diarrhea	4	9	11	11
Abdominal Pain	5	6	6	7
Dyspepsia	3	4	5	3
Dry Mouth	2	2	3	5
Vomiting	2	1	2	3
Gastroenteritis	1	3	3	2
Hearing and Vestibular Disorders				
Tinnitus	1	<1	1	2
Metabolic and Nutritional Disorders				
Weight Decrease	1	6	9	11
Thirst	<1	2	2	1
Musculoskeletal System Disorders				
Arthralgia	2	7	3	1
Neoplasms				
Neoplasm NOS	<1	2	<1	<1
Psychiatric Disorders				
Anorexia	6	9	15	14
Somnolence	5	8	7	10
Difficulty with Memory NOS	2	7	7	11
Difficulty with Concentration/Attention	2	3	6	10
Insomnia	5	6	7	6
Anxiety	3	4	5	6
Mood Problems	2	3	6	5
Depression	4	3	4	6
Nervousness	2	4	4	4
Confusion	2	2	3	4
Psychomotor Slowing	1	3	2	4
Libido Decreased	1	1	1	2
Aggravated Depression	1	1	2	2
Agitation	1	2	2	1
Cognitive Problems NOS	1	<1	2	2
Reproductive Disorders, Female				
Menstrual Disorder	2	3	2	2
Reproductive Disorders, Male				
Ejaculation Premature	0	3	0	0
Resistance Mechanism Disorders				
Viral Infection	3	4	4	3
Otitis Media	<1	2	1	1
Respiratory System Disorders				
Upper Respiratory Tract Infection	12	13	14	12
Sinusitis	6	10	6	8
Pharyngitis	4	5	6	2
Coughing	2	2	4	3

Bronchitis	2	3	3	3
Dyspnea	2	1	3	2
Rhinitis	1	1	2	2

(Continued)

Table 10: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Migraine Trials Where Rate Was ≥2 % in Any Topiramate Group and Greater than the Rate in Placebo-Treated Patients [a]

	TOPAMAX® Dosage (mg/day)			
Body System/ Adverse Event	Placebo (N=445)	50 (N=235)	100 (N=386)	200 (N=514)
Skin and Appendages Disorders				
Pruritis	2	4	2	2
Special Sense Other, Disorders				
Taste Perversion	1	15	8	12
Taste Loss	<1	1	1	2
Urinary System Disorders				
Urinary Tract Infection	2	4	2	4
Renal Calculus	0	0	1	2
Vision Disorders				
Vision Abnormal	<1	1	2	3
Blurred Vision [b]	2	4	2	4
Conjunctivitis	1	1	2	1

[a] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

[b] Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for > 50 % of events coded as vision abnormal, a preferred term.

Of the 1,135 patients exposed to topiramate in the placebo-controlled studies, 25% discontinued due to adverse events, compared to 10% of the 445 placebo patients. The adverse events associated with discontinuing therapy in the topiramate-treated patients included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%).

Patients treated with topiramate experienced mean percent reductions in body weight that were dose-dependent. This change was not seen in the placebo group. Mean changes of 0%, –2%, – 3%, and – 4% were seen for the placebo group, topiramate 50, 100, and 200 mg groups, respectively.

Table 11 shows adverse events that were dose-dependent. Several central nervous system adverse events, including some that represented cognitive dysfunction, were dose-related. The most common dose-related adverse events were paresthesia, fatigue, nausea, anorexia, dizziness, difficulty with memory, diarrhea, weight decrease, difficulty with concentration/attention, and somnolence.

Table 11: Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Migraine Trials[a]

			TOPAMAX® Dosage (mg/day)	
Adverse Event	Placebo (N =445)	50 (N = 235)	100 (N = 386)	200 (N = 514)
Paresthesia	6	35	51	49
Fatigue	11	14	15	19
Nausea	8	9	13	14
Anorexia	6	9	15	14
Dizziness	10	8	9	12
Weight decrease	1	6	9	11
Difficulty with Memory NOS	2	7	7	11
Diarrhea	4	9	11	11
Difficulty with Concentration/Attention	2	3	6	10
Somnolence	5	8	7	10
Hypoaesthesia	2	6	7	8
Anxiety	3	4	5	6
Depression	4	3	4	6
Mood Problems	2	3	6	5
Dry Mouth	2	2	3	5
Confusion	2	2	3	4
Involuntary Muscle Contractions	1	2	2	4
Abnormal Vision	<1	1	2	3
Renal Calculus	0	0	1	2

[a] The incidence rate of the adverse event in the 200 mg/day group was ≥2% than the rate in both the placebo group and the 50 mg/day group.

Other Adverse Events Observed During Migraine Clinical Trials

Topiramate, for the treatment of prophylaxis of migraine headache, has been administered to 1,367 patients in all clinical studies (includes double-blind and open-label extension). During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology.

The following additional adverse events that were not described earlier were reported by greater than 1% of the 1,367 topiramate-treated patients in the controlled clinical trials:

Body as a Whole: Pain, chest pain, allergic reaction.

Central & Peripheral Nervous System Disorders: Headache, vertigo, tremor, sensory disturbance, migraine aggravated.

Gastrointestinal System Disorders: Constipation, gastroesophageal reflux, tooth disorder.

Musculoskeletal System Disorders: Myalgia.

Platelet, Bleeding, and Clotting Disorders: Epistaxis.

Reproductive Disorders, Female: Intermenstrual bleeding.

Resistance Mechanism Disorders: Infection, genital moniliasis.

Respiratory System Disorders: Pneumonia, asthma.

Skin and Appendages Disorders: Rash, alopecia.

Vision Disorders: Abnormal accommodation, eye pain.

Postmarketing and Other Experience

In addition to the adverse experiences reported during clinical testing of TOPAMAX®, the following adverse experiences have been reported worldwide in patients receiving topiramate post-approval. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, pancreatitis, pemphigus, and renal tubular acidosis.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of TOPAMAX® has not been evaluated in human studies.

OVERDOSAGE

Overdoses of TOPAMAX® have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-drug overdoses involving TOPAMAX®.

Topiramate overdose has resulted in severe metabolic acidosis (see **WARNINGS**).

A patient who ingested a dose between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.

In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate *in vitro*. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body.

DOSAGE AND ADMINISTRATION

Epilepsy

In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, or 1000 mg/day) have not been shown to improve responses in dose-response studies in adults with partial onset seizures.

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® therapy. On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®. Because of the bitter taste, tablets should not be broken.

TOPAMAX® can be taken without regard to meals.

Monotherapy Use

The recommended dose for topiramate monotherapy in adults and children 10 years of age and older is 400 mg/day in two divided doses. Approximately 58% of patients randomized to 400 mg/day achieved this maximal dose in the monotherapy controlled trial; the mean dose achieved in the trial was 275 mg/day. The dose should be achieved by titrating according to the following schedule:

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

Adjunctive Therapy Use

Adults (17 Years of Age and Over) - Partial Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome

The recommended total daily dose of TOPAMAX® as adjunctive therapy in adults with partial seizures is 200-400 mg/day in two divided doses, and 400 mg/day in two divided doses as adjunctive treatment in adults with primary generalized tonic-clonic seizures. It is recommended that therapy be initiated at 25-50 mg/day followed by titration to an effective dose in increments of 25-50 mg/week. Titrating in increments of 25 mg/week may delay the time to reach an effective dose. Daily doses above 1,600 mg have not been studied.

In the study of primary generalized tonic-clonic seizures the initial titration rate was slower than in previous studies; the assigned dose was reached at the end of 8 weeks (see **CLINICAL STUDIES, Adjunctive Therapy Controlled Trials in Patients With Primary Generalized Tonic-Clonic Seizures**).

Pediatric Patients (Ages 2 - 16 Years) - Partial Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome

The recommended total daily dose of TOPAMAX® (topiramate) as adjunctive therapy for patients with partial seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut Syndrome is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome.

In the study of primary generalized tonic-clonic seizures the initial titration rate was slower than in previous studies; the assigned dose of 6 mg/kg/day was reached at the end of 8 weeks (see **CLINICAL STUDIES, Adjunctive Therapy Controlled Trial in Patients With Primary Generalized Tonic-Clonic Seizures**).

Migraine

The recommended total daily dose of TOPAMAX® as treatment for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. The recommended titration rate for topiramate for migraine prophylaxis to 100 mg/day is:

	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

Dose and titration rate should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.

Administration of TOPAMAX® Sprinkle Capsules

TOPAMAX® (topiramate capsules) Sprinkle Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

Patients with Renal Impairment:

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m^2), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Geriatric Patients (Ages 65 Years and Over):

Dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate $\leq$70 mL/min/1.73 m^2) is evident (see **DOSAGE AND ADMINISTRATION: Patients with Renal Impairment** and **CLINICAL PHARMACOLOGY: Special Populations: Age, Gender, and Race**).

Patients Undergoing Hemodialysis:

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease:

In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

HOW SUPPLIED

TOPAMAX® (topiramate) Tablets are available as debossed, coated, round tablets in the following strengths and colors:
25 mg white (coded "TOP" on one side; "25" on the other)
50 mg light-yellow (coded "TOPAMAX" on one side; "50" on the other)

100 mg yellow (coded "TOPAMAX" on one side; "100" on the other)
200 mg salmon (coded "TOPAMAX" on one side; "200" on the other)

They are supplied as follows:
25 mg tablets – bottles of 60 count with desiccant (NDC 0045-0639-65)
50 mg tablets – bottles of 60 count with desiccant (NDC 0045-0640-65)
100 mg tablets – bottles of 60 count with desiccant (NDC 0045-0641-65)
200 mg tablets – bottles of 60 count with desiccant (NDC 0045-0642-65)

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain small, white to off white spheres. The gelatin capsules are white and clear.

They are marked as follows:
15 mg capsule with “TOP” and “15 mg” on the side
25 mg capsule with “TOP” and “25 mg” on the side

The capsules are supplied as follows:
15 mg capsules – bottles of 60 (NDC 0045-0647-65)
25 mg capsules – bottles of 60 (NDC 0045-0645-65)

TOPAMAX® (topiramate) Tablets should be stored in tightly-closed containers at controlled room temperature (59 to 86°F, 15 to 30°C). Protect from moisture.

TOPAMAX® (topiramate capsules) Sprinkle Capsules should be stored in tightly-closed containers at or below 25°C (77°F). Protect from moisture.

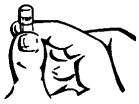
TOPAMAX® (topiramate) and TOPAMAX® (topiramate capsules) are trademarks of Ortho-McNeil Pharmaceutical.

HOW TO TAKE TOPAMAX® (topiramate capsules) SPRINKLE CAPSULES

A Guide for Patients and Their Caregivers

Your doctor has given you a prescription for TOPAMAX® (topiramate capsules) Sprinkle Capsules. Here are your instructions for taking this medication. Please read these instructions prior to use.

To Take With Food
You may sprinkle the contents of TOPAMAX® Sprinkle Capsules on a small amount (teaspoon) of soft food, such as applesauce, custard, ice cream, oatmeal, pudding, or yogurt.



Hold the capsule upright so that you can read the word "TOP".

Carefully twist off the clear portion of the capsule. You may find it best to do this over the small portion of the food onto which you will be pouring the sprinkles.

Sprinkle <u>all</u> of the capsule's contents onto a spoonful of soft food, taking care to see that the entire prescribed dosage is sprinkled onto the food.

Be sure the patient swallows the entire spoonful of the sprinkle/food mixture immediately. Chewing should be avoided. It may be helpful to have the patient drink fluids immediately in order to make sure all of the mixture is swallowed. IMPORTANT: Never store any sprinkle/food mixture for use at a later time.

To Take Without Food
TOPAMAX® Sprinkle Capsules may also be swallowed as whole capsules

For more information about TOPAMAX® Sprinkle Capsules, ask your doctor or pharmacist.

OMP Division
ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey 08869

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

MEDICAL REVIEW(S)

MEMORANDUM

DATE: January 17, 2005

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-505/S-018 & NDA 20-844/S-015

SUBJECT: Action Memo for NDA 20-505/S-018, Topamax (topiramate) Tablets & NDA 20-844/S-015 Topamax (topiramate) Sprinkle Capsules for the use of topiramate as monotherapy in adults and children 6 years of age and older with newly diagnosed epilepsy

NDA 20-505/S-018, Topamax (topiramate) Tablets & NDA 20-844/S-015 Topamax (topiramate) Sprinkle Capsules for the use of topiramate as monotherapy in adults and children 6 years of age and older with newly diagnosed epilepsy, were submitted by Johnson & Johnson Pharmaceutical Research & Development, L.L.C., on 10/29/02. The application contained the results of four controlled trials in which topiramate was used as monotherapy, although only one study, Study 106, in newly diagnosed patients, was considered potentially sufficient, by design and conduct, to support ultimate approval (topiramate is currently approved as adjunctive treatment for partial seizures). The sponsor was sent an Approvable letter on 11/26/03. The interpretation of the analysis of Study 106 (a study in which patients were randomized to receive treatment with topiramate 50 mg/day or titrated to 400 mg/day, with time to next seizure as the primary effectiveness assessment), was complicated by the presence of a large number of dropouts in patients before they met the study endpoint or completed the nominal treatment period (75/236 randomized patients discontinued early in the high dose group and 39/234 patients in the low dose group discontinued early). In addition, there was a marked disparity in the reasons for discontinuation by treatment group (e.g., there were 3 times as many early discontinuations in the high dose group for adverse events-40-compared to the number in the placebo group-13). Although the primary analysis (log-rank test of time to event) was highly significant (p=0.0002), the loss of so many patients has the potential to introduce a significant bias.

In an attempt to convince the Agency that these dropouts did not introduce a significant bias into the study results, the sponsor undertook numerous analyses to demonstrate that no such biases were likely. Specifically, they performed numerous comparisons of the patients discontinuing early compared to the patients completing (or meeting study endpoints), with the goal of demonstrating that there were no important differences between these groups (and that, therefore, there was no obvious reason to conclude that the patients leaving early would have had a different potential for seizures than those who stayed in the trial). Most of these analyses, which we found reasonable at the time,

yielded highly significant results in favor of the high dose. Further, they imputed varying seizure rates for the patients leaving the study early (although in these analyses, they imputed the same rates for the high and low dose groups); according to these analyses, statistical significance was lost only when a rate of 50% or greater was assigned to both groups (see my memo of 11/26/03 for a brief overview of the sponsor's analyses and results).

However, because none of these analyses could have been considered definitive, we were unable to conclude at that time that the study provided substantial evidence of effectiveness for topiramate as monotherapy. Therefore, in our Approvable letter, we asked the sponsor to perform additional analyses to try to investigate the possibility of informative censoring and also to impute various other possible seizure rates for the two groups (including, and especially) different seizure rates for the two groups. We had hoped that these additional analyses would shed light on the effect of early censoring on the results.

In addition, there was another important issue that was raised in the Approvable letter.

We had noted disturbing results in an early study, Study 104. This study was of similar design to Study 106, except the primary outcome was time to second seizure; the p-value for the analysis of this outcome was completely insignificant, although the p-value for the time to first seizure (the outcome in Study 106) approached nominal significance. This (near) significance on the same outcome as was use considered primary in Study 106 (and which seemed to be a reasonable outcome with which to assess topiramate's, or any, AED's effectiveness as monotherapy), but complete lack of significance on time to second seizure, raised serious questions about the appropriateness of time to first seizure as a primary outcome (if a drug delayed the time to the next seizure, but lost all effectiveness after that, that would be an entirely inadequate clinical effect on which to base approval). For this reason, we asked the sponsor to address this finding as well.

After we issued the Approvable letter, we had numerous discussions with the sponsor about the best way to address our concerns. In a meeting on 2/11/04, the sponsor proposed several statistical approaches to the problems noted in Study 106. Specifically, we agreed with certain aspects of their proposed approach to the question of imputing various and differential times to failure (although we did not agree, a priori, to any specific interpretation of the results of these analyses, of course). Further, the sponsor proposed a novel approach to the problem of potential informative censoring. We agreed to consider the results of these analyses, although we could not agree that we would find these latter analyses acceptable.

The sponsor responded to the Approvable letter on 7/18/04. This submission has been reviewed by Dr. Howard Chazin, medical officer, Dr. Kun He,

statistician, and Dr. John Feeney, Neurology Drugs Team Leader. The clinical review team has concluded that the sponsor has not provided substantial evidence that topiramate is effective as monotherapy. I will present a brief overview of the sponsor's re-analyses, and provide the rationale for the division's decision.

Multiple Imputations

As noted above, we had asked the sponsor to perform additional analyses in which they imputed various (and differential) times to first seizure for the patients in both groups who discontinued early. Also, as noted above, we had agreed with the sponsor that the interpretation of the p-values generated through simulations was acceptable (this was a particular concern of ours, as expressed in our 11/26/03 Approvable letter). The results of these analyses have been described by the review team. Below, I present only those differential rates associated with a loss of nominal significance:

Imputed Seizure Rates for Subjects Who Withdrew From the Study Early

				TOP 400 mg			
TOP 50 MG	30%	40%	50%	60%	70%	75%	80%
30%				.082	.231		
40%					.151	.238	
50%					.094	.165	
60%						.092	.168
70%							.100
75%							.065
80%							

In fact, although the chart displays seizure rates for the cohorts that discontinued early, the sponsor's analyses (that is, the p-values) were based on an imputation of time to first seizure generated based on an exponential distribution, conditioned upon the time to discontinuation (Dr. He gives a lucid explanation of the sponsor's analysis on page 7 of his review, with details attached in an appendix).

As can be seen from the chart, significance is lost only when imputed rates for the high dose patients who discontinued early are 1) relatively high and 2) when the rates are greater for the high dose than the low dose patients (in the original analysis, the seizure rate in the high dose group was 21% compared to 38% in the low dose group).

Informative Censoring

As noted above, independent of the question of what seizure rates should be imputed for the patients who discontinued early, we had asked the sponsor to address the question of the effect that any non-informative censoring might have on the interpretation of the trial.

In response, the sponsor undertook a sensitivity analysis designed to evaluate various reasonable values for the (non-knowable) dependence between the time to first seizure and the censoring times, utilizing what is known as a censoring bias function. Quoting Dr. He, (page 8 of his review), "In particular, the cause-specific hazard of premature censoring is modeled as a parameterized function of the time to first seizure.". In these analyses, the (cause-specific) hazard of early censoring is assumed to be independent of the time to the first seizure.

The censoring bias function depends upon two parameters, alpha and tau. Again, quoting Dr. He, (page 8 of his review), "The parameter alpha is interpreted as the log hazard ratio of prematurely [sic] withdrawal at time t between subjects who are at risk at time t, but differ by one day in their ultimate times to first seizure. The parameter tau roughly represents the mean time (in days) to first seizure for subjects who would not experience a seizure prior to 500 days (the trial's primary analysis date) after enrollment.".

As Dr. He notes, this function provides bounds for the analyses, depending upon the choice for alpha and tau. For example, if alpha=0, this is equivalent to non-informative censoring (which the sponsor assumed in their original, highly significant analysis). If alpha=-? , this is equivalent to each censored patient having a seizure at their next observed time (analogous to a worst case analysis Dr. He had performed earlier, and which gave a p-value of about 0.57). As he further notes, when alpha is negative, "…subjects with shorter times to next seizure are more likely to be censored at any time t than subjects with longer times to next seizure.".

According to Dr. He, the sponsor performed numerous analyses using this censoring function, in which they varied alpha over the range of negative values and kept tau constant at 730 days. As Dr. He presents in his Table 3.1.2.1 on page 9 of his review, significant between-treatment contrasts favoring the high dose group were seen for alphas between 0 and -2.

The sponsor also examined the effects of varying alpha and tau. As can be seen in Dr. He's Table 3.1.2.2 on page 13 of his review, the results were fairly insensitive to varying tau to 630 and 830 days.

Because the clinical meaning of (especially) alpha is not immediately obvious, the sponsor has made several attempts to establish its clinical meaning. One way the sponsor has done this is to compare the results of the analyses of the censoring bias function with those based on the multiple imputations analyses. In this way, the sponsor has hoped to draw a relationship between specific values of alpha and tau and seizure rates in the early discontinuation cohorts.

As described by Dr. He on page 13 of his review, the sponsor compared Kaplan-Meier curves (actually, the mean of 1000 simulations) for an assumed 75% seizure rate for the early discontinuations in both groups and the K-M curves with a=-1.5 and tau=730 days. As he shows, the K-M curves for the censoring bias approach lie entirely above the K-M curves for the multiple imputations analyses. This implies that the seizure rates for patients who discontinued early, when alpha and tau are set as above, will be greater than 75% (as we have seen, the p-value for the censoring bias approach with alpha=-1.5 and tau=730 days is 0.018).

Another way the sponsor has attempted to demonstrate the relationship between specific values of alpha and tau is to derive, for a given alpha, the implied distribution of time to first seizure for patients discontinued early.

As Dr. He describes on pages 10-12 of his review, the sponsor has constructed the probabilities, for various values of alpha, of having a first seizure in each 50 day period for a patient who was prematurely censored at Day 8 in the low dose group (this was the earliest time of censoring in the study in this group) and for a patient in the high dose group who was censored at Day 4 (for the same reason).

As Dr. He describes, and as would be expected, the probabilities shift to earlier times after the patient was censored with increasingly negative values of alpha; as above, the distributions of times to first seizure shift significantly at alpha=-2 and lower.

Explanation of Results of Study 104

As described above, analysis of the time to second seizure (the primary outcome measure) in Study 104 yielded a p-value of 0.78, in the face of a nearly nominally significant p-value for the analysis of time to first seizure (the primary outcome measure in Study 106). The clear lack of significance on the time to second seizure analysis raised serious concerns that such an outcome could have occurred in Study 106. If this were true, it would call into question the clinical meaning of a finding of a difference between treatments on the time to first seizure. For this reason, we asked the sponsor to address this concern.

As described by Dr. Chazin, the sponsor presents two arguments that support their view that the results of Study 104 should not call into question the results of Study 106.

First, the duration of the randomized observation period in Study 104 was about 6 months, too short, in the view of the sponsor, to detect any treatment difference in this measure, and second, the sponsor asserts that the increased heterogeneity of the study population compared to that in Study 106 made a straight forward comparison between the two studies inappropriate.

In Study 104, 39% of the low dose group were seizure free and 18% had only a single seizure. As noted above, the time to first seizure in the high dose group (median 317 days) was clearly longer than for the low dose group (median 108 days). In addition, the sponsor asserts that time to second seizure could have been influenced by a drug effect that either causes remission or prolongs the time to first seizure (at the least, this latter phenomenon was observed). In the sponsor's view, given that seizures are not evenly distributed in time, a shorter duration to the next seizure would be expected in a patient who had frequent seizures at baseline (in other words, more severely affected patients would be more likely to have more frequent seizures). Conversely, patients with few baseline seizures have, in the sponsor's view, a higher probability of remission, with a resultant increased time to a next seizure, which, of course implies that a longer duration of observation would be necessary to detect this next seizure.

According to this line of reasoning, and as expressed by the sponsor, the "propensity" to have a second seizure, then, is both related to the severity of the patient's epilepsy and necessary to consider when explaining the results of Study 104.

Therefore, the sponsor has presented analyses of the subgroups defined as patients having had 1 or 2 seizures at baseline and those with at least 3 seizures at baseline. As Dr. Chazin describes in pages 16-19 of his review, the results on time to first seizure and time to second seizure were both significant in favor of the high dose in the low baseline seizure group, but not the high baseline seizure group.

In Study 104, 56% of patients were in the low baseline seizure frequency group (again, results on time to first and second seizure were significant in this group, and these analyses were not significant in the high baseline seizure group). In Study 106, 100% of patients had either one or two seizures at baseline (63% had only 1 seizure). For this reason, the sponsor asserts that the results in the low baseline seizure group in Study 104 are more directly comparable to the results of Study 106.

COMMENTS

The sponsor has addressed the three major questions we had directed to them in the Approvable letter: they have performed analyses by imputing various time to event dates, they have performed (novel) analyses designed to address the effect of informative censoring on the results of Study 106, and they have provided explanations for why the results of Study 104 on the time to second seizure should not be considered powerful evidence that a positive result on time to first seizure in Study 106 is clinically uninterpretable.

Before I discuss the sponsor's arguments, it is worth noting that at least some of the work that the sponsor had undertaken to address some aspects of these issues were considered, at the time of the first action, relatively compelling. Specifically, both Dr. Feeney and I had concluded that the sponsor had, as I had written in my 11/26/03 memo, "…undertaken reasonable efforts to evaluate whether or not the patients who discontinued the trial early (and especially those who left early secondary to an adverse event…) can be considered to not be fundamentally different (vis-à-vis their intrinsic seizure propensity) than those who did not discontinue early within each treatment group." I would add to this statement that the patients who left early due to an adverse event represented the group with the major disparity in early discontinuers between treatment groups: as I noted earlier, 3 times as many high dose patients than low dose patients left early because of an adverse event. Indeed, we had acknowledged as much in the Approvable letter. However, despite our finding on this one point, at that time, we had concluded that the sponsor needed to do further work on both issues in Study 106.

Regarding the imputation approach, the sponsor has performed the requested analyses, (in particular they conducted 1000 simulations/imputed seizure rate), and we have previously agreed with them that their interpretation of the p-values generated was reasonable and that the overall approach was also reasonable, if not necessarily definitive. The question before us now (at least with regard to this point) is whether the results obtained support a conclusion that Study 106 is a "positive" study.

According to Dr. Chazin, the literature reports rates of between 43-63% seizure recurrence within 1 year in newly diagnosed patients. He also reports seizure free rates of 40% and 60% at 6 and 12 months, respectively, after the diagnosis of epilepsy (I assume these rates are under treatment). He also reports another study in which 73% of patients who had had 2 or 3 unprovoked seizures had further seizures within 4 years, with or without treatment. Based on these data, presumably, Dr. Chazin concludes that we should assume a seizure rate of 40-80% for patients in Study 106.

In my view, the seizure rates reported in the literature do not seem to be directly applicable to the patients in Study 106, because the durations and/or treatment

status reported in the literature are not particularly relevant as comparators. That is, I do not believe that the literature data help us decide what rate of seizures (or what time to event) to impute for the patients who discontinued treatment early in Study 106.

Under these circumstances, then, I think it is useful to examine the results of the analyses the sponsor performed in response to our request.

These imputation analyses demonstrate that only when the imputed seizure rate in the high dose group is "high" (above 60%) and the imputed seizure rate in the low dose group is lower than that in the high dose group (and often considerably lower) is statistical significance lost. It is worth noting that in my 11/26/03 memo, I concluded that the potential imputation of a seizure rate of about 70% (which was the rate in the low dose group in Study 104), "…surely represents a worst-case analysis of some sort. If we utilized the high dose rate from Study 104 (under the assumption that the response to the high dose in Study 106 is more likely to be similar to the response to the high dose in Study 104-46%), the between-treatment comparison in Study 106 becomes significant.". I would add now that, based on the sponsor's re-analyses, for an imputed seizure rate of 70% in the high dose group, the rate in the low dose group would need to be 50% or lower for significance to be lost. I am as convinced now as I was earlier that doing so would certainly be a more stringent worst-case scenario. In my view, the range of results generated by the sponsor in this analysis demonstrate, for any reasonable imputed seizure rates for the discontinuations in both treatment groups, that a statistically significant difference between high dose and low dose topiramate can be concluded.

However, based on the team's discussions with the statisticians, there are reasons to question the p-values generated by the sponsor.

Specifically, as Dr. He notes in his review (page 7), the p-value generated by the sponsor for the comparison based on imputed seizure rates of 99% for both treatment groups is 0.24. When Dr. He performed his worst-case analysis (in which all discontinuations were considered to have had a seizure), he obtained a p-value for that contrast of 0.57. According to the statisticians, these two analyses should have yielded essentially identical p-values. Because they do not, Drs. He and Jin have concerns that the other p-values generated by the sponsor may not be accurate. Until we can be confident that the p-values generated by the sponsor are accurate, we cannot definitively conclude that this study establishes the effectiveness of topiramate as monotherapy.

Interpreting the results of the censoring bias function analysis is more complex.

I believe that the results of these analyses are encouraging and highly suggestive that high dose topiramate is effective as monotherapy in the treatment of partial seizures (to the extent that I understand what they are trying

to achieve). In particular, I find the comparisons to the imputation analyses and the results of the implied distribution of time to first seizure interesting and certainly supportive of the sponsor's claims. However, as Dr. He concludes, the choice of the particular alpha, and, especially, how that choice is to be made and its clinical meaning, are anything but clear or obvious. Indeed, the sponsor acknowledges that the biggest challenge with this approach is communicating the meaning of these parameters to clinical experts so that they can, "…provide plausible range [sic] for the parameters,…". The sponsor acknowledges, in fact, that the choice of these parameters by experts is critical to the interpretation of the data, because, "…the data contain no independent evidence about [the] parameters…". However, we have no evidence that the sponsor has, in fact, consulted clinical experts about the choice of these parameters.

In addition, and critically, as Dr. He describes, the assumptions underlying the analysis are unproven, and the method is not validated. Our statistical colleagues are quite uneasy about basing a regulatory decision on an analysis for which there is no precedent and for which the method is unvalidated and the theory of the method is not established. Although encouraging and intriguing (and, of course, consistent with the sponsor's contention that the high dose is an effective dose), I must agree with Dr. He that it would be problematic to rest the conclusion that the high dose is effective on the results of these analyses. Rather, as I described above, I believe it would be reasonable to base the conclusion that the high dose is effective on the results of the imputation method, but I cannot definitively reach this conclusion until and if the sponsor can adequately address our concerns about the accuracy of the p-values they have generated (see above). Although the statisticians (and the clinical review team and I) do not believe the censoring bias function methodology can support, at this time, the effectiveness decision, based on my conversations with statisticians, it is my view that the sponsor has performed all analyses that could reasonably be expected to have been performed; certainly, in this sense, they have adequately addressed our concerns.

With regard to the sponsor's explanations about the lack of significance of the analyses of time to second seizure in Study 104, and their irrelevance for Study 106, I am inclined to agree with them. It is my reading of Dr. Chazin's review that he, too, in general, agrees with the sponsor's explanations. They are, of course, post hoc explanations, and, as such, could not be used to support definitive conclusions, but they are reasonable for the purpose at hand; namely, to justify not considering the results as being fatal to utilizing time to first seizure as a reasonable primary outcome.

Therefore, I would be willing to conclude that the sponsor has provided substantial evidence that topiramate, 400 mg/day, is an effective treatment as monotherapy for the treatment of partial seizures, when and if they can address the questions raised above about the accuracy of the p-values produced for the contrasts in the multiple imputations approach.

This conclusion, however, poses significant other problems.

Specifically, in their proposed product labeling, the sponsor has provided the K-M curves for Study 106. They have further provided dosing recommendations that declare doses lower than 400 mg/day to be effective doses, presumably because analyses by individual week, starting from the first week of titration, first reached nominal significance at week 2, at which time patients were treated with 100 mg/day. Presumably, the high dose-low dose difference continued to increase at all weeks after that, and all high dose-low dose comparisons also continued to be nominally significant.

These analyses were not specified in the protocol and it is not at all obvious what the best (or appropriate) method is to detect the onset of drug effect, particularly when those analyses were not prospectively designated. Certainly, we have not performed these analyses or confirmed the sponsor's results. There are precedents for permitting a sponsor to include in product labeling similar graphs that display the time course of drug effect (for example, for the onset of control after treatment for the acute migraine treatments), but in those cases, no p-values are permitted to be described. This prohibition represents our view that the assignment of p-values to the between-treatment comparisons at those points in time are inappropriate.

Further, patients were treated with these lower doses for only one week. It is not immediately obvious that, had patients been maintained at these doses for extended durations, the results for a given dose would mirror those seen at one week of treatment. It might be possible to ultimately conclude that, given the titration scheme employed in the study, effectiveness was first noted at doses lower than 400 mg/day, but this is not identical to concluding that these lower doses are effective, in themselves. Even the conclusion that effectiveness seems to occur at doses lower than 400 mg/day cannot be made definitively at this point, given the problems about potential informative censoring, which have not been addressed at these earlier time points.

The question of the effective dose in monotherapy is, actually, a very important issue here, although it is an issue that we have not previously considered.

Specifically, if we conclude that the study supports the conclusion that only 400 mg/day is an effective dose in monotherapy, this raises a thorny problem. In this study, it took 6-7 weeks for this dose to be achieved, and then, 17% of patients discontinued because of an adverse event. We have previously taken the position that it is inappropriate to approve a treatment as initial monotherapy in epilepsy if it takes a prolonged period of time to achieve a therapeutic dose. In those cases, we have permitted a drug to be indicated as monotherapy only in patients who have been on adjunctive therapy and who are converted to monotherapy; in that way, we can be sure that patients are never on a

subtherapeutic dose of an AED for extended periods of time. I would argue that 6-7 weeks might be an inappropriate duration in this setting.

We could, theoretically, approve topiramate for conversion to monotherapy, of course, despite the fact that the sponsor has never studied it in that setting. This is problematic, however, for two reasons.

First, we have no empirical evidence that would support a conversion dosing recommendation. That is, dosing conversion paradigms can be complex, and are not necessarily predictable (that is, we are on solid ground usually only when we have clinical experience with a particular regimen). In these regimens, the intention is to maintain a therapeutic plasma level of the monotherapy drug in question throughout the conversion regimen. This usually requires detailed knowledge of the interaction of the various drugs in question, so that we can be certain that this can be achieved in the midst of decreases in the dose of the adjunctive treatments and increases (if necessary) in the topiramate dose.

More problematic, however, would be the question of the effectiveness of topiramate as monotherapy in that setting.

Specifically, the sponsor has shown that topiramate is effective as monotherapy in newly diagnosed patients; in particular, in patients with up to 2 seizures prior to treatment (in fact, almost 2/3 of the patients had only 1 seizure prior to treatment). Indeed, the sponsor has highlighted this fact by 1) proposing that it be indicated as monotherapy only in newly diagnosed patients, and 2) by demonstrating, in Study 104, that there were significant between-treatment differences for the low baseline seizure patients, but not the high baseline seizure patients (the sponsor used this finding to support the validity of the results of Study 106). Patients on adjunctive therapy who are being considered for conversion for monotherapy would be most likely those patients who have relatively frequent seizures; it is highly questionable if the results of Study 106 sufficiently support the conclusion that topiramate would be effective in these patients.

Indeed, we have never granted a claim for the treatment of newly diagnosed patients, or patients with "mild" epilepsy, and it is fair to consider the propriety of doing so. First, it is not immediately obvious who these patients are, how uniform they are, and how closely they compare to the patients studied (for example, patients may be newly diagnosed, not because they have had only 1 or 2 seizures, but because, even though they may have had many seizures, they have only recently come to medical attention). Further, one can imagine a sponsor legally promoting such a drug as the only or first approved drug for newly diagnosed patients, despite the fact that this would actually be a significantly restricted claim.

Finally, the sponsor has proposed that the claim for use in monotherapy be extended to patients down to the age of 6 years. In their studies, they have treated 20 patients below the age of 10 years. It is fair to ask if this experience adequately supports a conclusion that the treatment should be approved for these younger patients, especially given the (potentially) effective dose of 400 mg, a relatively high dose associated with a significant risk of adverse events (including a significant risk of metabolic acidosis).

For the reasons discussed above, then, I will issue a second Approvable letter. As with the first action letter, because fundamental questions still remain about the ultimate approvability of the application, as well as the fact that there are still important labeling issues unaddressed, I will not attach draft labeling.

Russell Katz, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
1/19/05 04:24:04 PM
MEDICAL OFFICER

MEMORANDUM

NDA 20-505/S-018 Topamax Tablets
NDA 20-844/S-015 Topamax Sprinkle Capsules

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Response to Approvable Letter / Efficacy of Topamax as Monotherapy

DATE: January 3, 2005

Background

An Approvable Letter was sent to the sponsor, describing DNDP's concerns about the results of the pivotal study, Study 106, submitted in support of a claim for monotherapy of partial seizures and primary generalized tonic-clonic seizures in adult and pediatric patients 6 years of age and older. DNDP was concerned about the large number of dropouts during the trial (see below) and the effect of the dropouts on the reliability of the primary analysis.

Study 106 was a randomized, double-blind study comparing the efficacy of Topamax monotherapy at a target dose of 400mg/day with Topamax monotherapy 50mg/day in adult and pediatric (6 years and older) patients with newly diagnosed (within 3 months) or recurrent (while off AEDs) seizures. Patients were required to weigh 25 kg or more. Seizure types allowed included partial seizures and primary generalized seizures. The primary generalized seizures could include tonic-clonic, clonic, or the seizures of juvenile myoclonic epilepsy.

	Study 106 Low-dose	Study 106 High-dose
Randomized	234	236
Dropouts	39 (17%)	75 (32%)
First seizures	90 (38%)	49 (21%)
Ratio Dropouts/Seizures	0.43	1.5

A simple analysis of time-to-first-seizure for Study 106 yielded a p-value of 0.0002. In contrast, an analysis imputing failure each time a patient was censored yielded a p-value of 0.57.

The Approvable Letter asked the sponsor to address four main issues:

First, the sponsor was asked to investigate some newly described statistical techniques for dealing with the problem of informative censoring. DNDP met with the sponsor after the Approvable Letter issued and it was agreed that the sponsor would provide additional analyses of Study 106 using an approach described by Scharfstein and Robins. These authors had described an approach to model censored data for a single sample. To address Study 106, the approach had to be extended to a two-sample scenario.

Second, the sponsor was asked to expand on the simulations that had been supplied during the first review cycle. These early simulations imputed failure times for censored patients based on assumptions about the possible seizure frequencies for censored patients.

Third, the sponsor was asked to address the surprising finding in an earlier study, Study 104, in which the two randomized groups diverged for time-to-first-seizure but had superimposable curves for time-to-second-seizure.

Fourth, DNDP requested a postmarketing commitment from the sponsor to perform a juvenile animal toxicity study.

Because of the unresolved issues above, draft labeling was not issued with the Approvable Letter.

Dr. Howard Chazin has performed the primary clinical review and Dr. Kun He has performed the primary statistical review.

I. Censoring Bias Function Analysis (Scharfstein and Robins)

This method was developed to model the relationship between failure-time and censoring-time. The model that the authors created has two parameters, α and tau. Neither parameter can be easily understood in clinical terms as discussed by Dr. Kun He. To help understand the parameters, the sponsor has provided survival curves for Study 106 imputing a range of values for the two parameters. A review of these curves provides some understanding of the effect of the different parameters on the curves and, more importantly, the separation of the curves.

To investigate the model, the sponsor looked to another study of Topamax monotherapy, Study 105, in which patients who stopped Topamax for any reason were still followed forward in time for the occurrence of seizures. Using the data from Study 105, values for α and tau were computed: α = -1.4 and tau = 577 days. The sponsor contends that these values should provide **conservative** bounds for the sensitivity analysis parameters for Study 106. The argument made is that baseline seizure frequency for the patients enrolled in Study 105

was greater than the baseline seizure frequency for the patients enrolled in Study 106 (even the subset of patients who withdrew prematurely in Study 106).

Imputing these values for α and tau to the two-sample model for Study 106, the sponsor found that the between group difference was statistically significant with a p-value of approximately 0.02.

Dr. Kun He notes this result in his review but expresses the following reservations about its validity.

First, he notes that many assumptions have to be made about Study 105 and Study 106 to state that the parameters from Study 105 represent a conservative boundary for Study 106. I would agree. A greater baseline seizure frequency in Study 105 does not absolutely predict a stronger relationship between premature withdrawal and time of first seizure compared to Study 106. Post-withdrawal, multiple confounding variables are introduced to include the particular AEDs to which the patients are converted and, then, their particular response to those medications. I believe the parameters derived from Study 105 represent one realized result, but not necessarily an extreme result. Following on this, if α = -1.4 in Study 105, it seems possible that in another study like Study 106, α could just as easily be in the range of -2.0 to -2.5, a range that would yield a non-significant p-value by the sponsor's methods.

Second, Dr. Kun He believes that the method used by the sponsor to compute the test statistic for the two-sample censoring bias function has not been proven to be valid. According to the FDA statistical team, the sponsor "employed an ad-hoc bootstrap method to calculate the p-value." At this time, the FDA statisticians are not comfortable accepting this approach for calculation of the p-value.

Third, Dr. Kun He notes that the clinical meaning of the parameters cannot be easily understood so that clinical experts cannot intuitively establish a reasonable range of values for α and tau. I would agree.

II. Multiple Imputations

Prior to the Approvable Letter, in order to impute failure times for censored patients, the sponsor first created exponential distributions of failure times for a population of patients with a range of given seizure frequencies. Then, for any censored patient, a failure time was randomly chosen from this distribution and applied for the given patient (having subtracted the actual observed time for the patient). The sponsor performed only a single simulation for each patient for any seizure frequency and then computed a nominal p-value.

In the Approvable Letter, DNDP asked the sponsor to repeat this approach, but doing multiple runs for any assumed seizure frequency. Multiple runs would

result in a range of p-values. The sponsor was asked to explore how best to report and interpret the range of p-values generated.

In the Approvable Letter, DNDP also asked the sponsor to further explore the range of possible seizure rates for censored patients. In particular, the sponsor had applied equal seizure rates to both treatment arms. Now they were asked to assume varying seizure rates for the two treatment arms and provide those results. All of this was meant to better explore the range of outcomes under various assumptions.

In the current response, the sponsor has complied with the first request, performing 1000 simulations for any assumed seizure rate. Likewise, the results are provided for varying seizure rates across the two treatment groups. The results of these simulations are provided in Dr. Kun He's review (p.6). The resulting table of p-values using combinations of assumed seizure rates suggests that, only when the cumulative seizure rate at day 500 is assumed to be $\geq$60% for the high-dose group and the corresponding rate for the low-dose group is assumed to be somewhat lower than the high-dose group, does the comparison become nominally non-significant.

Note that the p-values from these new simulations are lower than the p-values from the previous single-run simulations for any assumed seizure rates. This is an unexpected result according to Dr. Kun He, a result that the FDA statisticians cannot explain. Note that each of the new 1000-run simulations has only one p-value linked to it, not a *family of p-values* that the Approvable Letter anticipated. Subsequent to the Approvable Letter, the FDA statisticians agreed to an analysis method resulting in only a single p-value for each of the 1000-run simulations. That these p-values are lower than expected may be method-related.

The question also remains: what seizure rate to best assume?

III. Study 104

This was a randomized, double-blind study comparing the efficacy of Topamax monotherapy at a dose of 500/200mg/day (based on weight greater than or less than 50 kgs) with Topamax monotherapy 50/25mg/day (again based on weight greater than or less than 50 kgs) in adult and pediatric (3 years and older) patients with "recently" diagnosed partial seizures. A total of 252 patients were randomized equally to the high dose and the low dose groups. The post-randomization treatment period lasted until the last patient completed 4 months.

The protocol-specified primary outcome was time-to-exit, with the exit criterion defined as the occurrence of a second seizure (or a generalized seizure, if not previously experienced, or status epilepticus). By this analysis, a statistically significant result favoring the high dose group was not found, p=0.78. In fact, the survival curves for this outcome are superimposable (see bottom of page 6).

Almost the same numbers of patients met this exit criterion in the two treatment arms, 52 in the high dose group and 57 in the low dose group.

A secondary outcome in the trial was time-to-first seizure. This analysis favored high dose Topamax over low dose Topamax, with a nominal p-value of 0.062. Median time to first seizure was 317 days in the high dose group and 108 days in the low dose group (see top of next page). A total of 76 patients in the low-dose group had a first seizure versus 59 patients in the high-dose group. The sponsor was asked to address these surprising results.

The sponsor argues that the duration of the study was not adequate to observe enough second seizures for many patients. Given the large number of second seizure observed, I am not convinced by this line of reasoning. Second, the sponsor argues that the enrolled population was heterogeneous, including both newly diagnosed patients and refractory patients. The sponsor argues that the more refractory patients were unequally randomized, resulting in 52% of patients in the high-dose group and 38% of patients in the low-dose group with more than 2 seizures during the baseline phase. The sponsor believes these patients would be more likely to have a second observed seizure. A definitive answer to the question will probably not be forthcoming.

Figure 4: Plot of Cumulative Rates for Time to First Seizure (Kaplan-Meier Estimates)
(Intent-to-Treat Population; Protocol TOPMAT-EPMN-104)

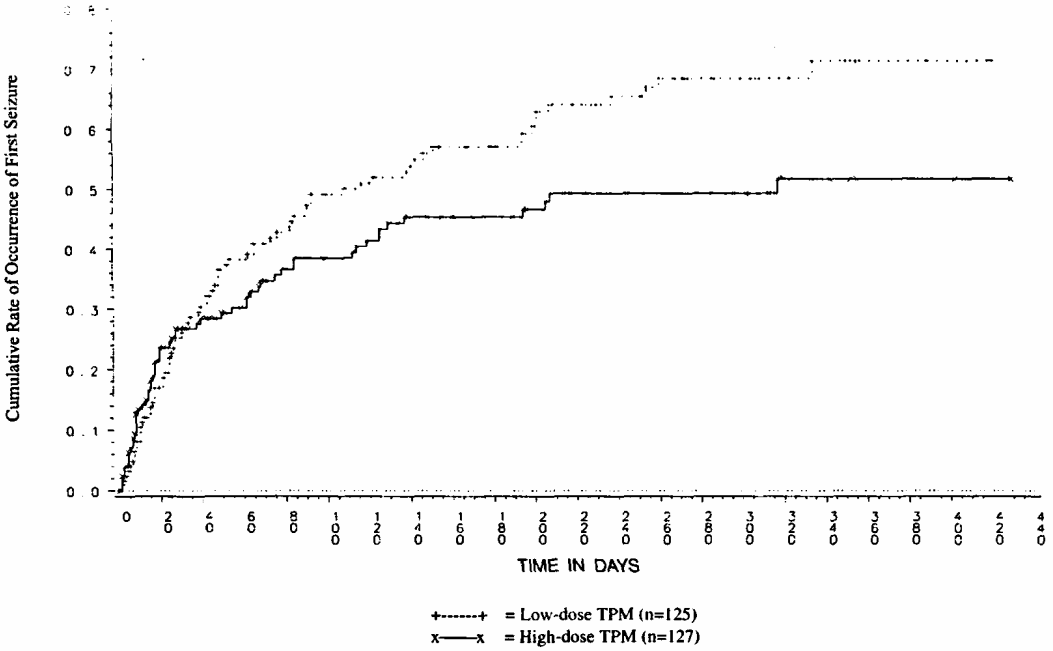
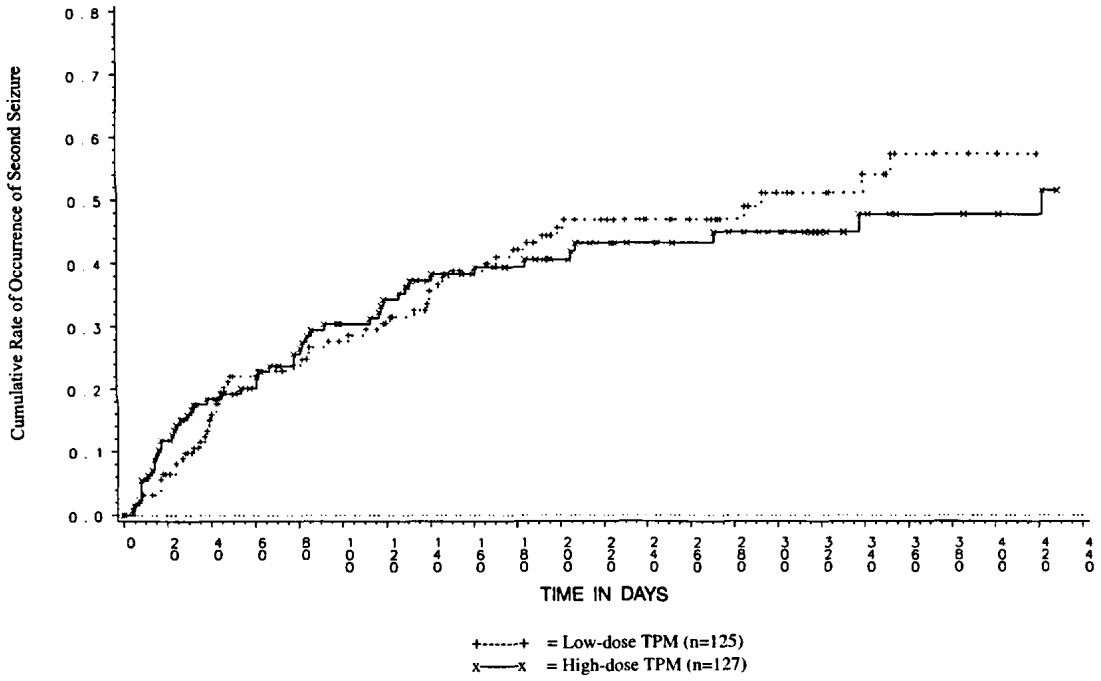


Figure 5: Plot of Cumulative Rates for Time to Second Seizure (Kaplan-Meier Estimates)
(Intent-to-Treat Population; Protocol TOPMAT-EPMN-104)



IV. Postmarketing Commitment

The sponsor has agreed to perform a juvenile animal toxicity study as a Phase 4 commitment. The protocol for this study has already been submitted to DNDP and is currently under review by pharm/tox review staff.

Conclusions

The sponsor has performed a number of sensitivity analyses of the Study 106 results to address the high dropout rate.

For any assumed seizure rates, the new 1000-run analyses yield lower p-values than the previously performed single run analyses. The reasons for this are not clear to the FDA statisticians and raise questions about the validity of the results. At 500-day seizure rates of 60% and greater, non-significant results can be observed for Study 106.

The censoring bias function analyses are difficult to interpret. The two parameters, α and tau, cannot be easily defined clinically. Values derived from Study 105 and applied to Study 106 provide a p-value that is nominally statistically significant, but the FDA statistical group is not comfortable that the p-value is valid. Even if the statistical test was valid, it is not clear that parameters from one study can be easily transposed to another.

Given the arguments provided by the sponsor, I agree with the FDA statisticians and cannot conclude that Topamax has been shown to be effective as monotherapy.

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/s/

John Feeney
1/19/05 02:41:08 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	20-505/S-018 and 20-844/S-015
Submission Number	
Submission Code	BZ
Letter Date	April 21, 2005
Stamp Date	April 21, 2005
PDUFA Goal Date	July 11, 2005
Reviewer Name	Howard D. Chazin, MD
Review Completion Date	June 28, 2005
Established Name	topiramate
(Proposed) Trade Name	Topamax ®
Therapeutic Class	Epilepsy
Applicant	Johnson & Johnson
Priority Designation	S
Formulation	Capsules
Dosing Regimen	oral
Indication	epilepsy-monotherapy
Intended Population	epilepsy patients

Table of Contents

1 INTRODUCTION AND BACKGROUND

This review relates sponsors answers to clinical concerns raised in a response to approvable letter sent on January 19, 2005 regarding this supplemental NDA application.

This document does not discuss the ongoing statistical issues related to the efficacy analysis of this supplemental NDA. Readers are referred to the statistical review of Kun He, PhD.

In October of 2002, Johnson and Johnson Pharmaceutical Research and Development, LLC (Sponsor) submitted a supplemental NDA for the use of Topamax ® (topiramate) tablets (NDA 20-505 S018) and sprinkle capsules (NDA 20-844 S015) as monotherapy in adults and children six years of age and older with newly diagnosed epilepsy.

This supplemental NDA relied on a single efficacy study, TOPMAT-EPMN-106 (Study 106). Study 106 was a multinational, randomized, double-blind, parallel group efficacy and safety study enrolling 470 adult and pediatric patients. The primary objective was to compare the safety and efficacy of 2 doses of topiramate - a low, minimally efficacious dose (50 mg/day) versus a high, presumably fully efficacious and generally tolerable higher dose (400 mg/day).

Efficacy was to be assessed based on the data from the intent-to-treat population. A survival analysis of the primary efficacy variable, time to first seizure (partial onset or generalized tonic-clonic) during the double-blind phase (excluding taper), was performed. Initial efficacy results were robust as reported by the sponsor, as comparison of the Kaplan Meier survival curves of time to first seizure favored topiramate 400mg/day over topiramate 50mg/day (p=0.0002; 2-sided log-rank test). However, Division statisticians were concerned with the much higher rate of dropouts seen in the high dose group (32%) compared to the low dose group (17%). An all cause analysis, presuming that all withdrawals were treatment failures, showed no significant difference between the two treatment groups (p=0.57, log rank test).

An approvable letter was sent to the sponsor on November 26, 2003 due to statistical concerns related to the possibility of a potential bias introduced into the primary efficacy analysis of Study 106 due to the differential withdrawal patterns in the 2 topiramate dose groups. The sponsor responded to our requests in their May 25, 2004 submission. There were continued statistical concerns after review of that submission and a response to approvable letter was sent back to the sponsor on January 19, 2005. Additional clinical problems of concern were introduced in that letter. These are reproduced below (in italics) with the sponsors response followed by discussion by this reviewer.

2. CLINICAL ISSUES FROM THE APPROVABLE LETTER OF JANUARY 19, 2005

For each of the sections below, the appropriate paragraph from the approvable letter is reproduced in italics followed by the sponsor's response to each question. Following the sponsors response, this reviewer has provided discussion.

2.1 Regarding the dose titration and safety of the topiramate latency period.

In Study 106, the effective dose of 400 mg/ day was reached in 6- 7 weeks. In our view, this prolonged duration until an effective dose is reached raises serious questions about the propriety of approving topiramate as " initial" monotherapy (we recognize, of course, that you are proposing that topiramate be approved as monotherapy for " newly diagnosed patients"; we will have additional comments on this proposal below). That is, we would expect that a treatment to be used as monotherapy in epilepsy should be able to be titrated to an effective dose in a minimal amount of time, given that, at least as initial monotherapy, patients will not be receiving any other treatment. In order to support approval for initial monotherapy (or any similar claim), you must justify the safety of the long latency until an effective dose is achieved.

We note, of course, that you have presumably concluded, based on our reading of your proposed labeling, that doses of 100 mg and greater are effective doses. This conclusion is based on analyses you have done that have yielded nominally significant p- values at early weeks during the titration phase. We disagree with your conclusion that the nominally significant comparisons at these earlier weeks establish that the doses attained at those time points are effective. Specifically, patients were treated with these lower doses for only one week; an effect seen at a dose given for only one week cannot reliably predict the effect at that same dose if patients were to stay on that dose for some longer, more reasonable, duration. It is theoretically possible that the data generated at these earlier weeks might be able to support a conclusion that, under this specific titration scheme (employed to reach the target dose of 400 mg/ day), effectiveness appears to first be observed at a particular lower dose (or doses), but we do not consider this to be equivalent to concluding that these lower doses are, in themselves, effective. Further, we do not believe that we can even conclude, at this time, that effectiveness appears to be observed at doses lower than 400 mg/ day, because we are unsure (given the difficulties associated with potential informative censoring) how best to analyze the data at these earlier time points.

Sponsor's response to the Division

> Study TOPMAT- EPMN- 106 did not result in a delay in achieving seizure protection. The seizure rate during the titration period is significantly reduced in subjects assigned to the high- dose group compared with the low- dose group and the risk of seizures is similar to that observed during the subsequent dose

> stabilization period. Furthermore, during the titration phase, the separation between the high- and low- dose topiramate groups, in favor of the high- dose group, occurs early and is statistically significant after 2 weeks post randomization (p= 0.046; 2- sided log- rank test) when according to the dosing regimen used, the subjects in the high- dose group achieved a topiramate dose of 100 mg/ day. This is supported by the Kaplan- Meier curves separating early and remaining separated for at least 500 days. Therefore, topiramate can be safely titrated to efficacy, when administered per the dosing scheme used in Study TOPMAT- EPMN- 106. As such, the Sponsor recommends that the dosing instructions for patients receiving topiramate monotherapy for epilepsy should reflect the doses achieved by the intent- to- treat population in the TOPMAT-EPMN- 106 study per the titration schedule outlined in the protocol and that the maintenance dose and titration rate should be guided by clinical outcome.

Reviewer Discussion regarding dose titration and effective dosage

This reviewer is in agreement that the Kaplan Meier curves do separate early in the study implying early efficacy during the titration phase. However, patients continued to titrate and did not maintain on lower doses for any persistent length of time. Therefore, none of the lower doses can be said to be "effective" due to a lack of data related to time on drug at those lower interim doses. If the sponsor would like to explore the efficacy of lower doses, they may pursue fixed dose studies to ascertain the minimal and other lower effective doses.

The phrase suggested in labeling and used by the sponsor, "(b) (4) ", should be avoided. The sponsors only tested one dose in the pivotal Study 106, 400mg daily. This is the only effective dose from any statistical measurement and should be the goal dose of monotherapy treatment for this supplemental NDA.

This reviewer noted in the original review of the NDA that the majority of patients in the original study maintained doses lower than 400mg (mean dose for that group was 275mg/day). The protocol allowed patients to reduce their dosage in 50mg increments as much as 100mg daily at the discretion of the investigator. Per the sponsor, only 58% of patients achieved a dose of 400mg daily. The most common reason for dose reductions in the trial were due to neuropsychiatric effects of the drug. Because of this, the goal dosage of 400mg, albeit the only dosage tested in the study that was considered efficacious, may not be tolerated by a large number of patients who would then require dose reductions.

This reviewer has few concerns regarding the dose titration of 6 weeks time. There is no real alternative as faster titration (even if agreed to between the sponsor and the Division) is limited due to the side effect profile of topiramate.

A potential phase 4 commitment would be to test lower, less toxic doses to see if they are truly as efficacious as the 400mg dosage.

2.2 Regarding conversion to monotherapy

We could consider (all other things being equal) granting approval for conversion to monotherapy, despite the fact that you have not studied this setting. However, such a claim would be problematic for two reasons.

First, we cannot be certain that the patients who would be candidates for conversion to monotherapy are sufficiently similar to the patients you studied to permit us to conclude that it would be effective in that population. Specifically, it is our understanding that patients on multiple other drugs who are being considered for conversion to monotherapy typically have a more severe form of epilepsy than patients being treated initially with monotherapy. In this regard, not only did the patients enrolled in Study 106 have very few seizures prior to enrollment, but your re- analysis of Study 104 strongly suggests that it is just these patients (and not patients with more severe epilepsy) who benefit from topiramate monotherapy. Second, before we could approve a treatment for a conversion to monotherapy claim, we would need to be able to provide dosing recommendations for the conversion. In the absence of empirical data supporting such a recommendation, it might be possible to provide dosing recommendations based on pharmacokinetic considerations (although this is less preferable than empirical data). In either case, you have not addressed this issue.

Sponsors response to the Division

The sponsor is not pursuing a conversion to monotherapy claim.

Reviewers response

None

2.3 Regarding the term , “newly diagnosed patients”

Although you have proposed that topiramate be approved as monotherapy for newly diagnosed patients, we believe that this indication is also potentially problematic. In our view, it would be difficult for prescribers to understand which patients would benefit from such a treatment. It is not clear which patients are subsumed under this designation. For example, patients with a history of many seizures might be " newly diagnosed" if they have not sought medical attention early in their course; as discussed above, we have questions about whether or not topiramate would be effective in these patients (assuming, of course, that we conclude it is effective at all as monotherapy). If we were to approve topiramate for patients with " mild" epilepsy, we are not confident that this designation is standard in this field; that is, each practitioner would presumably have his or her own definition of which patients meet this definition, and, again, we are not

confident that topiramate would be effective in patients with more frequent seizures. Finally, if we were to approve this claim, this might support, legally, advertising that described such a drug as the first, or only, treatment specifically approved for newly diagnosed patients, when, in fact, this claim would represent a restricted claim, and we consider all previously approved treatments for monotherapy to subsume this use as well as use in other settings. We would like you to address these issues.

Sponsors response to the Division

> The Sponsor has revised the indication statement in an effort to more clearly define the patient population in the TOPMAT- EPMN- 106 study to read "TOPAMAX (topiramate) Tablets and TOPAMAX (topiramate capsules) Sprinkle Capsules are indicated as (b) (4) "

Reviewer Discussion

This reviewer considers that the sponsor terms "(b) (4)" and "(b) (4)" are misleading. (b) (4) imply that seizures started very recently, perhaps within the last few weeks or months. (b) (4) implies ongoing seizures in a patient who may have had seizures for any amount of time, just now they are poorly controlled and "(b) (4)". In fact, all epilepsy is (b) (4) otherwise separate single seizures would be symptomatic of another process (infection, brain tumor, electrolyte abnormality, drug effect, etc.).

The inclusion criteria for Study 106 listed the following:

"A new diagnosis of epilepsy within 3 months prior to study entry, or a recurrence of epilepsy while off of AEDs, including 1 or 2 (but no more than 2) documented seizures within the 3 months before enrollment."

The sponsor provided a breakdown of demographic and baseline characteristics for Study 106 in Attachment 8 below.

Attachment 8: Demographic and Baseline Characteristics:
(Study TOPMAT-EPMN-106: Safety Population)

	TPM 50 (N=234)		TPM 400 (N=236)		Total (N=470)	
Time since diagnosis (mos.): n, %						
≤1	122	52	137	58	259	55
2	43	18	30	13	73	16
3	14	6	14	6	28	6
4	6	3	6	3	12	3
5	2	<1	0		2	<1
6	3	1	1	<1	4	1
≤12	193	82	192	81	385	82
≤24	196	84	195	83	391	83
>24	37	16	41	17	78	17
Missing information	1	<1	0		1	<1
N	233		236		469	
Mean	19.3		27.0		23.2	
SD	56.27		72.21		64.83	
Median	1.0		1.0		1.0	
Range	0.0 - 408.0		0.0 - 456.0		0.0 - 456.0	
Seizure count during 3-month Baseline[c]: n,%						
1 Partial Onset[a]	81	35	78	33	159	34
1 Generalized[b]	67	29	69	29	136	29
2 Partial Onset[a]	45	19	58	25	103	22
2 Generalized[b]	34	15	29	12	63	13
1 Partial Onset[a] + 1 Generalized[b]	7	3	2	1	9	2
Number of AEDs used before randomization: n,%						
0	109	47	119	50	228	49
1	118	50	111	47	229	49
≥2[d,e]	7[e]	3	6	3	13[e]	3

[a] Includes simple partial, complex partial and partial evolving into secondarily generalized seizures.
[b] Includes generalized tonic-clonic, tonic, and clonic seizures.
[c] Seizures experienced by the subjects during the 3-month retrospective baseline phase of the study.
[d] Twelve subjects used more than 1 anti-epileptic drug (AED) before randomization. Of these, only 1 subject (Subject 534001) used 3 AEDs; another subject, Subject 554003, used both AEDs concomitantly for 3 days. The remaining 10 subjects used their 2 AEDs sequentially, not concomitantly, and 1 of the 2 AEDs was used only for short-term treatment.
[e] In case of Subject 550001 in TPM 50 group, who received only 1 AED (fosphenytoin) at baseline, topiramate was also coded in error as a baseline AED, bringing the number of subjects using 2 or more AEDs in that group to 7.

There was a bimodal distribution of enrolled patients with a large group of patients (approximately 3/4) diagnosed within 3 months of entering the trial and another smaller cohort diagnosed greater than 2 years prior to the study. This reviewer would not consider a patient with a 2 year history of seizures on treatment to be "newly diagnosed" or "(b) (4)". What is more striking about the breakdown of patients is how few seizures they had during the baseline 3 month period. Also interesting is that half of the patients had used one or two AEDs prior to enrollment, again not consistent with "newly diagnosed" but probably consistent with infrequent or "less refractory" epilepsy. There should be some consideration as to the quantitative assessment of seizure severity in

these patients and in the label to avoid confusion. At the very least, if we can agree with the terminology, we should choose one label whether it be "(b) (4)" or "(b) (4)" rather than two. My choice would be to propose that the drug be used for infrequent seizures. I would not use the term "(b) (4)".

2.4 Regarding enrollees down to the age of 6.

Finally, we note that wish to have the claim for monotherapy apply to children down to the age of 6 years. In your studies, you have enrolled a total of 20 patients below the age of 10 years. Given that the dose studied was 400 mg/ day, a relatively high dose associated with significant risk of adverse events (including a high rate of metabolic acidosis), we question whether such minimal experience in these younger patients justifies approving the claim in these patients. Please address this issue.

Sponsors response to the Division

> Based on the limited experience that the sponsor has with topiramate monotherapy in children below the age of 10, the Sponsor has revised the monotherapy indication to reflect a minimum age of 10 years and added a statement to the Pediatric Use section of the TOPAMAX label that safety and effectiveness in patients below the age of 10 years have not been established for monotherapy treatment of epilepsy.

Reviewers discussion

None. However the sponsor will have to adjust enrollment in a future pediatric study to evaluate these lower age groups that have been excluded from this NDA submission.

3. LABELING ISSUES

The Division's requests are in italics followed by the sponsor's responses and reviewer discussion in regular text.

1. *In your most recently proposed draft labeling, you have not updated the Cognitive/ Neuropsychiatric Adverse Events section of the labeling with information for monotherapy in epilepsy. Specifically, you should draft language under the subheadings Cognitive- Related Dysfunction, Psychiatric/ Behavioral Disturbances, and Somnolence/ based on the adult data from Study 106. The analyses should mirror those already described adjunctive therapy in epilepsy and migraine.*

> The sponsor has revised the Cognitive/Neuropsychiatric Adverse Event Warning as requested by the Agency.

Reviewer discussion –

Under warnings, the sponsors have added,

> *"For the monotherapy epilepsy population in the 50 mg/ day and 400 mg/ day groups, the incidence of somnolence was dose- related and the incidence of fatigue was comparable in both treatment groups."*

Using the supplied table, Incidence of Adverse Events by Preferred Term (attachment 11), the incidence of somnolence was 9% in the 50mg/day group and 15% in the 400mg group, a 60% difference and not "comparable". The incidence of fatigue was the same (14%) in both treatment groups.

The sponsors have added the following under somnolence/fatigue in the neuropsychiatric warnings section

> *"The most frequently reported neuropsychiatric events in pediatric patients in the 50 mg/ day and 400 mg/ day groups during the monotherapy double- blind study were headache, dizziness, anorexia, and somnolence."*

The sponsor is correct and accurate with the above statement.

(b) (4)

This statement is misleading in that although the total number of pediatric patients who discontinued treatment was 8, it breaks down into 1 patient from the TPM 50 group and 7 patients in the TPM 400 group. The sponsor's statement is also misleading in that even though the most common adverse event associated with discontinuation of therapy in pediatric patients was difficulty with attention/concentration, no patients in the TPM 50 group were reported to have this problem and 3 patients in the TPM 400 group (5%) carry the entire weight for that sub category.

2. *Under the subheading Pediatric Patients, you should describe the discontinuations due to adverse events, if any, in Study 106.*

> The sponsor has added a new paragraph under the subheading, "Patients" to describe the discontinuations due to adverse events in Study TOPMAT- EPMN-106. Please note, as per Agency agreement, since the monotherapy indication has been revised to reflect use in children 10 years of age and above, the discontinuation rates provided are only for patients 10 to 16 years of age (10- 15 years of age, inclusive) from Study TOPMAT- EPMN- 106. Eight of the 114 patients, ranging in age from 10 to 16 years old (10- 15 years, inclusive), and discontinued treatment due to any adverse events in the TOPMAT- EPMN- 106

study. The most common adverse event associated with discontinuation was difficulty with concentration/ attention.

Reviewer Discussion - The sponsor has provided data regarding discontinuations due to adverse effects, these are already discussed in the previous question.

3. *In the Monotherapy Adverse Events Tables you provided, there are columns for daily doses of* (b) (4) *mg/ day. Because these will not be recommended daily doses, we ask you to remove these columns. Further, because of differences in study design across the monotherapy studies, we believe that only the data from Study 106 should be described in the tables for both adult and pediatric patients.*

The Sponsor has revised the monotherapy adverse event tables (adult and pediatric) as requested by the Agency. In addition, the Sponsor has revised the text in the Adverse Reactions, Monotherapy section (which precedes the Monotherapy Adverse Events Tables) to discuss only the data from the 400- mg/ day topiramate group in Study TOPMAT- EPMN- 106. Please note, as per Agency agreement, since the monotherapy indication has been revised to reflect use in children ages 10 to < 16 years of age, the incidence of treatment- emergent adverse events provided in the pediatric table is only for patients, age 10 to < 16 years from Study TOPMAT- EPMN- 106. Refer to the annotated labeling located in Item 2. The data that support the proposed labeling changes are provided in Attachments 11, 12, and 13. In addition, based on the Agency's request to only include safety data from the TOPMAT- EPMN- 106 study into the label, the Sponsor has revised the Other Adverse Events Observed During All Epilepsy Clinical Trials section to reflect this change for subjects 10 years of age and older. Refer to the annotated labeling located in Item 2. The data that support the proposed labeling changes is provided in Attachment 14.

This reviewer has looked over the tables in the proposed labeling and they appear adequate. My only concern is whether the 5% cutoff is appropriate.

4. In the pediatric Adverse Events Table, (b) (4) *is listed with an incidence of* (b) (4) *in all but the* (b) (4) *mg/ day dose column. Based on the analyses of lab data you provided, we believe this may be misleading. Please address this issue.*

Abnormal laboratory values are not always classified as adverse events. Therefore, despite 25% of pediatric subjects from all the monotherapy trials presenting with a decrease to less than 20 mEq/ L in serum bicarbonate levels, only subjects in the (b) (4) - mg/ day dose group actually reported these laboratory findings as an adverse event. To assure that the difference in adverse event reporting versus the incidence of abnormal serum bicarbonate values being reported by patients is not misleading, the Sponsor has updated the Metabolic Acidosis Warning section to include the incidence of persistent treatment-emergent decreases in serum bicarbonate levels in both adult and pediatric

> patients, aged 10 years and older, from Study TOPMAT- EPMN- 106. Please note, due to the Agency's request that the Sponsor revise the monotherapy adverse event tables to only include data from Study TOPMAT- EPMN- 106 and to remove the [redacted] (b) (4) mg/ day daily dose columns, [redacted] (b) (4) is no longer listed as an adverse event.

This reviewer has no problems with this approach.

5. Please update the Metabolic Acidosis Warning section to include monotherapy data from 106.

> The Sponsor has revised the Metabolic Acidosis Warning as requested by the Agency. Please note, as per Agency agreement, since the monotherapy indication has been revised to reflect use in children ages 10 years of age and above, the incidence of persistent treatment- emergent and markedly abnormally low serum bicarbonate levels is only provided for patients age 10 years and older from Study TOPMAT- EPMN- 106.

This section of the label appears adequate as written.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Howard Chazin
6/28/05 09:48:21 AM
MEDICAL OFFICER

John Feeney
6/29/05 03:25:41 PM
MEDICAL OFFICER
see my cover memo

MEMORANDUM

DATE: June 28, 2005

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-505/S-018 & NDA 20-844/S-015

SUBJECT: Action Memo for NDA 20-505/S-018 & NDA 20-844/S-015, for the use of Topamax (topiramate)Tablets and Sprinkle Capsules, respectively as initial monotherapy in the treatment of partial and primary generalized tonic-clonic seizures

NDA 20-505/S-018 & NDA 20-844/S-015, for the use of Topamax (topiramate)Tablets and Sprinkle Capsules, respectively, as initial monotherapy in the treatment of partial and primary generalized tonic-clonic seizures, were submitted by Ortho-McNeil Pharmaceutical, Inc., c/o Johnson & Johnson Pharmaceutical Research and Development, L.L.C., on 10/29/02. This application has been the subject of two Approvable letters (11/26/03 and 1/19/05). The application contains the results of a single controlled trial in patients with newly diagnosed epilepsy, Study 106, in which patients were randomized to receive either 50 mg or 400 mg/day of topiramate and were followed until certain exit criteria were met or they completed the trial (either by completing the maximum duration of the trial or discontinuing early). The results of the primary analysis were highly statistically significant (p=0.0002), but there were many early discontinuations (75/236 in the high dose and 39/234 in the low dose groups). The subsequent submissions have incorporated the sponsor's attempts to address the question of the introduction of any potential biases in the analyses in the face of such a large and differential number of early discontinuations.

In our last AP letter (1/19/05), we remarked on the sponsor's attempt to evaluate the effects on the outcome by varying the rates of failure that might have been seen in the two dropout cohorts. The sponsor addressed this (theoretical) question by employing an exponential distribution of days to dropout in these two cohorts, and then generating p-values for the many comparisons that result. That is, the sponsor generated an array of p-values for the between-treatment comparisons corresponding to failure rates of between 30-80% for both treatment groups (see, for example, Dr. Kun He's review of 1/3/05, page 6). The resultant array suggested that only under quite unrealistic assumptions of failure rates in the two early dropout cohorts of the two treatment groups was statistical significance lost.

However, our statisticians noted problems with the statistical analyses used to generate these p-values, and we have had numerous discussions with the

sponsor on this point. In brief, we have not been convinced that the exponential distribution analysis used to generate these p-values is reliable. As a result, we asked the sponsor to perform analogous analyses, in which various failure rates are imputed to the two dropout cohorts, but assuming that these rates occurred on the first day on which the patients dropped out (for example, for the imputed failure rate of 50% in the high dose dropout cohort, it was assumed that 50% of these patients met the exit criteria on the first day they left the trial).

The last AP letter raised additional questions.

The sponsor had proposed that the drug be indicated in "newly diagnosed" patients, but it was not clear how this entity was to be defined, or how prescribers would understand this designation. In the trial, patients were enrolled only if they had no more than 2 seizures in the 3 months prior to enrollment in the trial, but it was clear that the sponsor did not intend the drug to be limited to patients with such a small number of seizures, and, in any case, approving the drug for use in patients with "mild" epilepsy is also problematic for the same reason (that is, there is no commonly understood definition of "mild" epilepsy).

Further, we noted that, in Study 106, the high (active) dose was reached only after 6-7 weeks of titration. Although the sponsor asserted that the drug was effective at doses as low as 100 mg/day, we did not agree because, although we acknowledged that statistically significant between-treatment differences had been noted at those lower doses, patients had been treated with those doses only for about 1 week, a duration far too short to conclude that they are "effective" in any clinically meaningful sense.

Finally, we noted that the sponsor wished to indicate the drug down to the age of 6 years, but in fact had enrolled very few patients below the age of 10 in the study.

The sponsor responded to the AP letter in a submission dated 5/10/05. At the time of this writing, the only completed review has been performed by Dr. Kun He, statistician, although I have discussed the relevant issues in detail with the review team, including Dr. Howard Chazin, medical officer, and Dr. John Feeney, Neurology Drugs Team Leader.

The primary issue identified in the AP letter was the array of p-values generated when various failure rates are imputed for the two dropout cohorts. The goal of these analyses was to examine how different from the patients included in the primary analyses (those who met exit criteria or who completed the duration without having done so) the dropout cohorts would have to be in order for statistical significance to be lost. As noted above, the sponsor's original array demonstrated that only under highly pathologic assumptions (that is, when we imputed failure rates for the high dose dropout group that far exceeded those of

the low dose group) was significance lost. Unfortunately, as described above, inconsistencies in these analyses rendered them unreliable.

It is important to note here that these analyses are, in many senses, artificial, and not only because the failure rates used to generate the array are clearly imputed. The point I wish to make is that the failure rates (which in the latest analyses are considered to be group means that have occurred at Day 1 after discontinuation from the study), are to be taken as, in a sense, surrogates for how these patients would have behaved had they stayed in the trial, **despite the fact that the failure rates imputed are considered to have occurred after the patients discontinued from the trial**. In particular, it is clear that there is no reason to assume or conclude that patients, having left the trial, would fail at a differential rate that depended upon their previous treatment assignment. That is, assuming randomization created equivalent groups, a patient who discontinued early after having been in the high dose group should be just as likely to fail as a patient who had discontinued early from the low dose group (I am here excluding considerations related to any effect of persistent blood levels of drug after discontinuation). I note this point because were this not true, we should not examine the effect on the analyses of any imputed failure rates other than those that are equivalent in the two groups. Indeed, it is not obvious that examining failure rates in patients who have discontinued treatment is meaningful for our purposes, other than as an indirect (and, again, hypothetical) measure of how different these dropout cohorts need to be to affect the results as originally presented.

Having said this, then, we can examine the “new” array of contrasts that the sponsor has generated. It is worth noting here that the sponsor believes that these new analyses are flawed in that they are “unrealistic”; that is, they do not believe that it is appropriate to consider that the failure rates would have occurred on Day 1. I agree that this is a highly unrealistic assumption, although according to the statisticians, it makes the analyses more tractable. I would only add that, based on my previous comments, it is fair to consider any of these analyses as “unrealistic”.

In any event, examination of the new table makes clear that the “Day 1” assumption increases the number of non-significant p-values. Perhaps the first observation is that the line of equivalent seizure rates is no longer uniformly significant. That is, in the sponsor’s original table, the p-values for all of the contrasts in which the imputed failure rates are equivalent between the two groups are significant; in the new table, when the equivalent rates are 55% and greater, statistical significance is lost. Further, there are several contrasts which are not significant even when the imputed seizure rates for the high dose group are lower than those in the low dose group (for example, the p-value for the contrast in which the high dose failure rate is 65% and the low dose failure rate is 70% is 0.093). In the earlier table, as previously noted, only when the high dose failure rate was assumed to be much greater than that in the low dose group was

significance lost. However, even in the new table, the vast majority of the contrasts in which the failure rate in the high dose group is assumed to be lower than that in the low dose group (even by a small increment) are significant. For example, for a failure rate in the high dose group of 55% and a failure rate of 60% in the low dose group, the p-value is 0.054, and for the high dose rate of 55% and a low dose rate of 65%, the p-value is 0.04.

It must be acknowledged that the results of these new analyses are less impressive than those generated earlier. Nonetheless, in my view, the data, taken as a whole, provide substantial evidence of effectiveness for topiramate as monotherapy. In particular, the study as originally analyzed yielded a highly significant between treatment difference (p=0.0002). We have previously concluded that the sponsor made all reasonable attempts to establish that the patients who discontinued early (and in particular those who withdrew early because of adverse events) were similar to those who were not censored (and, therefore, would not have been expected to respond differently to their assigned treatment than those who did not discontinue early; see my memos of 11/26/03 and 1/19/05). Finally, although the new analyses are less impressive than those done previously, I believe that they too establish, to a degree with which I am comfortable, that reasonable assumptions about failure rates (again, these are simply "surrogates" for how these patients might have performed had they stayed in the trial) strongly suggest that there are no important biases introduced by the early discontinuation of these patients (based on discussions with, and preliminary analyses done by, Dr. He, it seems clear that, had a day later than Day 1 been used to calculate the p-values, all of the p-values would have been smaller than those presented here by the sponsor). We have already concluded, of course, that topiramate is an effective anti-seizure medication, at least in the adjunctive setting, and the effective dose in that setting is 400 mg/day, equal to the dose tested in the monotherapy setting (that is, our prior belief is quite high that it "should" be effective as monotherapy). For these reasons, then, I conclude that topiramate is effective as monotherapy in patients with epilepsy.

There are, of course, other issues to consider.

As noted earlier, we have expressed concern that it takes about 6-7 weeks to achieve the effective dose of 400 mg/day. In a monotherapy setting, this raises concerns that patients will remain "unprotected" for an unacceptably long duration.

Although we do not agree with the sponsor that lower doses have been shown to be effective, in a regulatory sense (that is, we would not recommend a dose that had been maintained for only one week), it is clear that these lower doses are associated with statistically significant between-treatment contrasts, clearly demonstrating that patients are "protected" in a real sense, although, it must be acknowledged, not as well protected as they ultimately will be at a higher dose. However, it must also be acknowledged that we cannot state with certainty that

the “effective” dose here (400 mg/day) provides the maximum degree of effectiveness. Given these considerations, then, it seems to me that it would be appropriate to approve the treatment with labeling that makes clear that 400 mg/day is the effective dose, that it takes 6-7 weeks to achieve this dose, and that lower doses have not been adequately demonstrated to be effective in the longer term. Nonetheless, I believe it is appropriate to permit the recommendation of this titration regimen in labeling.

The problem of the specific language to be used in the indication is still a thorny one, although one that I believe can be adequately addressed. The sponsor has now proposed to use the terms “(b) (4)” epilepsy.

I do not believe that either term adequately addresses the problem. “(b) (4)” epilepsy is not, in my view, materially different than “newly diagnosed”, although I do acknowledge that it has the **appearance** of being linked to the onset of the epilepsy, and not the onset of the diagnosis. Further, in a very real sense, all epilepsy (or at least seizures in patients with epilepsy) is “(b) (4)”, so it is difficult to conclude that these terms can reliably be interpreted by potential prescribers.

However, it should be noted that Study 106 can be seen as providing proof of principle that topiramate is effective as “initial” monotherapy (as opposed to being effective in patients who need to be converted from a current regimen to monotherapy; this is a distinction we have previously made for anti-convulsant drugs). Although the patients enrolled in Study 106 are not necessarily representative of all patients who may initiate treatment with AEDs, few if any studies in any condition include patients who are representative of all patients with the condition under study; in a real sense, all, or most, clinical trials provide similar proof of principle. I believe that topiramate can be indicated in the treatment of initial monotherapy, but I also believe that a brief description of the type of patients included in the trial, and the fact that it has not been studied in patients on current alternative AED regimens, should be included in the Indications section of labeling.

Finally, the sponsor has now agreed to indicate the treatment for patients age 10 years and older.

For these reasons, then, I will issue the attached Approval letter, with appended agreed upon labeling.

Russell Katz, M.D.

APPEARS THIS WAY IN ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
6/29/05 08:42:50 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	20-505/S-018 and 20-844/S-015
Submission Number	
Submission Code	BZ
Letter Date	May 25, 2004
Stamp Date	May 27, 2004
PDUFA Goal Date	January 19, 2005
Reviewer Name	Howard D. Chazin, MD
Review Completion Date	January 18, 2005
Established Name	topiramate
(Proposed) Trade Name	Topamax ®
Therapeutic Class	Epilepsy
Applicant	Johnson & Johnson
Priority Designation	S
Formulation	Capsules
Dosing Regimen	oral
Indication	epilepsy-monotherapy
Intended Population	epilepsy patients

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The supplemental NDA application for the use of topiramate as monotherapy in epilepsy, despite the statistical modeling approaches, continues to be non-approvable.

- The sponsors failed to show statistically significant evidence of efficacy in time to first seizure in their pivotal trial TOPMAT-EPMN-106 between the low and high dose groups. This was due to the almost threefold incidence of dropouts due to adverse events seen in the high dose group leading to fewer seizure events in this group. The two statistical models used to replace the clinical information from the dropouts in both dose groups do not convince the statisticians or this clinician that topiramate would be efficacious as monotherapy.

- The sponsors failed to show a statistically significant evidence of efficacy in time to first seizure between the low and high dose groups in supportive study TOPMAT-EPMN-104

(p=0.062, log rank test). However, the sponsor discussed possible reasons for this disparity including length of the study and heterogeneity of the population. The study did indicate a statistically significant result in a subpopulation of epilepsy patients with milder seizures, however this subgroup analysis may not be properly powered to give meaningful results.

This reviewer remains concerned that if topiramate was approved for monotherapy, that it would only benefit mild patients or those with newly diagnosed epilepsy. In addition, there is a separate safety issue of tolerability of a dose of 400mg which explains much of the reason for the higher number of dropouts seen in the high dose group. Taken together, the issue of narrow efficacy and high rate of adverse events at the goal dose limits the use of this drug as monotherapy. Consequently, this reviewer would not approve topiramate for monotherapy.

1.2 Recommendation on Postmarketing Actions

This reviewer continues to have safety concerns regarding the high dose of 400mg, but these are discussed fully in the original NDA review dated November 25, 2003.

The sponsor has agreed to perform a juvenile animal toxicity study as a Phase 4 commitment. The protocol for this study has already been submitted to DNDP and is currently under review by pharm/tox review staff.

1.3 Introduction and Background

Johnson and Johnson Pharmaceutical Research and Development, LLC (Sponsor) submitted a supplemental NDA for the use of Topamax ® (topiramate) tablets (NDA 20-505 S018) and sprinkle capsules (NDA 20-844 S015) as monotherapy in adults and children six years of age and older with newly diagnosed epilepsy.

This supplemental NDA relied on a single efficacy study, TOPMAT-EPMN-106 (Study 106). Study 106 was a multinational, randomized, double-blind, parallel group efficacy and safety study enrolling 470 adult and pediatric patients. The primary objective was to compare the safety and efficacy of 2 doses of topiramate - a low, minimally efficacious dose (50 mg/day) versus a high, presumably fully efficacious and generally tolerable higher dose (400 mg/day).

Efficacy was to be assessed based on the data from the intent-to-treat population. A survival analysis of the primary efficacy variable, time to first seizure (partial onset or generalized tonic-clonic) during the double-blind phase (excluding taper), was performed. Initial efficacy results were robust as reported by the sponsor, as comparison of the Kaplan Meier survival curves of time to first seizure favored topiramate 400mg/day over topiramate 50mg/day (p=0.0002; 2-sided log-rank test). However, Division statisticians were concerned with the much higher rate of dropouts seen in the high dose group (32%) compared to the low dose group (17%). An all cause analysis, presuming that all withdrawals were treatment failures, showed no significant difference between the two treatment groups (p=0.57, log rank test).

Study TOPMAT- EPMN- 104 (Study 104) was a supportive study that was similar in design to Study 106. Study 104 was a randomized, double-blind, parallel-group study conducted at multiple sites to evaluate topiramate dosages based on body weight of 25 or 50mg/day (low dose) and 200 or 500 mg/day (high dose) as monotherapy in 252 subjects three years of age and older The primary efficacy endpoint variable, time to exit (equivalent to time to second seizure) was assessed. The study failed to demonstrate a difference between dose groups for the primary endpoint (p=0.781, log-rank test). However, the difference in time to first seizure between the two treatment groups did approach statistical significance (p=0.062, log-rank test), potentially supporting the results from Study 106, but raising questions as to the results for time to second seizure had that endpoint been assessed in Study 106.

An approvable letter was sent to the sponsor on November 26, 2003 due to statistical concerns related to the possibility of a potential bias introduced into the primary efficacy analysis of Study 106 due to the differential withdrawal patterns in the 2 topiramate dose groups. Considering the similar study designs of Study 104 and 106, the Division also questioned the failure of the primary analysis of Study 104, the time to second seizure, although the analysis of time to first seizure appeared to approach statistical significance. The Division also noted that both studies had similar results for time to first seizure, and thus might have had similar results for time to second seizure had that outcome been observed in Study 106. The Division was also uncertain as to the clinical meaning of time to first seizure as a measure of effectiveness of topiramate as monotherapy.

The sponsor responded to our requests in their May 25, 2004 submission. That submission discussed in detail the statistical and clinical issues of concern to the Division.

1.4 Statistical issues

To address the issue of noninformative censoring relating to the high number of dropouts in Study 106, the sponsor performed several analyses by simulating events among censored patients. These two sensitivity analyses methods, the *multiple imputations method* and the *censoring bias function method*, generated results in favor of the high dose group. However, despite this, Division statisticians felt, "it is difficult to interpret these results with relevance to the regulatory decisions."

The *multiple imputations method* is one where the statistician simulates random events for those missing data under an exponential distribution with various seizure rates. Here the sponsor imputed data for the 114 subjects who prematurely withdrew from Study 106, regardless of treatment group. One thousand repeated runs were performed for each combination of assumed seizure rates. If the assumption could be clinically justified and seizure rates appropriately selected, the simulation results would provide some information to evaluate the significance of treatment effect. However, with missing data, the Division statisticians believed that the validity of this approach was "difficult to establish."
Even more complicated was the sensitivity analysis of *censoring bias function method* which assessed the impact of informative censoring on the original primary analysis. This is a method developed by Scharfstein and Robbins (2000) and was extended to Dr. Scharfstein to specifically

address this type of problem and to allow for separation of informative and administrative censoring. This method was an unproven, newly developed analysis assessed in a peer-reviewed article. Per the statisticians, regarding this method, "the sensitivity analysis was done by varying the values of two parameters α and τ. Because the data contain no independent evidence about parameters, final substantive conclusions would depend on which values of parameters are considered plausible by relevant subject matter experts."

Both these statistical methods assumed a great deal and did little to convince this reviewer that they should replace the data from the dropouts in the primary efficacy Study 106.

1.5 Efficacy Issues

The sponsor related that Study 104 failed to demonstrate the superiority of the higher dosage regimen with respect to the primary efficacy endpoint time to second seizure (time to exit). The sponsor related that the failure of Study 104 to detect the between group difference with respect to the time to second seizure was due to 2 reasons, the short duration of the study (median of 6 months vs. median of over 9 months in Study 106) and the heterogeneity of the study population in Study 104 compared to Study 106. In addition, Study 104 was poorly designed, with time to second seizure chosen as an inappropriate endpoint for the types of seizure patients enrolled. The duration of Study 104 was 6 months. The sponsor believes that this was not enough time to observe the second seizure in 39% of subjects in the low dose group who remained seizure free and 18% of subjects who experienced only 1 seizure before the study was terminated. The sponsor's support their argument further relating that the median time to first seizure was longer (317 days) in the high dose group compared with the low dose group (108 days). The sponsor believes that this is evidence to show that topiramate prolonged the time to first seizures since the "cumulative percent of subjects who had experienced their first seizure was lower in the high dose group than in the low dose group."

The patients chosen for Study 104 were to have at least one partial seizure during the three month retrospective phase, to average no more than 2 partial seizures a month and to have no more that three partial seizures in any given month. Even so, the enrollment was very heterogeneous with two main subgroups, one with frequent seizures and one with infrequent seizures. The sponsor did a post hoc analysis of the data from Study 104 and showed a separation in Kaplan Meyer curves at time to first seizure among those patients with more benign seizures. Differences between the 2 studies are summarized in Table 9.

Table 9: Subject Populations in Studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106: Key Baseline Characteristics

Characteristic	TOPMAT-EPMN-104	TOPMAT-EPMN-106
Type of seizures	Partial onset only	Partial-onset or generalized
Type of epilepsy	Newly diagnosed or recently diagnosed (≤3 years)	Newly diagnosed (≤3 months) or recurrent epilepsy off of AEDs
Prior AED therapy	Conversion from prior AED therapy (1 or 2 AEDs) allowed	Uncontrolled epilepsy while on AEDs excluded 1 AED allowed for emergency or temporary purposes only
Seizure counts during 3-month baseline (% subjects)	1 seizure: 34% 2 seizures: 21% 3 seizures: 15% 4-6 seizures: 23% ≥7 seizures: 6%	1 seizure: 63% 2 seizures: 37%

From Table 9, the population in Study 106 was more homogenous in terms of the baseline seizure counts and Study 104 enrolled more refractory seizure patients. If the sponsors associations are correct, it would be difficult to assess success with such a heterogeneous population. However, Study 104 is more representative of typical seizure population.
Time to first seizure was the primary endpoint in Study 106. The sponsors realized that, in clinical practice, the time to first seizure after starting a new medication represented a marker for failure of the current treatment and the need to reevaluate the treatment strategy in terms of adjusting the dose, changing the regimen to improve compliance, or considering an alternate AED. In contrast, the time to second seizure is not a realistic clinical endpoint as most practitioners would not keep a patient on a fixed dose of medication after the first seizure. This reviewer agrees that the standard of care in epilepsy treatment is to adjust a patient's medication to avoid further seizures unless the patient is noncompliant, there is no alternative regimen, or the seizures are mild, brief and well tolerated by the patient.

This reviewer agrees with the conclusions and discussion raised by the sponsor. Study 104 results indicated that for at least the first 6 months of use that patients with only mild seizure types will benefit. Study 106 confirms that this population of seizure patients would derive potential benefit. Study 106, unfortunately, had the problem with dropouts that have not been satisfactorily resolved. Even if the study was accepted regardless of the problem with dropouts, the sponsor's initially reported "robust" results from Study 106 are potentially magnified due to possible patient selection bias with patients selected with had fewer that 2 partial seizures within the 3 month baseline period and therefore more likely to respond favorably to the drug.

2 INTRODUCTION AND BACKGROUND

J&JPRD submitted to the Division a supplemental NDA for the use of topiramate for epilepsy monotherapy in October, 2002. That submission utilized a single efficacy study, TOPMAT-EPMN- 106 (Study 106). Study 106 was a multinational, randomized, double-blind, parallel group efficacy and safety study enrolling 470 adult and pediatric patients. The primary objective was to compare the safety and efficacy of 2 doses of topiramate. The doses chosen to demonstrate a dose-response relationship were hypothesized to be a low, minimally efficacious dose (50 mg/day) versus a high, presumably fully efficacious and generally tolerable higher dose (400 mg/day).

Efficacy was to be assessed based on the data from the intent-to-treat population, which comprised subjects who were randomized, entered the double-blind phase, and had at least 1 study visit after randomization. A survival analysis of the primary efficacy variable, time to first seizure (partial onset or generalized tonic-clonic) during the double-blind phase (excluding taper), was performed.

Initial efficacy results were robust as reported by the sponsor, with regards to the primary efficacy endpoint, as comparison of the Kaplan Meier survival curves of time to first seizure favored topiramate 400mg/day over topiramate 50mg/day (p=0.0002; 2-sided log-rank test). However, Division statisticians were concerned with the much higher rate of dropouts seen in the high dose group (32%) compared to the low dose group (17%). This was especially noted in the subgroup of patients who withdrew due to an adverse event. This is summarized in the following table reproduced from the original NDA

	TPM 50	TPM 400
Intent to treat (N)	234	236
Withdrawals	39 (17%)	75 (32%)
Adverse event	13(6%)	40 (17%)
Subject choice	9(4%)	13 (6%)
Lost to follow up	9(4%)	10 (4%)
Other	8(3%)	12(5%)
Completed DB phase	195 (83% of ITT)	161 (68% of ITT)
Experienced 1st Seizure (failures)	90 (38% of ITT, 46% of completers)	49 (21% of ITT, 30% of completers)
Completed at Termination	105(45% of ITT, 54% of completers	112 (47% of ITT, 70% of completers)

An all cause analysis, presuming that all withdrawals were treatment failure showed no significant difference between the two treatment groups (p=0.57, log rank test).

Study TOPMAT- EPMN- 104 (Study 104) was a supportive study that was similar in design to Study 106. Study 104 was a randomized, double-blind, parallel-group study conducted at multiple sites to evaluate topiramate dosages based on body weight of 25 or 50mg/day (low dose) and 200 or 500 mg/day (high dose) as monotherapy in subjects three years of age and older with recently diagnosed epilepsy characterized by partial onset seizure with or without secondarily generalized seizures. 252 patients were enrolled and received double blind topiramate treatment. The primary efficacy endpoint variable, time to exit (equivalent to time to second seizure) was assessed. The study failed to demonstrate a difference between dose groups for this endpoint (p=.781, log-rank test). However, the difference in time to first seizure between the two treatment groups did approach statistical significance (p=0.062, log-rank test), potentially supporting the results from Study 106, but raising questions as to the results for time to second seizure had that endpoint been assessed in Study 106.

An approvable letter was sent to the sponsor on November 26, 2003. The primary issue of concern prior to approving topiramate for monotherapy was statistical. The Division questioned the validity of the assumption of non-informative censoring, i. e., the assumption that the withdrawals from Study 106 and seizure occurrences were independent events. Specifically, the Division raised the possibility of a potential bias introduced into the primary efficacy analysis due to the differential withdrawal patterns in the 2 topiramate dose groups, with the higher dose group having significant more dropouts related to adverse events than the lower dose group.

Considering the similar study designs of Study 104 and 106, the Division questioned the failure of the primary analysis of Study 104, the time to second seizure, although the analysis of time to first seizure appeared to approach statistical significance. The Division also noted that the two studies had similar results for time to first seizure, and thus might have had similar results for time to second seizure had that outcome been observed in Study 106. The Division was also uncertain as to the clinical meaning of time to first seizure as a measure of effectiveness of topiramate as monotherapy.

2.1 From the approvable letter sent to the sponsor

The following is reproduced from the approvable letter sent to the sponsor relating to clinical issues raised.

Finally, we must take note of the results of the primary analysis of Study TOPMAT- EPMN- 104, the time to second seizure. As you know, this analysis revealed not only a non- significant between-treatment contrast, but the two Kaplan- Meier plots were nearly superimposable. We also note that the results of the analysis of time to first seizure (the primary outcome in Study TOPMAT- EPMN- 106) in that study was nearly nominally significant, and similar to that seen in Study TOPMAT- EPMN- 106. This, of course, raises the possibility that the time to second seizure in Study TOPMAT- EPMN- 106, had it been collected, would have been similar to that seen in Study TOPMAT- EPMN- 104. Were this situation to represent the true state of affairs, it would raise serious concerns about the clinical meaning of time to first seizure as a measure of effectiveness of topiramate as monotherapy, even if we could be convinced that the result of the

primary analysis of Study TOPMAT- EPMN- 106 was reliable. We are mindful that comparisons between studies can be misleading. Nonetheless, in this case the finding is of concern. We note that you had previously attempted to re- analyze Study TOPMAT-EPMN- 104 (presented in a submission to IND 28,549 dated 7/ 20/ 98), and that we did not find your proposal acceptable. More to the point, however, we do not believe that you have ever adequately addressed this finding, and its clinical meaning, especially in the face of a nearly nominally significant finding on the time to the first seizure. Before we could approve this application, therefore, you will need to provide an explanation for this finding, and provide a convincing argument that it should not preclude a conclusion that the drug is effective as monotherapy.

3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

3.1 Sources of Clinical Data

This reviewer read the submission from the sponsor entitled, Response to the FDA Regarding the Topiramate Monotherapy Approvable Letter, dated 25 May 2004. I also read the review by the statistician (Kun He) and discussed my findings with my team leader, John Feeney, MD.

4 REVIEW OF EFFICACY - SPONSOR'S RESPONSE RELATED TO EFFICACY ISSUES IN THE TOPIRAMATE MONOTHERAPY SUBMISSION.

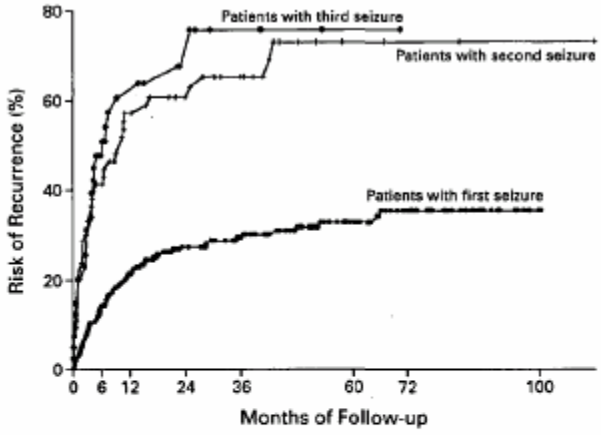
4.1 Statistical modeling

To address the issue of noninformative censoring relating to the high number of dropouts in Study 106, the sponsor performed several analyses by simulating events among censored patients. These two sensitivity analyses methods, the *multiple imputations method* and the *censoring bias function method*, generated results in favor of the high dose group. However, despite this, Division statisticians felt, "it is difficult to interpret these results with relevance to the regulatory decisions."

The *multiple imputations method* is one where the statistician simulates random events for those missing data under an exponential distribution with various seizure rates. Here the sponsor imputed data for the 114 subjects who prematurely withdrew from Study 106, regardless of treatment group. One thousand repeated runs were performed for each combination of assumed seizure rates. If the assumption could be clinically justified and seizure rates appropriately selected, the simulation results would provide some information to evaluate the significance of treatment effect. However, with missing data, the Division statisticians believed that the validity of this approach is "difficult to establish."

The seizure rate for the exponential distributions were chosen arbitrarily. However, the sponsor did discuss data from both the literature and their completed studies regarding epilepsy reoccurrences. Regarding the results from Studies 104, 105 and 106, the sponsor has incomplete information and had enrolled different populations of seizure patients into their trials. In addition, seizure rates in this population can range widely. The sponsor reports multiple articles relating the 1 year seizure reoccurrence rate in newly diagnosed patients. These rates range anywhere from 43-63%. The sponsor had previously submitted articles attending to this issue and this was discussed at length in the original NDA review.

Two representative articles from the literature provided by the sponsor during the initial NDA review reported that the probability of remaining seizure-free during treatment in a clinical practice setting 6 and 12 months after diagnosis of epilepsy is about 60% and 40%, respectively. Another study found that 73% of patients who experienced 2 or 3 unprovoked seizures would have further seizures within 4 years with or without treatment.[1] The following graph was reproduced from that article illustrating that the risk of reoccurrence of seizures increases with the number of background events with rates anywhere from 40-80% in the first 24 months after an initial seizure event.



PATIENTS AT RISK

With first seizure	204	176	153	117	100	60	42
With second seizure	63	36	24	19	13		
With third seizure	41	18	12	8	4		

Figure 1. Risk of a Second, Third, and Fourth Unprovoked Seizure after a First, Second, and Third Unprovoked Seizure.

P<0.001 for the comparison of the risk after one seizure with the risk after two seizures. P=0.47 for the comparison of the risk after two seizures with that after three seizures. The numbers below the figure show the numbers of patients remaining alive and free of seizures.

.

Even if we are to believe that this missing data can be imputed correctly, we have to assume a seizure rate of anywhere from 40-80% for those enrolled in Study 106. The multiple

1 Hauser WA et al. Risk of recurrent seizures after two unprovoked seizures. NEJM, 1998;338:429-434.

imputations table below provided by the statisticians relates that at seizure rates above 75%, the p values become insignificant.

Table 3: P values from 1,000 Simulated Runs
Using Combinations of Assumed Seizure Rates for Subjects who Withdrew from the Study
(Study TOPMAT-EPMN-106; Double-Blind Phase)

Seizure rate at Day 500	TPM 400						
TPM 50	30%	40%	50%	60%	70%	75%	80%
30%	.001**	.006**	.023**	.082*	.231		
40%	<.001***	.003**	.012**	.049**	.151	.238	
50%	<.001***	.001**	.006**	.025**	.094*	.165	.271
60%	<.001***	.001**	.003**	.013**	.051*	.092*	.168
70%	<.001***	<.001***	.001**	.006**	.026**	.054*	.100
75%		<.001***	.001**	.004**	.018**	.035**	.065*
80%			.	.002**	.013**	.025**	.052*

* $p < 0.1$
** $p < 0.05$
*** $p < 0.001$

Per the statisticians, "Assuming equal seizure rates in both treatment groups, as shown on the diagonal of the table, the high dose was statistically significantly superior (at the 0.05 level) for assumed seizure rates up to and including 79% ($p = 0.047$). In order for the difference between topiramate 400 mg/day and topiramate 50 mg/day to lose nominal statistical significance at the assumed seizure rates below 75%, the seizure rate in the high-dose group would have to exceed that in the low-dose group substantially - a clinically unlikely scenario." However, if you do go ahead and assume even small differences in seizure rates in each group above 60%, the P values rise, for example at a 70% seizure rate in the high dose group and 60% or 50% in the low dose group, the P values are above 0.05. This very simulation only works best when both baseline seizure rates are exactly the same, probably unlikely due to the range of seizure rates in the literature. Overall, to this reviewer, this statistical method assumes a lot. I cannot but agree with the statisticians when they say that the validity of this approach is difficult to establish.

Even more complicated is the alternative analysis provided. The sensitivity analysis of *censoring bias function method* assessed the impact of informative censoring on the original primary analysis. This is a method developed by Scharfstein and Robbins (2000) and was extended to Dr. Scharfstein to specifically address this type of problem and to allow for separation of informative and administrative censoring. This method was an unproven, newly developed analysis assessed in a peer-reviewed article. Per the statisticians, regarding this method, "the sensitivity analysis was done by varying the values of two parameters α and τ. Because the data contain no independent evidence about parameters, final substantive conclusions would depend on which values of parameters are considered plausible by relevant subject matter experts."

The sponsor provided multiple survival curves for Study 106 imputing a range of values for the two parameters. In addition, the sponsors formulated multiple survival curves for Study 105, another supportive study submitted with the NDA that also failed in terms of the primary outcome measure. In that study, patients who stopped Topamax for any reason were still

followed forward in time for the occurrence of seizures. Using the data from Study 105, values for α and τ were set as: $\alpha = -1.4$ and $\tau = 577$ days. The sponsor feels that since the baseline rates of seizures were higher in Study 105 than in Study 106 and that the types of seizure patients were much more refractory in Study 105, that these parameters would be conservative bounds for the sensitivity analysis parameters for Study 106. Imputing these values for α and τ to the two-sample model for Study 106, the sponsor found that the between group difference was statistically significant with a p-value of approximately 0.02. This result is difficult to interpret in view that one Study (105) is setting the boundaries for another (Study 106). It makes a great many assumptions about baseline seizure rates. Beyond that it does not relate to clinical parameters that are easily understood and to this reviewer, seems tailored to provide the very statistical significance needed from the data to provide assurances that Study 106 results are valid.

Because these two statistical methods make so many assumptions, it is difficult to reconcile the effect of the high rates of dropouts in Study 106. No amount of statistical modeling can replace real data that was not collected. Therefore, I agree with the statisticians that Study 106 is negative and the sponsors have not proven efficacy of topiramate as monotherapy.

4.2 Study 104 efficacy evaluation

The sponsor relates that Study 104 failed to demonstrate the superiority of the higher dosage regimen with respect to the primary efficacy endpoint. This endpoint, time-to-exit during the double blind phase was to be evaluated using survival analysis. The protocol specified endpoint included 2 partial onset seizures, with or without secondary generalization, 1 generalized tonic clonic seizure if none occurred during baseline or 1 episode of status epilepticus.

Of the 109 subjects who exited the double-blind phase, only 4 did so upon the occurrence of their first seizure (experienced either a generalized tonic clonic seizure or status epilepticus); the remaining subjects (N=105) experienced 2 partial-onset seizures. Thus, the primary endpoint of time-to-exit was essentially equivalent to time to second seizure. This endpoint allowed for the upward titration of topiramate, as it was expected that the first seizure might occur before the assigned topiramate dose was reached during titration.

The survival analysis did not show a significant difference between the dose groups (the Kaplan-Meier curves for both groups were essentially overlapping). However, this univariate analysis did not take into account the available data on time to first seizure. Subjects who were seizure free and subjects who had a single seizure were equated, i. e., censored for the analysis of time to second seizure, whereas in fact their risk of experiencing a second seizure was different. As seen in Table 8, more subjects in the higher dose group were seizure free, 54% vs. 39%, ($p = 0.022$). An analysis (the bivariate analysis mentioned above) incorporating both time to first seizure and time to second seizure favored the higher dose group, ($p = 0.01$). Therefore, the Study TOPMAT- EPMN- 104 data may suggest that topiramate is effective as monotherapy. However, the issues related to dropouts in both treatment groups have not been discussed regarding Study 104, which was a major flaw in Study 106. So conclusions regarding efficacy of topiramate relating to Study 104 and comparing them to those from Study 106 have to be done cautiously.

Table 8: Seizure Frequency Distribution in Study TOPMAT-EPMN-104 (Double-Blind Phase; Intent-to-Treat Population)

Number of Seizures	Low-dose TPM (25 or 50 mg/day) (N=125)	High-dose TPM [a] (200 or 500 mg/day) (N=127)
0	49 (39%)	68 (54%)[b]
1	22 (18%)	8 (6%)
2	54 (43%)	51 (40%)

[a] Treatment difference in seizure frequency distribution, p=0.008; chi-square test.
[b] Treatment difference in the number of seizure-free subjects, p=0.022; chi-square test.

The sponsor relates that the failure of Study 104 to detect the between group difference with respect to the time to second seizure was due to 2 reasons, the short duration of the study (median of 6 months vs. median of over 9 months in Study 106) and the heterogeneity of the study population in Study 104 compared to Study 106. This reviewer would add a third reason that Study 104 was poorly designed with time to second seizure an inappropriate endpoint for the types of seizure patients enrolled.

4.2.1 Duration of the Study

The duration of Study 104 was 6 months. The sponsor believes that this was not enough time to observe the second seizure in 39% of subjects in the low dose group who remained seizure free and 18% of subjects who experienced only 1 seizure before the study was terminated.

The sponsor's support their argument further relating that the median time to first seizure was longer (317 days) in the high dose group compared with the low dose group (108 days). The sponsor believes that this is evidence to show that topiramate prolonged the time to first seizures since the "cumulative percent of subjects who had experienced their first seizure was lower in the high dose group than in the low dose group."

The sponsor makes further assumptions as follows.

The time to second seizure could be influenced by a drug effect that resulted either in seizure remission or in prolongation of time to first seizure. The assumption that seizures are evenly distributed in time is not borne out by clinical evidence; in fact, seizures tend to "cluster", making it very difficult to "resolve" a treatment effect over a relatively short time period. A shorter interval to the next seizure event would therefore be expected in a patient who experienced frequent seizures at baseline, thus leading to a potentially shorter time to the second seizure.[6] On the other hand, in patients with fewer baseline seizures, there is a relatively high probability of remission, and the delay in time to the first seizure would lead to a delay in time to the next seizure, thus requiring more time to observe the second event. In a patient population with frequent seizures at baseline, a measurable decrease in seizure frequency would have been an appropriate endpoint, similar to that used in the original add-on studies. The demonstration of an effect on seizure frequency would be expected to require the observation of more than two seizures.

This would assume that the same phenomenon would be happening in both the high and low dose groups. It also surmises that a large percentage of patients with frequent seizures have clusters, which may not be so. The sponsors should have designed the study to capture frequent (or infrequent) seizures and should have known that they required more time for this type of analysis. Otherwise, they should have looked at reduction in seizure frequency considering that they enrolled a large number of refractory seizure patients (further discussed below). To this clinician, six months of seizure free treatment is a reasonable clinical outcome. Even if there was not enough time for many patients to have their second seizure, in exhibiting efficacy of topiramate, regardless of seizure type, there should have been a sizable difference between the high and low dose groups.

4.2.2 Heterogeneity of the enrolled seizure population

The patients chosen for Study 104 were to have at least one partial seizure during the three month retrospective phase, to average no more than 2 partial seizures a month, and to have no more that three partial seizures in any given month. Even so, the enrollment was very heterogeneous with two main subgroups, one with frequent seizures and one with infrequent seizures. Per the sponsor, dose cohorts were not evenly matched. "A higher percentage of subjects assigned to the high-dose topiramate group (52%), compared to those assigned to the low-dose group (38%), reported more than 2 seizures during the baseline phase. In retrospect, it became clear that the responses of these 2 subpopulations to treatment were qualitatively different, and that this imbalance affected the outcome of the analysis of time to second seizure."

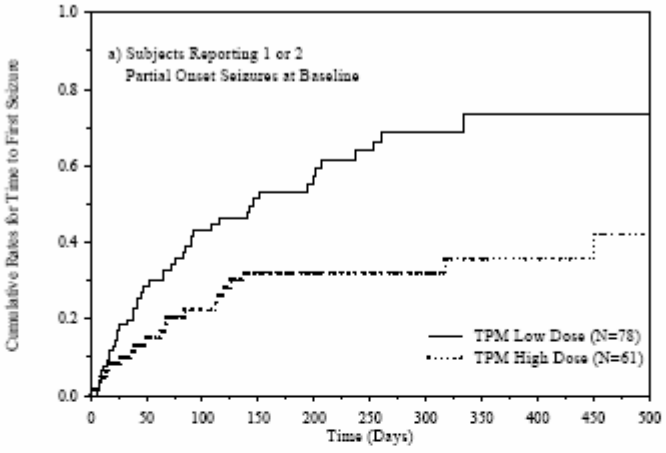
The sponsor did a post hoc analysis of the data from Study 104 and showed a separation in Kaplan Meyer curves at time to first seizure among those patients with more benign seizures.

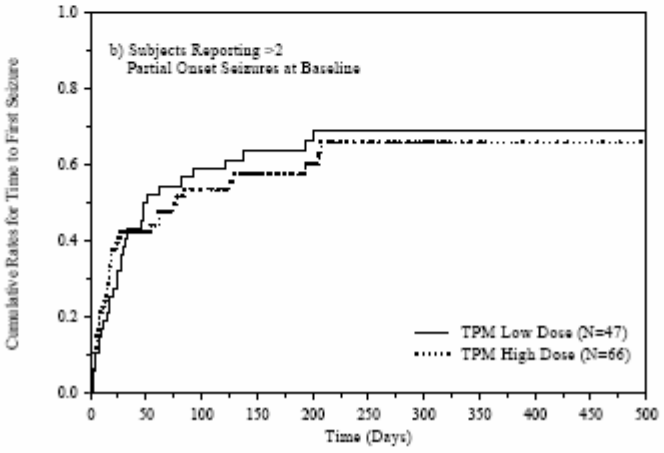
Time to first seizure

A post hoc analysis demonstrated a clear and statistically significant effect of topiramate in subjects with more benign epilepsy (see Figure 12). The treatment difference favoring the higher topiramate dosage group was statistically significant for the subset of subjects who reported only 1 or 2 seizures (p=0.001; log-rank test), but not for those reporting more than 2 seizures during baseline (p=0.871; log-rank test). Regarding the Agency's concern, it is noted that even for the subgroup with fewer baseline seizures, the results for time to second seizure are weaker (p = 0.052 based on log-rank test; hazard ratio = 1.8; 95% CI: 0.98, 3.32) than those for time to first seizure. This is most likely due to the reduced number of events and resulting lower statistical power.

APPEARS THIS WAY IN ORIGINAL

Figure 12: Cumulative Rates for the Time to First Seizure During the Double-Blind Phase (Study TOPMAT-EPMN-104)





We were well aware that the results for time to first seizure in Study 104 were positive for the total randomized group. A Kaplan Meier curve of the total population from 104 was included in the original submission. The sponsors now surmise that the difference in treatment responses between the 2 subpopulations may have obscured the results of the overall population. This is confusing as the results for time to first seizure were positive before the subgroups were split out and reanalyzed.

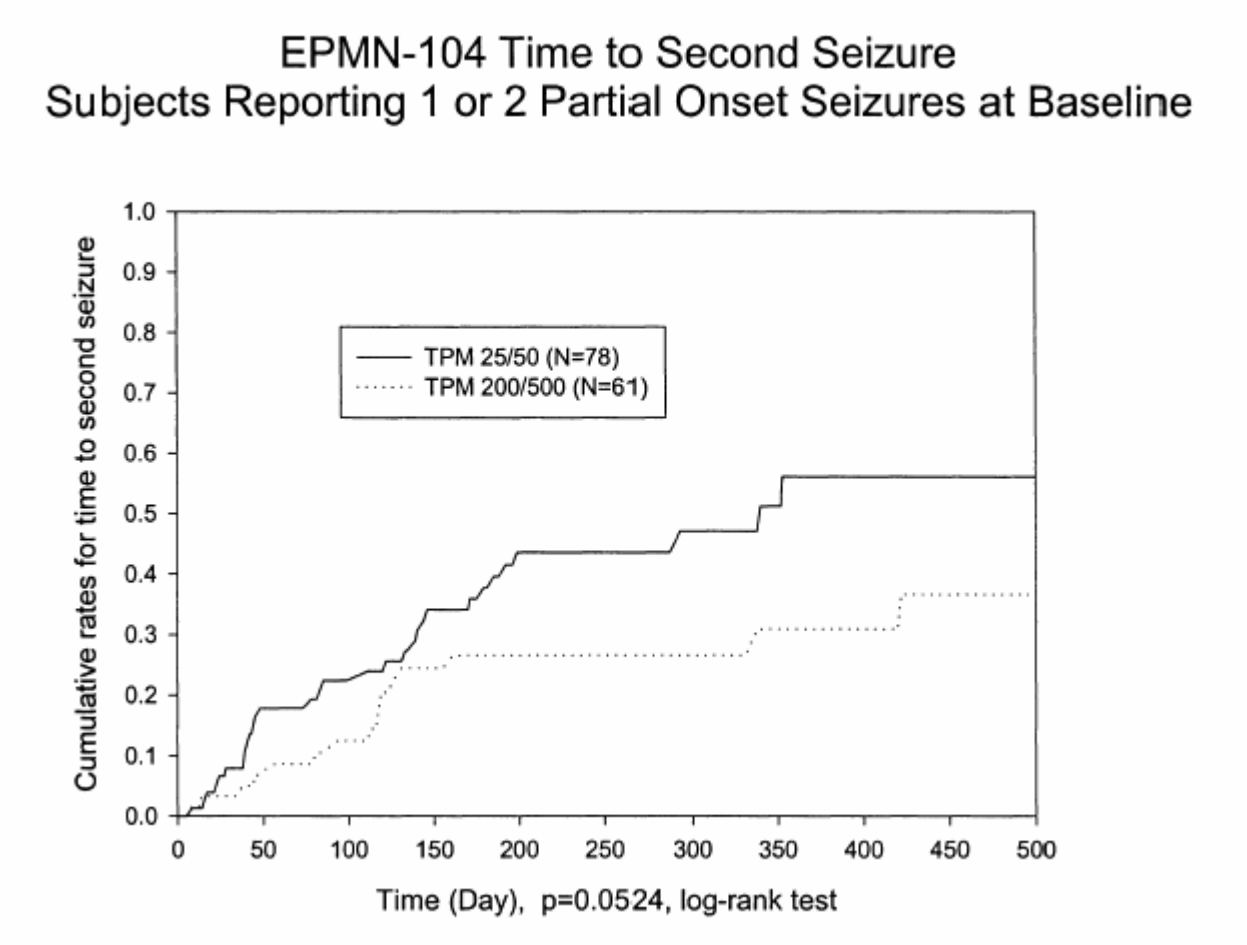
4.2.3 Time to second seizure

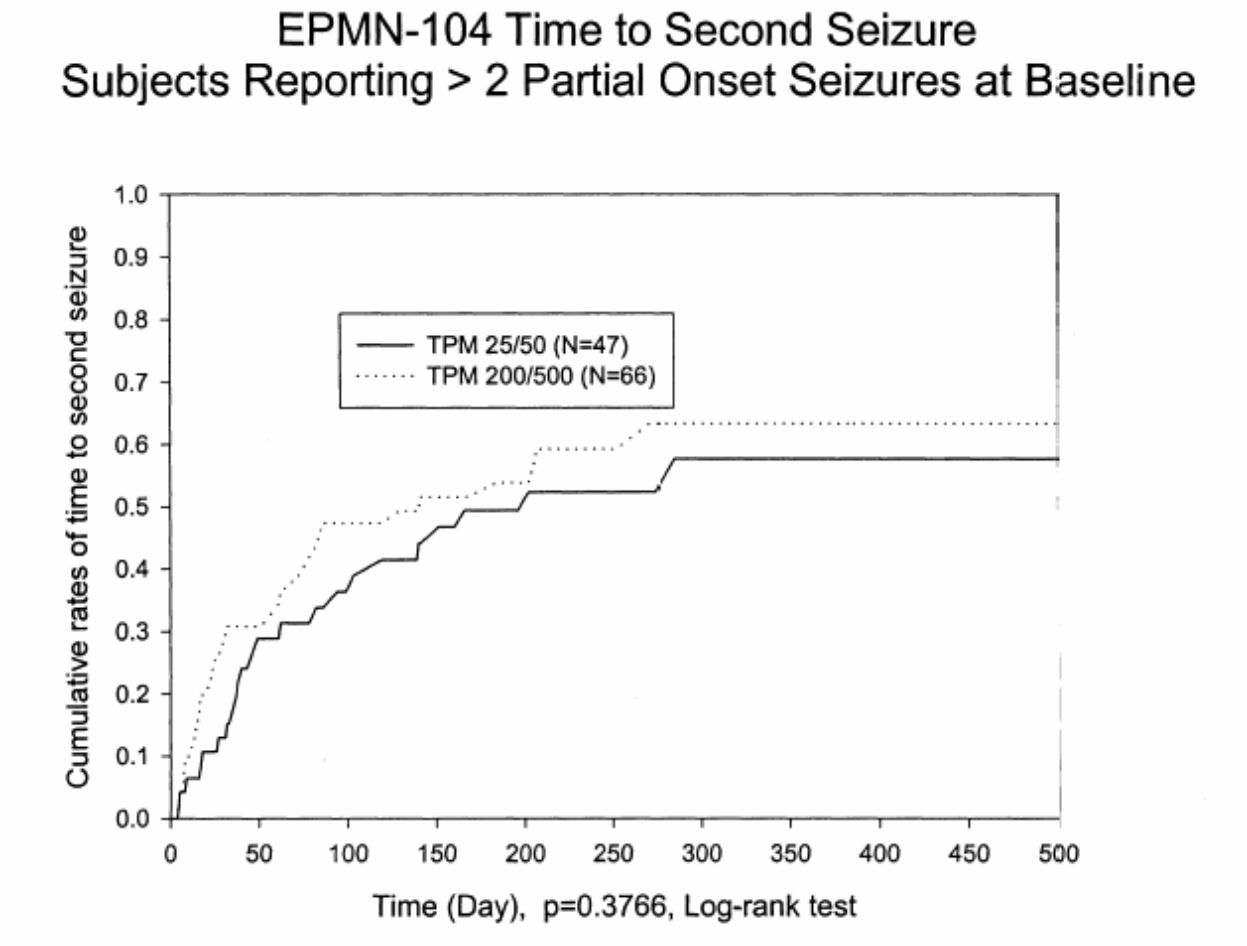
In terms of the analysis of time to second seizure, the sponsor offers the following.

> "An analysis of time to second seizure in Study TOPMAT-EPMN-104 for the subpopulation of subjects with 1 or 2 seizures at baseline approaches statistical significance (p=0.052, log-rank test). This is a dramatic shift from the lack of separation reported for the entire intent-to-treat population (p=0.7813). Considering that the sample size for the analysis of this subpopulation is fairly small (47 subjects in low dose group

and 66 subjects in the high dose group), it is reasonable to assume that a time to second seizure analysis, had it been performed on TOPMAT-EPMN-106 population, would have yielded statistically significant results."

We requested the Kaplan Meier curves related to time to second seizure from the sponsor to see how the subgroups affected the primary outcome measure. They were provided and reproduced below. It is very interesting to note that the curve for the subpopulation with fewer baseline seizures does separate well and reaches statistical significance. Even more interesting is the second graph showing slightly better results in the low dose group for the subpopulation of patients with more than 2 seizures at baseline.





The sponsor needs to be cautious when making comparisons between the types of epilepsy patients in Study 104 with Study 106 and that only looking at the result of a small group of patients in a subpopulation may not be powered correctly to detect any statistically meaningful results. These analyses do not account for any significant dropouts in Study 104 in each subgroup and how they would affect the overall statistics (much as they affected the results in Study 106).

4.2.4 Comparison of patient populations in Studies 104 and 106

Due to the mixed results of Study 104, the protocol for Study 106 was redesigned. (However, the potential for dropouts was not attended to despite FDA statistician comments prior to the initiation of studies – see discussion of this in the initial NDA review.) Differences between the 2 studies are summarized in Table 9.

Table 9: Subject Populations in Studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106: Key Baseline Characteristics

Characteristic	TOPMAT-EPMN-104	TOPMAT-EPMN-106
Type of seizures	Partial onset only	Partial-onset or generalized
Type of epilepsy	Newly diagnosed or recently diagnosed (≤3 years)	Newly diagnosed (≤3 months) or recurrent epilepsy off of AEDs
Prior AED therapy	Conversion from prior AED therapy (1 or 2 AEDs) allowed	Uncontrolled epilepsy while on AEDs excluded 1 AED allowed for emergency or temporary purposes only
Seizure counts during 3-month baseline (% subjects)	1 seizure: 34% 2 seizures: 21% 3 seizures: 15% 4-6 seizures: 23% ≥7 seizures: 6%	1 seizure: 63% 2 seizures: 37%

The population in Study 106 was more homogenous in terms of the baseline seizure counts. Study 104 enrolled more refractory seizure patients. If the sponsors associations are correct, it would be difficult to assess success with such a heterogeneous population. However, Study 104 is more representative of typical seizure population. To this reviewer, Study 104 results indicate that for at least the first 6 months of use that patients with only mild seizure types will benefit. Study 106 confirms this. Therefore the sponsor's initially reported "robust" results from Study 106 may be magnified due to selection bias (patients selected for partial seizures with few events and therefore more likely to respond favorably to the drug.)

4.2.5 Time to first seizure as an appropriate endpoint

Time to first seizure was the primary endpoint in Study 106. The sponsors realized that, in clinical practice, the time to first seizure after starting a new medication represents a marker for failure of the current treatment. Time to first seizure after initiation of an antiepileptic drug (AED) necessitates the need to reevaluate the treatment strategy in terms of adjusting the dose, changing the regimen to improve compliance, or considering an alternate AED. In contrast, the time to second seizure is not a realistic clinical endpoint as most practitioners would not keep a patient on a fixed dose of medication after the first seizure. This reviewer agrees that the standard of care in epilepsy treatment is to adjust a patient's medication to avoid further seizures unless the patient is noncompliant, there is no alternative regimen, or the seizures are mild, brief and well tolerated by the patient.

As already noted above, the results of the post hoc analysis of the data from Study 104 regarding time to first seizure in the subgroup of patients with more benign seizure types approximates the primary endpoint results from Study 106. At least for benign seizure types, that endpoint of time to first seizure appears reproducible across both studies. It is difficult, however, to know if the time to second seizure analysis had it been performed in Study 106, would have led to similar results to those in the subgroup of more benign seizures in Study 104.

5 OVERALL ASSESSMENT

5.1 Conclusions

The sponsors failed to provide meaningful statistical evidence to refute the problem of noninformative censoring seen in Study 106. These two sensitivity analyses methods, the *multiple imputations method* and the *censoring bias function method*, generated results in favor of the high dose group. However, both methods assume a great deal and appear to be designed to be adjustable, that is, if you pick a certain baseline seizure rate, it will give statistical support to the sponsors claim of monotherapy. However, the statisticians are not convinced that these methods are proper and I cannot refute their findings. Therefore, I still believe that the claim for monotherapy should be denied.

Regarding the issues remaining related to Study 104, this study was overall poorly designed. For some patients, the duration of the trial was too short, in that it did not give them enough time to have a second event. This may have been true for the more mild seizure patients who would have responded well to the initial dose of medication. Some patients with more frequent seizures at baseline with a history of clustered seizures may also not have had enough time to have a second event. However six months seizure free is a relatively good duration from a clinical perspective regardless of "clustering". The population was very heterogeneous making it difficult to assess the overall efficacy results. The sponsor's subgroup analyses indicate a potential statistically significant result in a subgroup of patients with fewer baseline seizures, but it is difficult to know whether or not the results are properly powered to be meaningful. The clinical endpoint of time to second seizure caused problems in the overall study design for Study 104 and has less clinical meaning than time to first seizure. These multiple shortcomings make it difficult to make too many direct comparisons between Studies 104 and 106.

If we negate out for a moment the general issue with patient dropouts and informative censoring and take the data at face value, Study 106 implies efficacy for the enrolled population (with less that 2 seizures during baseline). This efficacy is supported by the small subgroup analysis in Study 104. Even if we can accept these results, at face value, this reviewer is left with concerns that topiramate has only exhibited efficacy for mild seizures or for newly diagnosed seizure patients with little baseline history. Even more worrisome is that Study 104 had negative results for the subgroup of patients with greater than 2 seizures at baseline for both time to first seizure and time to second seizure. Therefore, if topiramate is used in a general population of seizure patients, including more refractory patients, many of those patients will fail monotherapy, even at moderate to high doses.

5.2 Recommendation on Regulatory Action

The supplemental NDA application for the use of topiramate as monotherapy in epilepsy, despite the statistical modeling approaches, continues to be non-approvable.

- The sponsors failed to show statistically significant evidence of efficacy in time to first seizure in their pivotal trial TOPMAT-EPMN-106 between the low and high dose groups. This was due to the almost threefold incidence of dropouts due to adverse events seen in the high dose group leading to fewer seizure events in this group. The two statistical models used to replace the clinical information from the dropouts in both dose groups do not convince the statisticians or this clinician that topiramate would be efficacious as monotherapy.

- The sponsors failed to show a statistically significant evidence of efficacy in time to first seizure between the low and high dose groups in supportive study TOPMAT-EPMN-104 (p=0.062, log rank test). However, the sponsor discussed possible reasons for this disparity including length of the study and heterogeneity of the population. The study did indicate a statistically significant result in a subpopulation of epilepsy patients with milder seizures. However that subgroup analysis may not be properly powered to give meaningful results.

This reviewer remains concerned that if topiramate was approved for monotherapy, that it would only benefit mild patients or those with newly diagnosed epilepsy. In addition, there is a separate safety issue of tolerability of a dose of 400mg which explains much of the reason for the higher number of dropouts seen in the high dose group. Taken together, the issue of narrow efficacy and high rate of adverse events at the goal dose limits the use of this drug as monotherapy. Consequently, this reviewer would not approve topiramate for monotherapy.

5.3 Recommendation on Postmarketing Actions

This reviewer continues to have safety concerns regarding the high dose of 400mg, but these are discussed fully in the original NDA review dated November 25, 2003.

The sponsor has agreed to perform a juvenile animal toxicity study as a Phase 4 commitment. The protocol for this study has already been submitted to DNDP and is currently under review by pharm/tox review staff.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Howard Chazin
1/24/05 02:40:19 PM
MEDICAL OFFICER

John Feeney
2/2/05 11:08:04 AM
MEDICAL OFFICER
See my cover memo

MEMORANDUM

NDA 20-505/S-018 Topamax Tablets
NDA 20-844/S-015 Topamax Sprinkle Capsules

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Efficacy of Topamax as Monotherapy

DATE: November 12, 2003

Background

Topamax is already approved as *adjunctive therapy* of partial seizures and primary generalized tonic-clonic seizures in adult and pediatric patients 2 years of age and older. It is also approved as adjunctive therapy for the seizures associated with Lennox-Gastaut syndrome. The sponsor is now seeking to expand this claim to include *monotherapy* of partial seizures and primary generalized tonic-clonic seizures in adult and pediatric patients 6 years of age and older. In support of this indication, the sponsor wishes to rely primarily on Study 106. Three additional studies were submitted in the application in support of the new indication: Study Y1, Study 104, and Study 105. The clinical review was performed by Dr. Howard Chazin and the statistical review was performed by Dr. Kun He. Dr. Chazin reviewed all 4 studies. Dr. He reviewed Study 106.

Prior to the conduct of Study 106, the sponsor interacted with DNDP to discuss the indication and the trial design. An important issue raised during those interactions was the impact that dropouts due to adverse events would have on an analysis of time to first seizure. The sponsor believed there would be such a low number of dropouts that the issue would not be problematic.

Unfortunately, the impact of dropouts on the interpretation of Study 106 has become pivotal to this application. On June 18, 2003 representatives of DNDP contacted the sponsor and emphasized how problematic the issue had become during the review process. The sponsor addressed the problem by performing numerous sensitivity analyses. Their response is dated July 31, 2003 and is incorporated into the reviews of Dr. Chazin and Dr. Kun He.

Study Y1

This was a randomized, double-blind study comparing the efficacy of Topamax monotherapy at a dose of 1000mg/day with Topamax monotherapy 100mg/day in adult patients with refractory partial seizures. These patients with refractory seizures had Topamax added to their background AEDs (no more than two) and then had the background AEDs withdrawn. Therefore the study design provides support primarily for a claim for conversion to monotherapy.

A total of 48 patients were randomized equally to the high dose and the low dose groups. The post-randomization treatment period was 3 months long (up to 11 weeks as monotherapy).

The protocol-specified primary outcome was time-to-exit, with the exit criteria defined as: doubling of the average monthly seizure frequency, doubling of the highest two-day seizure frequency, a single generalized seizure if none previously, or status epilepticus. By this analysis, a statistically significant result favoring the high dose group was found, p=0.002.

According to Dr. Chazin's review, aside from the patients who met the protocol-specified exit criterion, there were only 2 patients who dropped out of the study for other reasons, both in the high dose group. If these patients are counted as failures, 11/24 (46%) of patients failed in the high dose group, while 20/24 (83%) of patients failed in the low dose group, a difference that was nominally statistically significant, p=0.015 (Fisher's exact test).

Dr. Chazin's review does not provide a listing of the actual doses of Topamax achieved in the high dose group. Therefore, while this study provides evidence in support of the efficacy of Topamax monotherapy, it is not clear which dose of Topamax as monotherapy is supported.

It seems noteworthy that only 2/24 patients assigned to the 1000mg/day dose group dropped out for reasons other than efficacy, while in Study 104 (next section below) 34/125 dropped out of the 500mg/day group.

Conclusions: The study results suggest that the high dose was better than the low dose, but it is concerning that almost half the patients in the high dose group left the study because their seizure frequency doubled, compared to a baseline period with other AEDs. To view the post-randomization results from a trial of this design in isolation (without reference to baseline) seems counter to clinical intuition. At the same time, further information is needed about the doses achieved in the high dose group.

Study 104

This was a randomized, double-blind study comparing the efficacy of Topamax monotherapy at a dose of 500/200mg/day (based on weight greater than or less than 50 kgs) with Topamax monotherapy 50/25mg/day (again based on weight greater than or less than 50 kgs) in adult and pediatric (3 years and older) patients with “recently” diagnosed partial seizures. No more than one background AED was allowed prior to randomization; this would have to be tapered off by day 36 of the double-blind treatment period.

A total of 252 patients were randomized equally to the high dose and the low dose groups. The post-randomization treatment period lasted until the last patient completed 4 months.

The protocol-specified primary outcome was time-to-exit, with the exit criterion defined as the occurrence of a second seizure (or a generalized seizure, if not previously experienced, or status epilepticus). By this analysis, a statistically significant result favoring the high dose group was not found, p=0.78. In fact, the survival curves for this outcome are superimposable (see bottom of next page). Almost the same numbers of patients met this exit criterion in the two treatment arms, 52 in the high dose group and 57 in the low dose group.

A secondary outcome in the trial was time-to-first seizure. This analysis favored high dose Topamax over low dose Topamax, with a nominal p-value of 0.062. Median time to first seizure was 317 days in the high dose group and 108 days in the low dose group (see top of next page). A total of 76 patients in the low-dose group had a first seizure versus 59 patients in the high-dose group.

Aside from the patients who met the protocol-specified exit criterion, there were many patients who dropped out of the study for other reasons, including adverse events, 34 in the high dose group and 26 in the low dose group. Overall, 41/127 (32%) of patients completed the study in the high dose group, while 42/125 (34%) of patients completed in the low dose group. Dr. Kun He has performed a worst-case sensitivity analysis of Study 104, attributing a first seizure to each patient at the time of exit for non-seizure-related reasons (including adverse events). The p-value for that analysis is non-significant, p=0.3.

Figure 4: Plot of Cumulative Rates for Time to First Seizure (Kaplan-Meier Estimates)
(Intent-to-Treat Population; Protocol TOPMAT-EPMN-104)

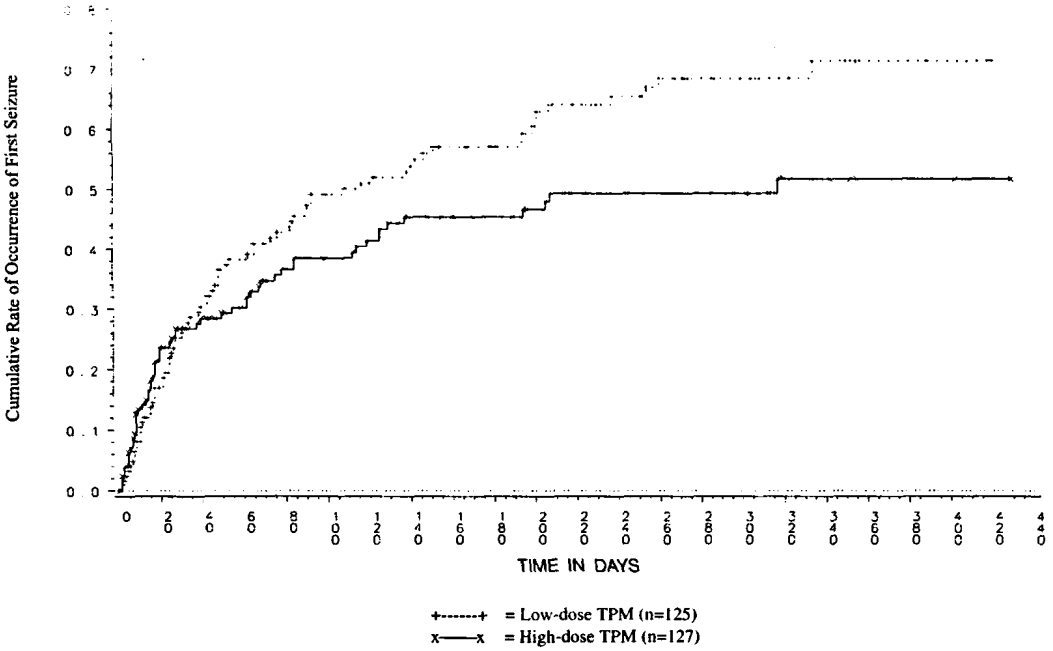
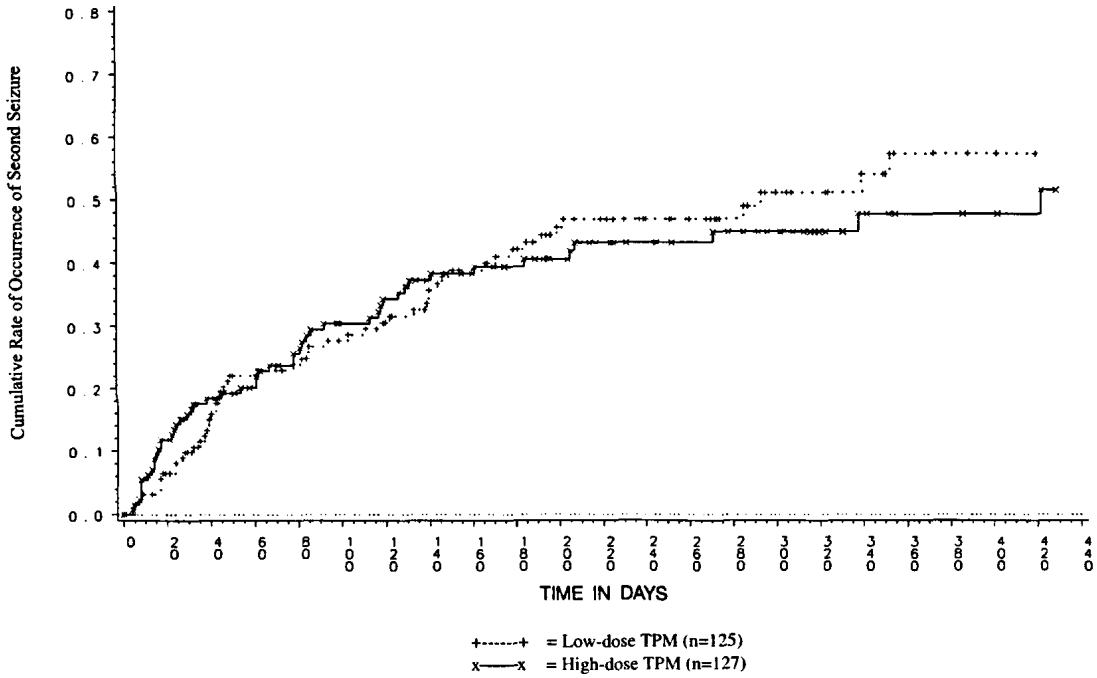


Figure 5: Plot of Cumulative Rates for Time to Second Seizure (Kaplan-Meier Estimates)
(Intent-to-Treat Population; Protocol TOPMAT-EPMN-104)



Dr. Chazin has requested information about the doses of Topamax actually achieved in the high dose group and the low dose group in this study. This information is important in interpreting the results.

Overall, Study 104 failed to show a convincing difference between the high and low dose groups. The fact that the difference in time-to-first seizure was almost nominally significant might be clinically important, but the time-to-second seizure was the primary outcome and was identical for the two treatment groups. The actual doses achieved for the two treatment arms (and the difference in these doses between the treatment groups) are needed to interpret the results more fully.

Conclusions: If the primary outcome of Study 104 had been time-to-first seizure, a significant result in favor of the high dose group was almost achieved. However, given the large number of dropouts for reasons other than efficacy (34 high dose and 26 low dose), further analyses would be required to assess the sensitivity of this overall result to these dropouts.

Study 105

This study will not be discussed in detail because it was an active control trial designed loosely to show equivalence of Topamax 100mg/day, Topamax 200mg/day, and standard therapy (carbamazepine 600mg/day or valproate 1250mg/day). This study design is generally not viewed as providing a rigorous test of effectiveness for regulatory purposes.

Overall, 621 adult and pediatric patients (at least 6 years of age and 30kg) with newly diagnosed epilepsy were enrolled. Patients could be on one baseline AED (for no more than 6 weeks) prior to entry. For these patients, the concomitant AED was tapered off after Topamax initiation. There were no limits placed on the seizure type for enrolled patients.

Patients were followed for up to six months. Exit criteria included perceived lack of efficacy on either the patient's or physician's part, adverse events, need to change dose, or need to add other AEDs.

Study 106

Study 106 was similar to Study 104. It was a randomized, double-blind study comparing the efficacy of Topamax monotherapy at a target dose of 400mg/day with Topamax monotherapy 50mg/day in adult and pediatric (6 years and older) patients with newly diagnosed (within 3 months) or recurrent (while off AEDs) seizures. Patients were required to weigh 25 kg or more. Seizure types allowed included partial seizures and primary generalized seizures. The primary generalized seizures could include tonic-clonic, clonic, or the seizures of juvenile myoclonic epilepsy. Criteria for distinguishing secondary generalized seizures from primary generalized seizures were not described in the protocol.

Eligible subjects were required to have 1 or 2 seizures during a 3-month retrospective baseline period. No more than one background AED was allowed prior to randomization; this would have to be tapered off during the 7-day open-label treatment period during which time all patients were started on Topamax 25mg/day.

It was originally estimated that 330 patients would need to be randomized in order to observe 108 first seizures. There was however a surprisingly low percentage of patients who experienced a first seizure. [Contrast the percentage of patients with a first seizure in this study with Study 104 above.] Because of this, enrollment had to proceed until 487 patients were randomized in order to capture at least 108 first seizures.

The post-randomization treatment period was to last until the last patient was enrolled for 2 months. Protocol amendments 3 and 5 increased this latter period first from 2 months to 4 months and, then, from 4 months to 6 months. At the time of amendment 5, enrollment was already complete (with 487 patients).

After randomization, dose titration for the high dose group occurred at weekly intervals: 50, 100, 150, 200, 300, 400mg/day. Patients were titrated to a maximum tolerated dose no greater than 400mg/day. Patients had to at least initially tolerate titration through 150mg/day (third week of titration) or be dropped from the study. After the third week, the dose for any patient could be reduced by two 50mg/day decrements, but no more. [Note that the titration regimen is somewhat faster than currently approved for adjunctive therapy, in which no more than 50mg/day increases per week are recommended.]

The protocol-specified primary outcome was time-to-exit, with the exit criterion defined as the occurrence of a first seizure. By this analysis, a statistically significant result favoring the high dose group was found, p=0.0002. The numbers of patients who met this exit criterion in the two treatment arms were 49/236 in the high dose group and 90/234 in the low dose group.

Aside from the patients who met the protocol-specified exit criterion, there were many patients who dropped out of the study for other reasons, including adverse events, 75 in the high dose group and 39 in the low dose group. Overall, 112/236 (47%) of patients completed the study in the high dose group, while 105/234 (45%) of patients completed in the low dose group. Dr. Kun He has performed a worst-case sensitivity analysis of Study 104, attributing a first seizure to each patient at the time of exit for non-seizure-related reasons (including adverse events). The p-value for that analysis is non-significant, p=0.57.

Dr. Chazin has requested information about the doses of Topamax actually achieved in the high dose group and the low dose group in this study. This information is important in interpreting the results.

Sensitivity Analyses

At the request of the division, the sponsor addressed the effect of dropouts on the overall analysis of results in Study 106. Both Dr. Chazin and Dr. He reviewed these analyses and were still left with uncertainty about the strength of evidence in Study 106.

I. Replacement using study data: The sponsor argues that there are no obvious differences in the population of patients in the Study 106 high-dose group who had adverse events and withdrew and those who had adverse events and remained in the study. Even the nature and severity of the adverse events appear similar across these two groups. Therefore, the sponsor argues that the seizure frequency of the patients who stayed in with adverse events can be used to model the seizure frequency of those who withdrew. The sponsor does this two ways: imputing the data from the low-dose non-dropouts for the high-dose dropouts and imputing the data from the high-dose non-dropouts for the high-dose dropouts. Either way, the sponsor consistently achieves a nominally statistically significant result in favor of the high dose group.

II. Replacement using simulated data: The sponsor provides a family of nominal p-values for the between group comparison when increasing seizure frequencies are assumed and used to impute data for dropouts. Imputed scores, derived by the above technique, are applied to the study in 3 ways. One, the scores are imputed for all withdrawals in both treatment arms. Two, the scores are imputed only for withdrawals due to adverse events in both treatment arms. And, three, the scores are imputed differentially, that is only for the withdrawals due to adverse events in the high-dose group (not in the low-dose group).

Imputing scores for all withdrawals in both treatment arms, for assumed seizure rates $\geq$ 60% at 500 days, the derived p-values are $\geq$ 0.10. The sponsor would argue that 60% is an overestimate *for this population*.

Imputing scores for patients who withdrew only for adverse events in both treatment arms, nominally significant p-values are achieved for assumed seizure rates $\leq$ 90%.

Pertinent to the above discussion, the Kaplan-Meier estimate of cumulative rate for time to first seizure in the Study 106 low-dose group was 45% at 500 days. In Study 104, the Kaplan-Meier estimate of cumulative rate for time to first seizure in the low-dose group was 71% at 500 days. Therefore, using the observed seizure rates from the low-dose group in Study 104 suggests possible p-values of 0.09 to 0.005 to 0.02 using the sponsor's three imputation methods described above.

Monotherapy Safety Data

Dr. Chazin has reviewed the safety data for Topamax used as monotherapy. In general, the adverse event profile does not appear to differ from the adjunctive experience. One particular area of interest was the occurrence of metabolic acidosis with Topamax. Bicarbonate data from Study 106 was reviewed by Dr. Chazin and Dr. Boehm (DNDP Safety Group).

In Study 106, patients (both adult and pediatric) were randomized to 50mg/day vs 400mg/day. For the 50mg/day group, 26% (57/219) had an on-study value <20 at any time; for the 400mg/day group, 36.5% (80/219) had such a value. Using a cutoff of <17, 5% of the low-dose group and 15% of the high-dose group had at least one such value during treatment.

Of note, the above data appears to have not been blinded during the conduct of Study 106. Dr. Chazin has asked the sponsor to confirm this. If not blinded, the differential occurrence of low serum bicarbonate between the two treatment groups may have potentially compromised the overall study blind.

Conclusions

Evidence to reasonably conclude that Topamax is effective as monotherapy has not been presented in this application. While a secondary analysis in Study 104 suggests that time-to-first-seizure is postponed by Topamax, the primary analysis, time-to-second-seizure, is arguably more clinically relevant and demonstrates no benefit from Topamax. Further, an excess of dropouts in the high-dose group of Study 104 offsets the excess in first seizures in the low-dose group.

In Study 106, the primary outcome was time-to-first-seizure and a difference in favor of high-dose Topamax was shown. Again, however, the excess of dropouts in the high-dose group offsets the excess in first seizures in the low-dose group. I find the results in the high-dose group of Study 106 particularly difficult to

interpret because the ratio of dropouts to first seizures is 1.5:1. Compare the ratio of dropouts to first seizures for each of the treatment arms in Studies 104 and 106 in the table below.

	Study 104 Low-dose	Study 104 High-dose	Study 106 Low-dose	Study 106 High-dose
Randomized	125	127	234	236
Dropouts	26 (21%)	34 (27%)	39 (17%)	75 (32%)
First seizures	76 (61%)	59 (46%)	90 (38%)	49 (21%)
Ratio Dropouts/Seizures	0.34	0.58	0.43	1.5

There really are 2 different issues related to the high dropout rates:

First, there is the possibility that the patients who dropped out would have behaved differently than those who did not drop out because of informative censoring. That is, the specific reason for dropping out might be directly predictive of an imminent seizure. It seems very unlikely to me that the occurrence of an adverse event would somehow predict an imminent risk of a seizure. It does become more possible, however, that at least a few patients would experience informative censoring as the total number of dropouts rose. This should not greatly affect the results of the study.

Second, there is the very real possibility that the group of dropouts as a whole would have had a much different risk of seizures than the population of patients left in the trial, by chance alone. It is this possibility that concerns me the most.

The sponsor has performed a number of sensitivity analyses in Study 106 to adjust for the possibility that the dropouts might have behaved differently. I believe the most reasonable of these imputes data for all patients who withdrew in both treatment groups, assuming a range of background seizure frequencies. Using a 500-day seizure risk of 50% or greater for the dropout population results in nominal p-values which are non-significant. The 50% seizure risk seems very possible to me, given that the background seizure risk from Study 104 was 71% by day 500.

While the sponsor would argue that the seizure risk for the enrolled population in Study 106 was much less than 70%, note that the study was originally designed expecting a higher-than-observed seizure rate. The originally stated sample size was 330 to capture 108 events. Ultimately, almost 500 patients were randomized to capture 108 events. One could argue that the observed seizure rate in the trial was lower than originally expected because the patients with the highest seizure risk were withdrawing early, before their seizures were observed. [Note that this need not necessarily be informative censoring; it may only be a chance occurrence.]

While the statistical review does not discuss the above 2 issues in any detail, I have discussed them at length with the reviewing statisticians. They have told me that the reliability of the sponsor's observed p-value for Study 106 is directly related to the number of dropouts, and that the observed p-value in no way accounts for the chance possibility that the population of dropouts would have a different seizure risk than those who did not drop out. Really the observed p-value is part of a family of possible p-values, some of which could be significant and some of which might not be significant. That the observed p-value is significant might alone be a chance occurrence, given the dropout rate.

Therefore, given the body of evidence provided by the sponsor, I cannot conclude that Topamax has been shown to be effective as monotherapy.

Several additional points should be made. First, Study 106 included several seizure types in adult and pediatric patients. While the sponsor has performed appropriate subgroup analyses, none of these subgroup analyses has been subjected to the above sensitivity analyses. Second, while the sponsor is seeking a claim for monotherapy, the dose titration followed in Study 106 required 4-6 weeks to reach the target dose. Such a long time might preclude a claim for initial monotherapy and make a claim for conversion to monotherapy more appropriate.

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/s/

John Feeney
11/26/03 05:00:05 PM
MEDICAL OFFICER

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name:	**Topamax**
Generic Name:	**topiramate**
Sponsor:	**Johnson and Johnson**
Indication:	**Epilepsy, monotherapy**
NDA Numbers:	**20-505 (S-018)** **20-844 (S-015)**
Original Receipt Date:	**October 29, 2002**
Clinical Reviewers:	**Howard D. Chazin, M.D.**
Review Author:	**Howard D. Chazin, M.D.**
Review Completed:	**November 25, 2003**

Table of Contents

1. Executive Summary/Conclusions

1.1 Efficacy Conclusions

The supplemental NDA application for the use of topiramate as monotherapy in epilepsy is non-approvable.

- The sponsors failed to show statistically significant evidence of efficacy in time to first seizure in their pivotal trial TOPMAT-EPMN-106 between the low and high dose groups. This was due to the almost threefold incidence of dropouts due to adverse events seen in the high dose group leading to fewer seizure events in this group. Assuming all withdrawals were treatment failures, an all cause analysis showed p=0.57 (log rank test). The sponsors responded to Division requests for further information regarding the dropouts, but the submission did not adequately explain the higher dropout rate in the high dose group.
- The sponsors failed to show a statistically significant evidence of efficacy in time to first seizure between the low and high dose groups in supportive study TOPMAT-EPMN-104 (p=0.062, log rank test). When subjected to the same all cause analysis, the endpoint no longer approached statistical significance (p=0.32, log rank test). Statistically significant evidence for time to second seizure (the primary endpoint of the trial) was not apparent by the sponsor (p=0.78, log rank test).
- The sponsors failed to show a difference between dose groups (100mg or 200mg daily) in regards to time to first seizure in study TOPMAT-EPMN-105.
- The sponsors did prove superiority of topiramate 1000mg daily over 100mg daily regarding time to exit and reduction in seizure rates. (p=0.002, log rank test).

1.2 Safety Conclusions/Recommendations

Several safety concerns regarding topiramate were raised during the review of the submission. Most apparent were dose-related increases in neuropsychiatric events,

paresthesias, weight loss and low CO2 related to metabolic acidosis in both the pivotal trial (Study 106) and in the ISS.

In Study 106, the 400mg (high, presumably efficacious) dose is not well tolerated and should be considered a maximum rather than a goal dose for treatment. At this dose level, the following was observed, raising concerns regarding the ability of those patients to continue to maintain this dose for an extended treatment time. Compared to the low dose group at 50mg daily, the following were noted in the high dose 400mg group.

- The number of withdrawals due to adverse events was 3 times higher at this dose.
- 24% of patients randomized to this group required a reduction in topiramate dosage or temporary interruption of treatment.
- The incidence of neuropsychiatric side effects, paresthesias, anorexia, difficulty with memory, mood and cognitive problems were at least twice as prevalent at this dose.

Additionally, overall decreases in BMI in the study population as a whole and the incidence of pediatric weight loss seen in this study are concerning for growth retardation. Further information regarding height assessment and failure to continue on a current growth curve would be use to assess possible long term side effects of topiramate in children and young adults.

Regarding the ISS review, this reviewer noted the higher number of dropouts seen at higher dose levels both in the double blind and extension phases. Adverse events leading to discontinuation of medication or reduction in medication in topiramate dosage were noted to be more significant in the higher dose groups (400mg and 500mg daily).

The overall incidence of neuropsychiatric events and encephalopathy are misleading in that primary and secondary terms are split out so that it appears these incidences are small individually than as a whole. The sponsor should consider reevaluating the encephalopathy and neuropsychiatric side effect profiles aggregates to obtain better information regarding the incidence of these adverse events of topiramate as used in monotherapy.

2. Background

Johnson and Johnson Pharmaceutical Research and Development, LLC (J&JPRD, RWJPRD, J&JRPI or Sponsor) submitted a supplemental NDA for the use of Topamax (topiramate) tablets (NDA 20-505 S018) and sprinkle capsules (NDA 20-844 S015) as monotherapy in adults and children six years of age and older with newly diagnosed epilepsy. Topamax has already been approved for adjunctive treatment of partial onset seizures with or without secondary generalization and for refractory generalized epilepsy including primary generalized tonic-clonic seizures in adults and children (ages 2-16

years). A supplemental NDA was also approved for adjunctive therapy for patients 2 years of age and older with seizures associated with the Lennox-Gastaut syndrome.

According to the sponsor, "the international birth date for topiramate is 18 July 1995, when topiramate was first approved for marketing for adjunctive therapy for adults with epilepsy in the United Kingdom. The registered formulations of topiramate are tablet and sprinkle capsule. Cumulatively, topiramate is licensed in approximately 80 countries worldwide. In February 1998, topiramate was also approved for adjunctive therapy for children with epilepsy. In a number of countries, topiramate has been approved for monotherapy in patients with newly diagnosed epilepsy or for conversion to monotherapy in patients with epilepsy."

Worldwide, the mean prevalence of active epilepsy, i.e., continuing seizures or the need for treatment, is estimated (as of February 2001) to be approximately 8.2 per 1,000 individuals in the general population; at any time, 50 million people are estimated to suffer from this condition. In developed countries, 70 to 80% of patients with epilepsy use antiepileptic drugs (AEDs) to achieve some measure of seizure control. Until recently, carbamazepine, phenytoin, valproic acid, and phenobarbital were the anticonvulsants most commonly used for the treatment of epilepsy. The availability of several new AEDs, including topiramate, has expanded treatment options for physicians treating patients with epilepsy. Adjunctive treatment with 2 or more AEDs is routinely used in clinical practice, especially in patients with medically refractory epilepsy. It is widely recognized, however, that treatment with a single AED has numerous advantages over polytherapy. These include avoidance of potential drug interactions, fewer adverse effects, better compliance associated with greater ease of administration, and lower cost.

Per the sponsor, in the original add-on trials, topiramate was shown to exert an independent antiepileptic effect that was consistent across a wide variety of concomitant AED regimens, including carbamazepine, phenytoin, valproic acid, primidone, phenobarbital, clobazam, and clonazepam. Efficacy of topiramate did not appear to be mediated through either pharmacokinetic or pharmacodynamic interactions with any of these standard AEDs. These findings suggested that topiramate may be efficacious as monotherapy in epilepsy.

2.1 Background regarding trials related to the monotherapy indication

According to the sponsor, the first trial on the efficacy of topiramate as monotherapy was Study YI, which compared topiramate 1000mg/day with topiramate 100mg /day in 48 subjects with refractory partial onset seizures. Topiramate 1000mg /day was found to be superior to topiramate 100 mg/day with respect both to the time until therapeutic failure and to the proportion of subjects who completed the monotherapy period without meeting the protocol-specified time to exit criteria.

Monotherapy was next evaluated in a less refractory subject population in Study TOPMAT-EPMN-104. (Study 104) This study compared a high, presumably fully efficacious, dose of topiramate (200 or 500mg/day, based on body weight) with a

presumably less efficacious dose (25or 50mg/day, based on body weight) in 252 subjects with recently diagnosed epilepsy characterized by partial onset seizures with or without secondary generalization. The study failed to demonstrate a difference between the dosage groups with respect to the pre-specified primary endpoint, the time to second seizure. Significant differences in favor of the high dose were reported with respect to seizure frequency and to the proportion of subjects who were seizure-free during the double-blind phase.

Study TOPMAT-EPMN-105 (Study 105) was the third randomized controlled trial in the monotherapy clinical development program, that assessed efficacy of 2 initial target doses of topiramate relative to standard AEDs in 621 subjects with newly diagnosed epilepsy inclusive of all seizure types and syndromes. The design was a simultaneous head-to-head comparison of topiramate monotherapy (at the doses of 100 mg/day and 200 mg/day) to physician's choice of either carbamazepine 600 mg/day or valproate 1,250 mg/day. Based on 95% confidence intervals, topiramate monotherapy was shown to be at least as effective as the physician's preferred AEDs in reducing seizures. Topiramate treatment and standard treatment were similar with respect to all endpoints, i.e., time to exit, remission of seizures during the last 6 months of the double-blind phase, and time to first seizure.

To demonstrate a dose-response relationship, and, by inference, efficacy of topiramate as monotherapy, study TOPMAT-EPMN-106 (Study 106), was conducted. This randomized, double-blind, parallel group study compared the safety and efficacy of 2 doses of topiramate (50mg/day and 400 mg/day) as monotherapy in pediatric (ages 6 and over) and adult subjects with newly diagnosed or recurrent epilepsy.

3. Regulatory History regarding Study 106

May 20, 1999 – The Division received a draft protocol for Study 106 that was reviewed by Richard Treasley, MD, who requested a statistical consultation.

July 28, 1999 - Statistical Review and Evaluation was completed by Sharon Yan, Kun Jin and George Chi

Jan 7, 2000 - Letter from the Division was faxed to the sponsor regarding the protocol. The Division sent the following comments to the Sponsor at that time.

- *The results of the log-rank test for the time to first seizure may be biased and difficult to interpret if a substantial number of subjects drop out due to toxicity. Please address this issue.*
- *Populations of pediatric and adult patients need to be stratified in randomization and analyses. The age limit of the pediatric population needs to be specified.*

Feb 23, 2000 - Teleconference with sponsor regarding protocol

Based on the Sponsor's records, the following were agreements made between the Division and J&JRPI at the Feb 23, 2000 teleconference.

- The sponsor would conduct a descriptive analysis stratified by the subjects' prior history of AED use to alleviate concern of the Division regarding potential differences between newly diagnosed vs. recurrent epilepsy subjects enrolled in the trial TOPMAT-EPMN-106. Per the sponsor, this study was not based on conversion to monotherapy in refractory epilepsy patients; the protocol specified that AED use prior to enrollment was for emergency or temporary treatment while a diagnosis of epilepsy was being established, and no subjects were receiving AEDs for a significant length of time.

- The sponsor would provide evidence to demonstrate that subjects tapering off other anticonvulsants were not experiencing withdrawal-induced seizures.

- The acceptability of pooling pediatric data from the existing monotherapy studies to satisfy the pediatric assessment rule was discussed. The Division stated that such an approach was possible, but emphasized that approval would be dependent on the strength of the data. The Division did request that adult and pediatric subjects be stratified in randomization and analysis. However, due to the difficulty in enrolling subjects, no stratification by age was performed at randomization; stratified efficacy analysis is presented in clinical study report TOPMAT-EPMN-106.

April 17, 2000 - Letter of Understanding was received from the Sponsor to the Division. The following statements are reproduced from that letter.

FDA suggested a stratified analysis be conducted to demonstrate whether any differences exist between the two populations being studies in the TOPMAT-EPMN-106 protocol: newly diagnosed patients who may have never been treated and patients who are currently on treatment that will withdraw to monotherapy. RWJPRI indicated this is not a trial to allow conversion to monotherapy in refractory epilepsy subjects. Given the clinical presentation of a possible newly diagnosed patients or patient with recurrent epilepsy, it is our intention to allow enrollment of subjects who may have been given an anti-epileptic drug for emergency or temporary use while a diagnosis of epilepsy was being established. We are not enrolling patients who have been on anti-seizure medication for a significant length of time. We indicated a descriptive analysis that compares the two groups could be performed. Dr. Katz stated when analyzing the study results, RWJPRI would need to address the issue that patients tapering off other anti seizure drugs were not having withdrawal seizures.

FDA also commented that the results of the log rank test for the time to first seizure might be biased and difficult to interpret if a substantial number of subjects dropped out of the study due to toxicity. The way the protocol is designed, time to event as an outcome will be used when censoring which may introduce bias. Since seizure

frequency data is not captured, it may become problematic to analyze the trial if the number of dropouts is high.

RWJPRI indicated that "we do not foresee this as being an issue. Based on the result of previously conducted monotherapy trials, we do not expect to see a high number of dropouts."

3.1 Pre NDA meeting and follow up letter (March-April 2002)

The major pre-NDA meeting occurred on March 12, 2002 with a follow up letter on April 15, 2002. Agreements from those interactions between the Division and Sponsor are noted below.

3.1.1 General exclusions

The Division agreed to allow the sponsor to cross-reference the following information contained within the approved Topamax NDA 20-505 to the monotherapy supplement: non-clinical pharmacology, toxicology and ADME information; human ADME, bioavailability/ bioequivalence and pharmacokinetic data that were generated to support the approval of topiramate as adjunctive therapy in epilepsy; and drug substance and drug product data.

For the Clinical section of the monotherapy sNDA, the Division indicated that an Integrated Summary of Efficacy (ISE) was not needed, since the monotherapy claim would be supported solely by the results of the pivotal trial TOPMAT-EPMN-106. In addition, since no new human pharmacology studies were conducted to support the monotherapy indication, the Table of Pharmacology Studies and Overall Summary of Clinical Pharmacology was not required.

3.1.2 Content and Format

The Division indicated that it was acceptable to limit discussion of foreign regulatory actions for the use of topiramate as monotherapy and not provide data on its use as adjunctive therapy in epilepsy in the Clinical Data section of the NDA, and that comprehensive foreign label review was not required.

The Division also found the following proposals made by the sponsor to be acceptable: to submit the application electronically; to not provide an Application Summary in the sNDA; to provide the annotated version of the product labeling in Item 2; to not submit Appendix 16.4 (individual subject data listings) as part of the individual clinical study reports; to not provide patient profiles in the monotherapy sNDA; to combine raw and derived SAS data sets; to provide case report forms only for subjects who died or discontinued due to an adverse event; to provide financial disclosure information only for Studies TOPMAT-EPMN-105 and TOPMAT-EPMN-106; and to cross-reference the monotherapy data to the Topamax Sprinkle Capsule NDA.

3.1.3 Pediatric monotherapy claim in the sNDA

At the pre-NDA meeting the Division reiterated that they would grant a monotherapy claim in adults and pediatric patients down to 6 years of age (inclusive) provided it were adequately supported by the results of the study TOPMAT-EPMN-106. At this time, the Agency also granted the sponsor a deferral for submitting monotherapy data in pediatric patients 1 month through 6 years of age until after the indication was approved in adults; a waiver was granted from conducting clinical trials in subjects 0 through 1 month of age. In addition, the Division agreed that it was not necessary for the sponsor to reanalyze previously issued study reports that used a pediatric cutoff age of 17 years, rather than the current definition (i.e., 16 years). The new definition was applied to the data analyses in study report TOPMAT-EPMN-106 and in the Integrated Summary of Safety (ISS).

3.1.4 Safety Data

Regarding this supplement application, the Division provided a number of requests regarding the presentation of safety data to be provided in the monotherapy sNDA. J&JPRD organized the ISS taking into consideration the Division's recommendations. As such, all adverse event and laboratory analyte data are summarized by study phase (double-blind and open-label extension) and period (titration and stabilization). The Division suggested that durations of the study periods of the double-blind phase (i.e., titration and stabilization) be calculated individually for each subject based on the increase or lack of change in the actual dosage of the study medication. Due to the design features of the Phase 3 trials, these durations were calculated based on blistercard records. Therefore, the last day of the titration period for each subject was defined as the last day the subject used blister cards; the stabilization period was defined based on the use of medication from the stabilization bottles.

3.1.5 Adverse events

The Division agreed with the sponsor's proposed cutoff date of February 15, 2002 for inclusion of data from the ongoing open-label extension phases of Studies 104 and Study 106. More recent cutoff dates were used for serious adverse events (July 31, 2002) and deaths (up to the time of sNDA filing). A four-month safety update (4MSU) was included in the safety database including updated safety summaries through a cutoff date of August 31, 2002. In the 4MSU, serious adverse events from August 31, 2002 to November 30, 2002 were presented.

3.1.6 Separate safety results from study YI and extension phase of EPMN-105

As per agreement with the Division at the monotherapy pre-NDA meeting, since the conversion Study YI was qualitatively different from the other Phase 3 studies with

regard to subject population and maximum dosage of topiramate studied, the safety results from this study were presented separately from the remaining phase 3 multicenter monotherapy trials in the ISS. In addition, the results of the extension phase of study TOPMAT-EPMN-105 were also presented separately since this phase of the study was based on a crossover design, during which subjects crossing over to alternative treatment had considerable exposure to another AED during the double-blind phase of the study.

3.1.7 Safety topics of special interest

Summaries of the following safety topics of special interest were included in the ISS, summarized separately for the double-blind and open-label extension study phases: hepatic events, metabolic acidosis, oligohydrosis/hyperthermia, encephalopathy/hyperammonemia, and visual adverse events.

3.1.8 Data on plasma levels of concomitant AEDs

Plasma levels of concomitant AEDs were not collected during the topiramate clinical trials, therefore this information is not provided in the ISS.

3.1.9 Overdose section as part of ISS

Based on agreement with the Division at the pre-NDA meeting, instead of providing a separate Drug Abuse and Overdose Section in the monotherapy sNDA, all spontaneous reports of overdose, regardless of therapeutic indication, received for topiramate as of April 30, 2002 were summarized in a subsection of the ISS.

3.1.10 No new clinical pharmacology studies included in monotherapy sNDA

In concurrence with the Division since no new human pharmacology studies were conducted to support the monotherapy indication, the Table of Pharmacology Studies and Overall Summary of Clinical Pharmacology were not provided in the monotherapy sNDA.

3.1.11 Limitation of discussion of commercial marketing and foreign regulatory actions

Based on agreement with the Division, J&JPRD limited discussion of the commercial marketing experience and foreign regulatory actions to the use of Topamax as monotherapy in epilepsy and did not provide data on the use of topiramate as an adjunctive agent in the treatment of epilepsy.

3.1.12 No comprehensive label review

In addition, since the ex-US countries who gained approval of the monotherapy indication did so based on the results from the YI, TOPMAT-EPMN-104 and TOPMAT-EPMN-105 studies, the Division indicated J&JPRD did not need to provide a comprehensive label review in the monotherapy sNDA.

3.1.13 Review of the published literature

The Division indicated that a comprehensive literature review, rather than one limited to the epilepsy monotherapy indication, be performed; this was to include a global search on any adverse events associated with exposure to topiramate, regardless of indication and presence or absence of concomitant AEDs. This review was conducted and included in the monotherapy ISS.

3.1.14 Postmarketing safety summary

At the Division's request, J&JPRD provided a comprehensive postmarketing safety summary based on data from all known topiramate uses, both adjunctive and monotherapy. Particular attention was given to the following safety topics: hepatic events, metabolic acidosis, oligohydrosis, encephalopathy/hyperammonemia, visual adverse events associated with secondary angle closure glaucoma, suicide, and exposure during pregnancy/lactation. The format/content of the comprehensive post-marketing safety document was based on J&JPRD's June 28, 2002 proposal, which the Division agreed to.

4. Pharmacokinetics

An extensive preclinical assessment of topiramate was previously conducted to support the approval of Topamax (topiramate) tablets as adjunctive therapy in epilepsy. In accordance with 21 CFR 314.50(g)(1) and per agreement with the Division, J&JPRD cross-referenced all the relevant non-clinical pharmacology, toxicology and ADME studies contained within the TOPAMAX (topiramate) Tablet NDA 20-505 to the monotherapy supplement. No new clinical pharmacology trials were conducted to support the monotherapy program.

The current Topamax ® (topiramate) label includes the following regarding Pharmacokinetics.

4.1 CLINICAL PHARMACOLOGY (ADME)

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady state is thus reached in about 4 days in patients with normal renal function. Topiramate is 13-17% bound to human plasma proteins over the concentration range of 1-250 µg/mL.

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

Pharmacokinetic Interactions (see also Drug Interactions):

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions mean plasma AUCs are summarized below in ***(Table 3)*** *in the*

Table 3: Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE

[a] = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.
[b] = Is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration.
AED = Antiepileptic drug.
NE = Not Evaluated.

PRECAUTIONS *section of the label.*

Special Populations: Renal Impairment:

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30-69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual dose is recommended in patients with moderate or severe renal impairment.

Hemodialysis:

Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20-30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may be required.

Hepatic Impairment:

In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood.

Age, Gender, and Race:

Clearance of topiramate in adults was not affected by age (18-67 years), gender, or race.

Pediatric Pharmacokinetics:

Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose.

Pediatric patients have a 50% higher clearance and consequently shorter elimination half-life than adults. Consequently, the plasma concentration for the same mg/kg dose may be lower in pediatric patients compared to adults. As in adults, hepatic enzyme-inducing antiepileptic drugs decrease the steady state plasma concentrations of topiramate.

4.2 Pharmacodynamics

The current Topamax label includes the following regarding Pharmacodynamics.

Pharmacodynamics:

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ *receptor antagonist, pentylenetetrazole. Topiramate is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia.*

5. Overall Data – Monotherapy Program

The submission was generally in electronic format. The sources of data included final study reports from J&JPRD's monotherapy program consisting of the pivotal study TOPMAT-EPMN-106 (Study 106) and 3 supportive studies (YI, TOPMAT-EPMN-104 and TOPMAT-EPMN-105- Studies YI, 104 and 105 respectively). Final study reports from the double-blind portion of these studies, as well as the completed extension phase of studies 105 and YI were also provided in the monotherapy sNDA. Per agreement with the Division, available data from the ongoing open-label extension phase of Studies 104 and 106, through a cut-off date of February 15, 2002, were provided in the Integrated Summary of Safety (ISS) only. Serious adverse events from the ongoing portion of the open-label phase of these studies were captured in the ISS through July 31, 2002 and deaths up to the time of the sNDA filing. The 4 month safety update (4MSU) was also reviewed. This included the additional exposure to topiramate in the open label and total monotherapy exposure groups through the cutoff date of August 31, 2002. Also in the 4MSU, serious adverse events from August 31, 2002 to November 30, 2002 were presented and reviewed.

5.1 Tables Listing the Clinical Trials

The following is a table listing the clinical trials reviewed for this indication. The pivotal trial is listed first followed by the supportive trials.

Summary of controlled monotherapy trials					
Controlled Study Reports	Type of trial	Number of subjects enrolled and included in intent to treat analysis	Dosage forms	Duration of double blind phase	Country

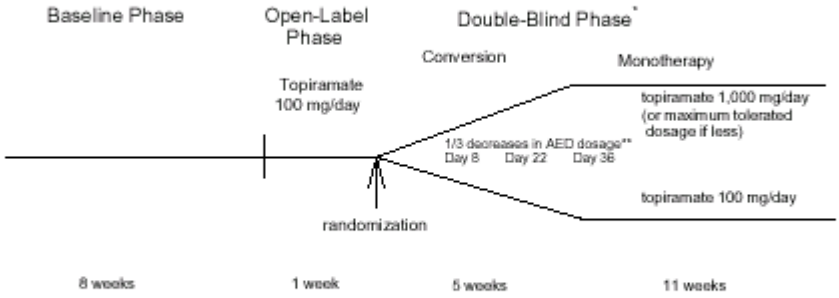
Summary of controlled monotherapy trials					
TOPMAT-EPMN-106 (PIVOTAL)	Randomized double blind parallel group efficacy and safety monotherapy study	470 total Adults Pediatric	50mg/day 400mg/day	6 months	Multinational
TOPMAT-EPMN-105 (Supportive)	Randomized double blind parallel compared efficacy and safety to standard monotherapy (VPA 1250mg/day or CBZ 600mg/day	613 total Adults Pediatric	100mg/day 200mg/day	6 months	Multinational
TOPMAT-EPMN-104 (Supportive)	Randomized double blind parallel group study in partial onset seizures with or without secondary generalization	252 total Adults Pediatric	Low dose group: 25mg/day or 50mg/day high dose group 200mg/day or 500mg/day	4 months	Multinational
YI (Supportive)	Randomized double blind parallel group study in subjects with refractory partial seizures with or without secondary generalization.	48 adults only	100mg/day 1000mg/day	16 weeks (monotherapy 11 weeks)	Single center USA

5.2 Study YI - Supportive

Study YI was a randomized, double-blind parallel-group study that evaluated topiramate monotherapy in 48 subjects with refractory partial-onset seizures with or without secondary generalized seizures. During the baseline phase of the monotherapy trial, subjects were maintained either on a constant dosage of a single standard AED at

therapeutic plasma concentrations, or on two standard AEDs, one at therapeutic plasma concentrations and one at a concentration no more than 50% of the therapeutic lower limit. These subjects were required to have an average of four partial-onset seizures per month prior to beginning topiramate therapy. Qualified subjects were randomly assigned to receive topiramate 100 mg/day or 1,000 mg/day. During the initial five weeks, baseline AEDs were gradually discontinued while topiramate was titrated up to 500 mg administered twice daily for subjects in the 1,000 mg/day group. Subjects were followed for a monotherapy period of up to 11 weeks on the assigned or maximum tolerated dosage. This is illustrated in the following sponsor figure.

Figure 1: Study Design for Protocol YI



* For subjects who discontinued study participation, tapering was conducted in double-blind fashion. Subjects who completed double-blind therapy or who met exit criteria could enter an open-extension phase.

** Titration of topiramate dosage. Second subtherapeutic AED, if any, discontinued on Day 8.

Subjects remained in the double-blind phase until they completed the planned 16-week duration (successes) or reached any four exit criteria: doubling in the average monthly seizure frequency, doubling of the highest two-day seizure frequency, single generalized seizure if none occurred during baseline, prolongation of generalized seizure duration, i.e. serial seizures or status epilepticus) All four exit criteria were determined by the investigator and compared to baseline events, defining a measure of worsening seizure control. The primary efficacy measure was time to exit. Efficacy was evaluated on the basis of data regarding seizure type and frequency obtained from seizure diaries.

5.3 Study TOPMAT-EPMN-104 (Study 104)-Supportive

Study 104 was a randomized, double-blind, parallel-group study conducted at multiple sites to evaluate topiramate dosages based on body weight of 25 or 50mg/day (low dose) and 200 or 500 mg/day (high dose) as monotherapy in subjects three years of age and older with recently diagnosed epilepsy characterized by partial onset seizure with or without secondarily generalized seizures. The trial included four phases, a retrospective baseline phase (three months), an open treatment phase (one week) a double-blind

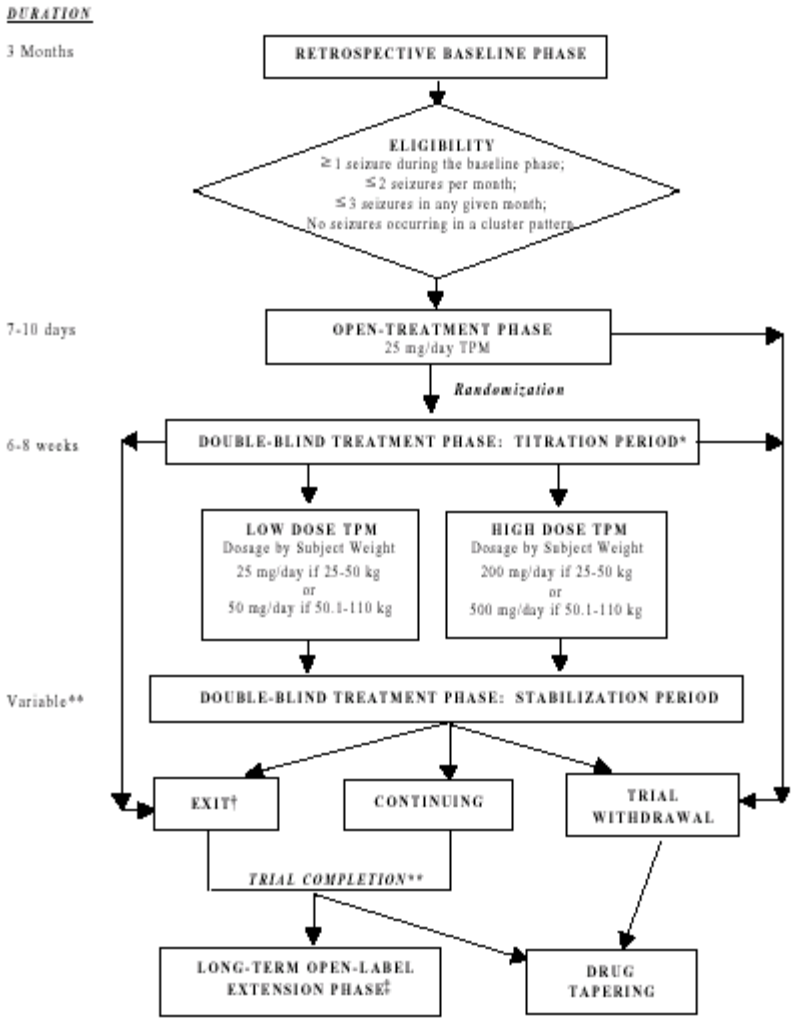
treatment phase that varied for individual subjects and a long term extension phase. No more that one AED was allowed during the retrospective baseline phase. Subjects were required to have at least one partial onset seizure during the three month retrospective baseline phase, to average no more that two partial seizures per month, and to have no more that three partial seizures in any given month. Eligible subjects entered the open treatment phase and received topiramate 25mg daily for 7-10 days. For the double-blind phase, patients were randomly assigned to the low dose or high dose groups. The first period of the double blind phase was titration. For those in each dose group, the following titration schedule was used. Baseline AEDs were tapered off by day 36.

Table 4: Dose Titration Schedule: Double-Blind Phase
(Protocol TOPMAT-EPMN-104)

Dose Group	Open-Treatment Days	Titration Period (Days)						Stabilization
Body Weight (kg)	-7 to -1	1 to 7	8 to 14	15 to 21	22 to 28	29 to 35	36 to 42	Period
Low								
25 – 50	25	25	25	25	25	25	25	25
50.1 – 110	25	50	50	50	50	50	50	50
High								
25 – 50	25	50	75	100	125	150	200	200
50.1 - 110	25	50	100	200	300	400	500	500

Subjects remained in the double blind phase until reaching one of the following exit criteria designed to correspond to therapeutic failure: 2 partial onset seizures with or without secondary generalization, a single generalized tonic clonic seizure if none occurred prior to randomization, or a single episode of status epilepticus. Subjects who met the exit criteria could continue to receive topiramate in the extension phase of the study. The study design is illustrated in the following diagram.

Figure 1: Study Design for Protocol TOPMAT-EPMN-104



* For subjects receiving a baseline AED, dosage reductions of one-third were recommended on Days 8 and 22 of the titration period with discontinuation of the baseline AED on Day 36.

** Subjects remained in the double-blind phase of the study until i) the subject met the exit criteria, ii) the double-blind phase was terminated, or iii) the subject withdrew from the trial. Subjects who discontinued study medication during the double-blind phase had their study medication tapered, but were to complete their remaining double-blind study visits until they either met the exit criteria or the double-blind phase was terminated.

† Exit criteria were: i) two partial onset seizures with or without a secondarily generalized component; ii) a single secondarily generalized tonic-clonic seizure if none occurred before randomization, or iii) a single episode of status epilepticus.

‡ Subjects who met the exit criteria during the double-blind phase and subjects who were still participating in the double-blind phase at the time it was terminated (four months after the last subject was randomized) could enter the long-term extension phase.

5.4 Study TOPMAT-EPMN-105 (Study 105)-Supportive

Study 105 was a randomized, double-blind, parallel, multicenter, multinational trial that compared the efficacy and safety of topiramate monotherapy to standard monotherapy

(carbamazepine or valproate) in subjects with newly diagnosed epilepsy. Eligible subjects were at least six years old, weighed 30kg and had at least one seizure within the three month baseline period. Subjects either had no AED use or single AED use for no longer than six weeks. The trial included three phases, a baseline phase, double-blind phase and blinded extension. The baseline stage lasted up to seven days whereby eligibility was determined. Before randomization, the investigators determined the preferred standard medication (carbamazepine or valproate) for each subject, based on clinical evaluation of the subject and seizure type. After assignment to either standard medication, subjects were randomly assigned in equal portions to one of the three treatment groups – topiramate 100mg/day, 200mg/day or standard therapy (carbamazepine 600mg/day or valproate 1250mg/day). The double blind phase was divided into titration and stabilization periods. Titration lasted 35 days. For subjects receiving a baseline AED that AED was tapered off during this period with concurrent upward titration of the study medication. Stabilization followed titration where the dose remained constant. Subjects remained in the double blind phase until a decision was made to: discontinue, change the study medication or dosing regimen, or add another AED. Either the investigator or subject could make such a decision based on protocol specified reasons: ineffective treatment, adverse events, subject choice, loss to follow up or death. Subjects were considered to have completed the double-blind phase when a decision was made to exit or when the trial was terminated (6 months after the last subject was randomized.) Upon exiting the double-blind phase, patients could enter the extension phase and take the alternative study medication within the branch in a blinded fashion. The study is illustrated in the following figure.

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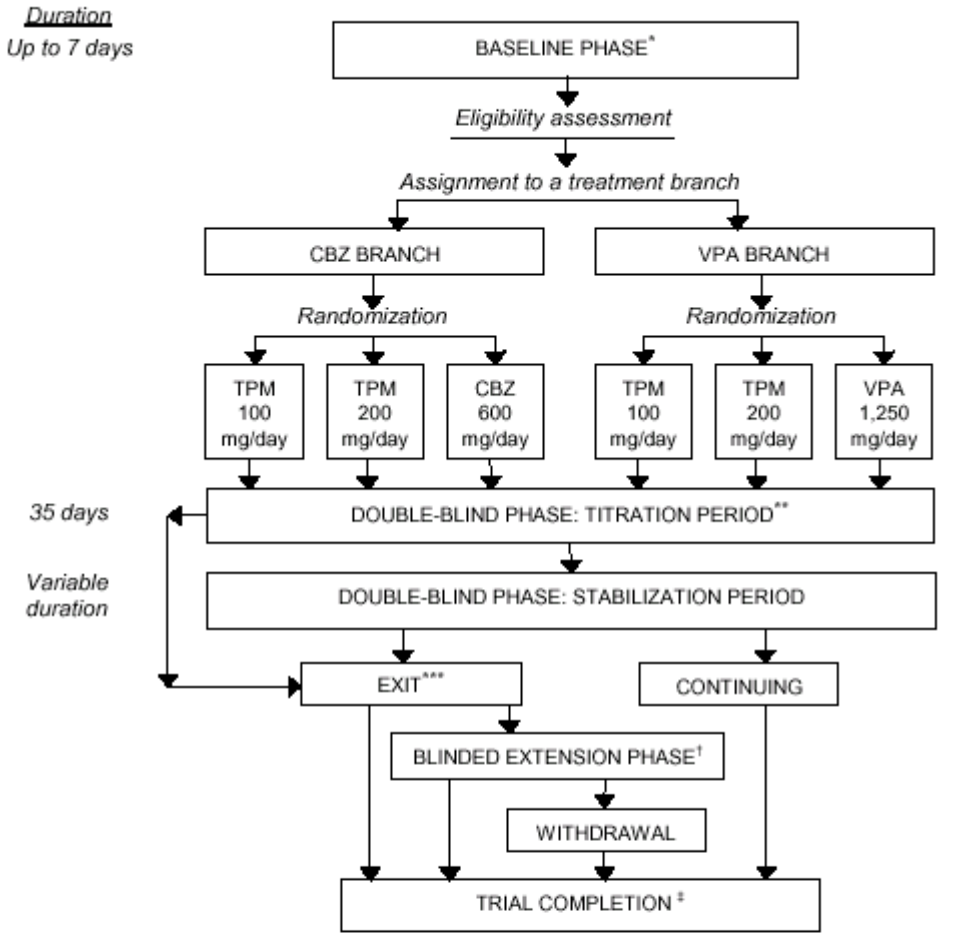
Figure 1: Study Design for Study TOPMAT-EPMN-105



* The prospective baseline phase lasted for up to seven days. Seizure data were collected retrospectively for the 3-month period prior to the study entry.

** For subjects receiving a baseline AED, this AED was discontinued in three stepwise weekly dosage reductions (at the beginning of Weeks 2, 3 and 4), each reduction equal to a one-third of the initial dose. The baseline AED was discontinued prior to Week 5, when the last incremental increase in the dosage of study medication took place.

*** In order for a subject to exit the double-blind phase, a clinical decision had to be made by either the investigator or the subject to discontinue the study medication, to change the study medication or dosing regimen, or to add another AED. The protocol-defined reasons for making this decision included: ineffective treatment, adverse events, subject choice, loss to follow-up, and death.

† Subjects who exited the double-blind phase were given the opportunity to enter the blinded extension phase and take the alternative study medication within their branch in a blinded fashion. The study medication administered during the double-blind phase was to be tapered off in approximately 35 days as the new medication was to be titrated upwards.

‡ Subjects completed the double-blind phase when a decision was made to exit, or when the trial was terminated (six months after the last subject was randomized). Subjects who were active in the trial at the time of its termination were allowed to continue receiving their blinded study medication until the database was finalized.

Per the sponsor and current labeling, the recommended dose of topiramate as adjunctive therapy for adults with epilepsy is 200 to 400 mg/day (400 mg/day in the U.S.). Administration of topiramate as an add-on to enzyme-inducing AEDs, however, is associated with an almost twofold increase in the plasma clearance of topiramate,

compared to that achieved with monotherapy. Furthermore, the optimal therapeutic response in patients with less severe epilepsy can be achieved at lower doses of topiramate. Thus, the doses of topiramate used in the Study 105, 100 mg/day and 200 mg/day, were expected to be effective in subjects with newly diagnosed epilepsy.

5.5 Study TOPMAT-EPMN-106 (Study 106 – Pivotal study)

5.5.1 Title

A randomized double blind, parallel group monotherapy study to compare the safety and efficacy of two doses of topiramate in the treatment of newly diagnosed or recurrent epilepsy.

5.5.2 Objective

The objective of this study was to compare the safety and efficacy of 2 doses of topiramate as monotherapy in pediatric and adult subjects with newly diagnosed (within 3 months) epilepsy characterized by partial-onset (with or without a secondarily generalized component and/or (generalized seizures (including tonic clonic, clonic or juvenile myoclonic epilepsy with or without myoclonic seizures) or with recurrent epilepsy while off of AEDs.

5.5.3 Design

A randomized, double-blind, parallel-group, multinational study to compare the safety and efficacy of 2 doses of topiramate 50mg/day (TPM 50) and 400mg/day (TPM 400) administered as monotherapy for the treatment of newly diagnosed or recurrent epilepsy. The doses chosen to demonstrate a dose-response relationship were hypothesized to be a low, minimally efficacious dose (50 mg/day) versus a high, presumably fully efficacious and generally tolerable higher dose (400 mg/day). There were 4 phases in this study: baseline, open-treatment, double-blind, and long-term extension. The design is illustrated in Sponsor Figure 1 below.

The 3-month retrospective **baseline phase** allowed for the assessment of seizure frequency and AED use prior to study entry. Both the new diagnosis of epilepsy and the diagnosis of recurrent epilepsy (relapse of epilepsy) were established during the 3-month retrospective baseline phase. All eligible subjects must have had either 1 or 2 well-documented seizures during the retrospective baseline phase. Eligible subjects entered the open-treatment phase within 14 days after screening procedures were performed.

The **open-treatment phase** was designed to ascertain the ability of each individual subject to tolerate the study medication and to allow for discontinuation of any AED therapy used for temporary or emergency purposes. All subjects who met the entry criteria received topiramate 25 mg/day for 7 days. Subjects were to have no more than 1 seizure between the screening visit and the end of the open-treatment phase. By the end

of this phase, subjects who had no significant tolerability problems were randomly assigned to 1 of the 2 topiramate dosage groups, 50 mg/day or 400 mg/day. Subjects who were taking an AED at any time during the baseline phase were required to discontinue this AED prior to randomization.

During the **titration period** of the double-blind phase, which lasted up to 42 days, topiramate was titrated to either the assigned dose or the maximum tolerated dose. If a subject experienced unacceptable difficulty tolerating topiramate during the initial 21 days of this period, the subject was withdrawn from the study. A total of (2) 50-mg dose reductions were allowed after Day 21 in the higher dose group. During stabilization period, which followed titration, the dose of topiramate was to remain constant, if possible. Dose reductions were allowed for subjects who had difficulty maintaining the assigned dose (or the maximum tolerated dose). Following dose reduction during titration or stabilization, the topiramate dose was not to be increased again.

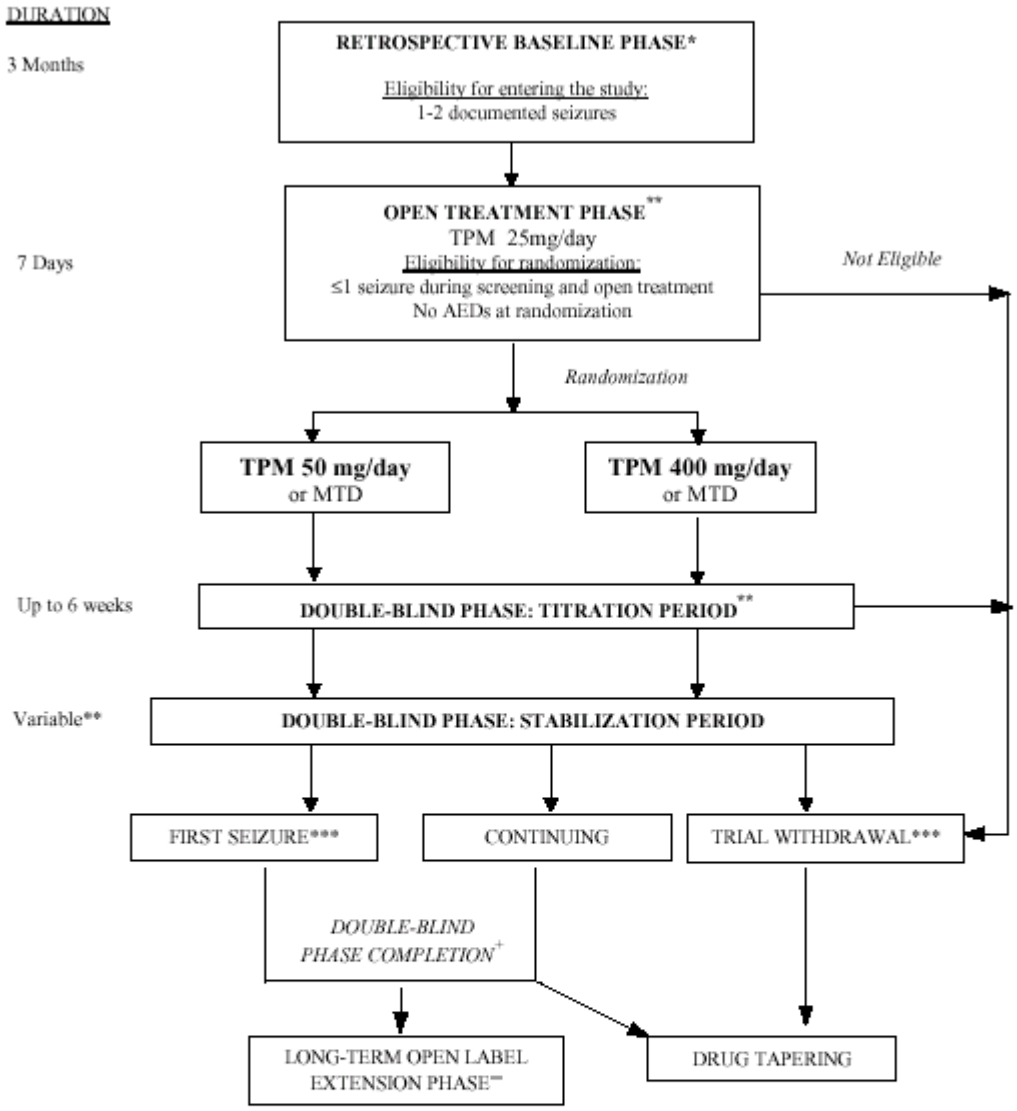
During **stabilization**, the dose of study medication was to remain constant, if possible. Dose reductions were allowed for subjects who had difficulty maintaining the assigned dose (or the maximum tolerated dose). Following dose reduction during the stabilization period, the topiramate dose was not to be increased. Dose reductions for subjects randomized to the 400 mg/day dose group were to occur in 50 mg/day increments; the reduced dose could not be lower than the dose of the titration week prior to the maximum dose achieved during titration. One dose reduction of 25 mg/day was allowed for subjects randomized to the 50 mg/day dose group.

Subjects remained in the double-blind phase until they experienced a first partial-onset or generalized tonic-clonic seizure, until termination of the double-blind phase by the sponsor (6 months after randomization of the last subject), or until withdrawal for protocol-specified reasons, which included adverse events, subject choice, and lost to follow-up.

Subjects, who completed the double-blind phase either at the time of their first seizure or at the time of termination of the double-blind phase by the sponsor, could continue to receive topiramate in the **long-term extension** phase.

During **blinded transition**, which lasted up to 49 days, the dosage of topiramate received by the subjects in the topiramate 50 mg/day group was titrated to 400 mg/day or the maximum tolerated dose; subjects in the topiramate 400 mg/day group continued to receive the same topiramate dose as during double-blind phase. Blinded transition was followed **by open-label treatment**, during which the dose of topiramate was adjusted according to individual tolerability and efficacy, and other AEDs were added if clinically indicated. The maximum daily dose of topiramate was not to exceed 1,600 mg/day for subjects 14 years and older. For subjects less than 14 years of age, the maximum daily dose was 24 mg/kg but was not to exceed 1,600 mg/day. Subjects could continue in the long-term extension phase until study termination by the sponsor or until withdrawal.

Figure 1: Study Design for Study TOPMAT-EPMN-106



NOTE: Dose reductions were allowed for subjects who had difficulty reaching or maintaining their assigned dose or maximum tolerated dose. Following dose reduction during the stabilization period, topiramate dose was not to be increased again.

* The first clinic visit occurred up to 14 days prior to starting the open-treatment phase (between Days -21 and -8). At that time, inclusion/exclusion criteria were reviewed and screening procedures were performed.

** Subjects who experienced significant tolerability problems during the open-treatment phase were not eligible for randomization; subjects who experienced significant tolerability problems during the first 21 days of the double-blind phase were withdrawn from the study.

*** Subjects remained in the double-blind phase of the study until i) the subject experienced a first seizure (partial onset or generalized tonic-clonic seizure); ii) the double-blind phase completed; or iii) the subject withdrew from the trial for reasons prespecified in the protocol (adverse events, subject choice, and lost to follow-up).

\+ The double-blind phase was terminated by the sponsor 6 months after the last subject was randomized; enrollment into the study continued until 108 subjects experienced a first seizure.

= Subjects who experienced a first seizure during the double-blind phase, or who were active in the study at the time the double-blind phase completed, could enter the long-term extension phase.

KEY: AED = antiepileptic drug; MTD = maximum tolerated dose
Cross-reference: Appendix 1.1

5.5.4 Location

The study was conducted in US, Canada, Europe, and Latin America.

5.5.5 Duration

The sponsor terminated the double blind phase 6 months after the last subject was randomized. Enrollment continued in the study until a total of 108 subjects experienced a first seizure. **The range of duration subjects spent in the trial was 9 months to 2 years.**

5.5.6 Sample Size

Sample size calculation was based on the number of subjects with a failure event (first seizure). To achieve sufficient power to demonstrate a significant difference between the treatment groups, randomization of subjects meeting the entry criteria continued until 108 subjects experienced a first seizure (partial onset or generalized tonic-clonic) during the double-blind phase. The estimated sample size required to yield 108 first seizures was 500 to 560 subjects.

A total of 487 adults and children with a recent (within 3 months) diagnosis of epilepsy or with recurrent epilepsy while off of AEDs who experienced either 1 or 2 well-documented seizures during the 3-month retrospective baseline were enrolled in this trial. Subjects who experienced unacceptable tolerability problems while receiving topiramate 25 mg/day during the open treatment phase were not eligible for randomization.

5.5.7 Key Inclusion Criteria

- Body weight of at least 25 kg.
- A new diagnosis of epilepsy within 3 months prior to study entry, or a recurrence of epilepsy while off of AEDs, including 1 or 2 (but no more than 2) documented seizures within the 3 months before enrollment.
- History of partial-onset seizures, with or without a secondarily generalized component, and/or generalized seizures, including tonic-clonic, tonic, clonic, or juvenile myoclonic epilepsy with or without myoclonic seizures.
- Either no current AED use or treatment with 1 standard AED, to be completely discontinued by the time of randomization.
- A computed tomography (CT) scan or an magnetic resonance imaging (MRI) confirming the absence of a progressive cerebral lesion, e.g., tumor, with no significant physical or neurologic changes occurring after this procedure.

- If female, either i) incapable of bearing children or ii) practicing adequate birth control methods and having a negative pregnancy test within 2 weeks before trial entry.
- An electroencephalogram (EEG) performed within 3 months before enrollment.

The additional inclusion criteria incorporated according to local requirements in Norway included a change in the lower age limit for eligibility to at least 14 years of age. Additional requirements regarding the use of hormonal contraception were added in Italy (requesting use of preparations containing 50 mg of estrogen per tablet) and France (excluding hormonal contraception as a method of birth control). In France, additional restrictions included narrowing of the definitions of premenarchal and postmenopausal female subjects eligible for study entry; premenarchal patients who could reach puberty during the trial were not eligible for enrollment.

5.5.8 Key Exclusion Criteria

- Nonepileptic seizures, e.g., psychogenic seizures or a treatable cause of seizures (e.g., metabolic disturbance, toxic exposure, an active infection, or neoplasm).
- Any of the following seizure types: absence (petit mal) or atypical absence seizures by EEG criteria, epilepsia partialis continua, myoclonic seizures only, seizures in cluster patterns, or serial seizures.
- Progressive neurologic or degenerative disorder (e.g., inborn errors of metabolism).
- Significant history (within 2 years before screening evaluation) of an unstable medical disease that could impair reliable participation in the study or necessitate the use of medication not allowed by the protocol.
- History (within 6 months before screening) of psychiatric or mood disorder requiring electroconvulsive therapy, major tranquilizers, monoamine oxidase (MAO) inhibitors, or centrally acting sympathomimetics (e.g., dextroamphetamine, methylphenidate).
- History of drug allergy or hypersensitivity to carbonic anhydrase inhibitors or sulfonamides.
- Mental retardation or impairment that could confound interpretation of the study.
- History of alcohol or drug abuse within a year before screening.
- Treatment with benzodiazepines or barbiturates on more than an occasional basis, unless approved by the medical monitor.
- History (within past year) of suicide attempt.
- History of nephrolithiasis.
- Clinically significant laboratory abnormalities.
- Inability to take medication either independently or with assistance. If assistance was required for reliable compliance, this assistance was expected to be consistently available throughout the trial.
- History of poor compliance with past AED therapy, as judged by the investigator.
- Use of an experimental drug or experimental device within 30 days prior to the screening evaluation; previous participation in a topiramate study or previous treatment with topiramate.

5.5.9 Concomitant Medications

Ideally, no treatment other than study drug or medication expressly permitted by the protocol should have been used during the study. The baseline AED, if any, was to be tapered off by the time of randomization. It was also recommended that subjects taking benzodiazepines or barbiturates 3 days per month or more often be approved for study entry by the sponsor's medical monitor.

The medical monitor was to be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies were administered.

If a subject received medication for the treatment of an adverse event, the name of the drug was recorded on the "Adverse Events" page of the CRF. For subjects who experienced serious adverse events, the investigator recorded concomitant medications or therapies the subject was receiving at the time of onset of the serious adverse event. These records included the medication or therapy name, the total daily dosage and route of administration, and the indication for such use.

5.5.10 Dosage

The doses chosen to demonstrate a dose-response relationship were hypothesized to be a low, minimally efficacious dose (50 mg/day) versus a high, presumably fully efficacious and generally tolerable higher dose (400 mg/day). During the double-blind phase, subjects received study medication in a twice-daily dosage regimen.

During the titration period, each subject's dose was titrated to his or her assigned dose or maximum tolerated dose within 42 days, with dose increases occurring weekly (see Sponsor Table 4). Subjects randomized to topiramate 50 mg/day continued to receive 25 mg/day for 14 days. At the beginning of the third week, the dose of topiramate was increased by 25 mg/day to the target dose of 50 mg/day. Subjects randomized to topiramate 400 mg/day received a dose of 50 mg/day for 7 days. At the beginning of the second week, the dose was increased to 100 mg/day. The dose was subsequently increased by 50 mg/day for 2 weeks to a dose of 200 mg/day and then by 100 mg/day for 2 weeks until a target dose of 400 mg/day or the maximum tolerated dose was reached.

Table 4: Dose Titration Schedule
(Study TOPMAT-EPMN-106)

	Open-Treatment	Titration Period (Days)						Stabilization
Dose Group	Days -7 to -1	1 to 7	8 to 14	15 to 21	22 to 28	29 to 35	36 to 42	Period
50 mg/day	25	25	25	50	50	50	50	50
400 mg/day	25	50	100	150	200	300	400	400

NOTE: Topiramate dosages are provided in mg/day.

(Clinical Reviewer comment: This dosing regimen is faster than in currently approved labeling.)

If a subject experienced difficulty tolerating the study medication, the investigator assessed the need to reduce the dose. If a subject experienced unacceptable tolerability difficulties during the initial 21 days of the titration period, the subject was withdrawn from the study. If a subject experienced unacceptable tolerability problems after Day 21, the dose may have been reduced, if necessary. The dose of study medication was not to be increased after the reduction (i.e., no rechallenge was allowed). In subjects randomly assigned to topiramate 400 mg/day group, the daily dose could be decreased in 50 mg/day increments and could not be reduced any lower than the prior week's dose. Between Days 22 and 28, the dose of topiramate could be reduced only once; a maximum of 2 dose reductions, including the one occurring between Days 22 and 28, could occur between Days 22 and 42. After a dose reduction, the subject completed the current week's blistercard and then proceeded into the stabilization period.

Subjects were to remain on their assigned dose or maximum tolerated dose throughout the stabilization period, if possible. Subjects who had difficulty maintaining their assigned dose or maximum tolerated dose could have their dose reduced. The dose of study medication was not to be increased after the reduction during the stabilization period. Dose reductions for subjects randomized to the 400 mg/day target dose occurred in 50 mg/day increments; the dose could not be reduced any lower than the dose of the titration week prior to the titration blistercard used last. Dose reductions for subjects randomized to the 50 mg/day target dose were in increments of 25 mg/day, but the dose was not to be decreased to less than 25 mg/day.

Subjects who discontinued the study for any reason were to have their topiramate dosage tapered off over a period of up to 4 weeks.

5.5.11 Schedule

Sponsor Table 5, Time and Events Schedule is copied from the submission.

Table 5: Time and Events Schedule: Study TOPMAT-EPMN-106

Procedures	Baseline	Open Treatment[a]	Double-Blind									
			Titration[b]			Stabilization						
	Visit 1 Day -21 to -8	Visit 2 Day -7	Visit 3 Day 1	Visit 4 Day 8	Visit 5 Day 22	Visit 6 Day 43	Visit 7 Day 71	Visit 8 Day 127	Visits 9 to 13 Day 128 to end of DBP	Visits 14, 25 Tapering Visits	Visit 26 Final Visit	Visit 27 Final Follow-up[d]
Screening												
Seizure and medical history	X											
Urine pregnancy test[e]		X	X									
Inclusion/exclusion criteria	X	X	X									
Record AEDs[f]	X	X	X									
Informed consent	X											
Urine drug screen	X											
Efficacy Assessments												
Compile seizure data	X	X	X	X	X	X	X	X	X	X	X	
Safety Assessments												
Adverse events			X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests	X		X		X		X	X[i]	X		X	X
Serum pregnancy test[e]	X								X		X	
Vital signs	X										X	X
Body weight	X	X	X	X	X	X	X	X	X	X	X	X
Height	X								X		X	
EEG	X[g]											
Neurologic examination	X										X	
Visual field testing[h]	X										X	
Physical examination	X										X	X
Pharmacokinetic Assessments												
Plasma samples for TPM levels				X				X			X[j]	
Administrative Procedures												
Dispense seizure diary	X	X	X	X	X	X	X	X	X	X	X[j]	
Collect & count unused medication			X	X	X	X	X	X	X	X	X	
Dispense study medication		X	X	X	X	X	X	X	X	X	X[j]	

[a] Subjects received 7 (and up to 10) days of open-label treatment with topiramate 25 mg/day before randomization into the double-blind phase. Day 1 is the first day of the double-blind phase.
[b] Refers to the first 6 weeks of the double-blind phase during which the subject's topiramate dosage was incrementally increased to the assigned or maximum-tolerated dosage.
[c] Visits occurred quarterly after Day 127 through the end of the double-blind phase.
[d] Any abnormal parameters noted at the Final Visit were evaluated; persistent adverse events were followed until resolution.
[e] Subjects were instructed to taper AEDs on Visits 1 and 2, if applicable.
[f] Chemistry panel only.
[g] Unless performed within the past 3 months.
[h] Performed at selected sites only for subjects 12 years or older.
[i] Collected at Final Visit if this visit occurred earlier than Day 127.
[j] Seizure diary and study medication dispensed for subjects entering the long-term extension phase.
[k] To be performed on females of childbearing potential.

Screening procedures were performed 7 days (and up to 14 days) before the start of open treatment and included evaluation of inclusion/exclusion criteria, documentation of informed consent, seizure and medical histories, physical and neurologic examinations, vital signs, height, and body weight measurements, clinical laboratory tests, and a serum pregnancy test for women of childbearing potential. EEG was performed for subjects who did not have an EEG in the previous 3 months. Visual field testing was performed at pre-selected sites for a subset of subjects who were at least 12 years old.

The first day of the open-treatment phase, before study medication was dispensed, inclusion/exclusion criteria were reviewed, body weight was measured, urine pregnancy test was performed for women of childbearing potential, and subjects were given seizure diaries for recording the date, time, and type of each seizure.

Qualified subjects took topiramate 25 mg every evening for the 7 days of the open-treatment phase. At the end of this phase, subjects were randomly assigned to 1 of the topiramate dose groups (50 mg/day or 400 mg/day) for the double-blind phase of the study, which started on Day 1. Concomitant AEDs, if applicable, were to be tapered off prior to initiating double-blind topiramate treatment.

The first 6 weeks of the double-blind phase comprised the titration period, the purpose of which was to gradually increase the topiramate dosage to the subject's assigned or maximum tolerated dosage. After completion of the titration period (up to Day 42 or at the time of reaching the maximum tolerated dose), the stabilization period of the double-

blind phase began and continued until its completion 6 months after randomization of the last subject.

Clinic visits were scheduled for Days 1, 8, 22, 43, 71, and 127, and quarterly thereafter during the double-blind phase. Samples for clinical laboratory evaluation were collected on Days 1, 22, 71, 127, and quarterly thereafter. Blood samples for measuring concentrations of topiramate in plasma were collected on Day 8 and Day 127 or and at the final visit, whichever occurred first. At each study visit, the seizure diary data were compiled and adverse events were recorded. Evaluations performed at the last double-blind phase visit included physical examination, neurologic examination, vital signs, body weight and height measurements, drawing of blood samples for measurement of topiramate plasma concentration, clinical laboratory evaluations (including serum pregnancy test for women of childbearing potential), and adverse event monitoring. In addition, visual field testing was performed at pre-selected sites for a subset of subjects who were at least 12 years old. Reason: sponsor concerns for drug toxicity)

Subjects who experienced a first seizure during the double-blind phase (excluding the taper phase) or who were active in the double-blind phase when it ended were able to continue receiving topiramate in the long-term extension phase of the study. Subjects who withdrew from the trial, or who chose not to enter the long-term extension phase of the study, had their dose of topiramate gradually discontinued, with concomitant AED(s) added at the investigator's discretion. Subjects were able to continue in the long-term extension phase until withdrawal, until the clinical development for this indication was terminated, or until the sponsor terminated the study.

Tapering visits were scheduled for any subject who discontinued the study during any phase. It was recommended that study medication be tapered off over a period of up to 4 weeks. At each tapering visit, adverse events and seizure data were recorded, and body weight was measured. At all visits except the final visit, the seizure diary was dispensed.

5.5.12 Efficacy Analyses Planned

Efficacy was to be assessed based on the data from the intent-to-treat population, which comprised subjects who were randomized, entered the double-blind phase, and had at least 1 study visit after randomization. A survival analysis of the **primary efficacy variable**, **time to first seizure** (partial onset or generalized tonic-clonic) during the double-blind phase (excluding taper), was planned. Data for subjects who did not have seizures before the end of double-blind phase were censored. Kaplan-Meier estimates for the distribution curves of time of retention were to be obtained. Statistical significance of the treatment effect was to be tested by using the log-rank test. A 2-sided p value < 0.05 was to be considered statistically significant. In addition, 6-month seizure-free rates were to be analyzed. No interim analysis was to be performed. Cox proportional hazards model was to be used for assessment of the effect of covariates, including sex, age, geographic region, baseline weight, baseline AED use, baseline seizure type, and duration since first diagnosis of epilepsy. The final Cox model was to

include treatment and significant covariates. The risk ratios and the 95% confidence limits of risk ratios for the treatment and covariates were to be displayed.

5.5.13 Null hypothesis and sample size calculation

Per the sponsor, "the *null hypothesis* stated that the ratio of hazard rates for time to first seizure (topiramate 50 mg/day over topiramate 400 mg/day) equaled 1. The alternative hypothesis, against which the power was calculated, was based on the data from the previous monotherapy epilepsy trial of similar design, Study TOPMAT-EPMN-104. This hypothesis stated that the hazard ratio equaled 0.525 and was assumed to be constant over time."

Per the sponsor, "the *sample size calculation* was based on the method of Lachin and Foulkes. It was calculated that the number of failure events (first seizures) needed to achieve 92.2% power to detect, at the 5% (2-sided) significance level, a statistically significant difference in favor of topiramate 400 mg/day, was 108. Thus, it was planned in the original protocol to stop enrollment when 108 subjects experienced a first seizure. Calculation of the sample size was based on the fact that the power of log-rank test used in primary efficacy analysis is driven by the number of treatment failures. Originally, it was anticipated that 108 subjects would experience a first seizure by the time 330 subjects were enrolled. This estimate was based on a number of non-critical assumptions, namely:

- exponential distribution of failures, the percentages of seizure-free subjects at 16 months being 45% (high-dose group) and 30% (low-dose group);
- uniform subject entry into the study during accrual period; and
- exponential distribution of losses to follow-up with a non-treatment-related cumulative dropout rate of 15% in each dose group at 16 months.

Again per the sponsor, "for administrative reasons, the estimate of sample size required to yield 108 first seizures was updated during the course of the trial.[1]. The new estimate of the sample size (approximately 500 to 560 subjects) was based on the review of blinded seizure data, which indicated that the actual seizure rates in the randomized subjects were lower than expected at the time the study was designed.[2]

5.5.14 Safety Monitoring

Safety was evaluated on the basis of incidence, type and severity of treatment-emergent adverse events, changes in clinical laboratory tests, vital signs measurements, body

[1] Reviewer Comment: see Protocol Amendment 4 below, which discusses the issue of changes in sample size.

[2] Reviewer Comment: Division statisticians felt that the multiple protocol amendments may have indicated unblinding of the study at various times. Further data was requested from the sponsor regarding the originally planned 2 month and 4 month data.

weight, and physical examination findings in all subjects, as well as visual field examination results in subjects 12 years and older at selected sites. In addition, to determine the differential exposure between treatment groups and to assess compliance, plasma concentrations of topiramate were measured at the beginning of the second week of titration (Day 8) and on Day 127 (Visit 8 of the stabilization period) or at the final double-blind visit if it occurred earlier.

5.5.15 Adverse events

An adverse event was defined as any untoward medical occurrence, such as an intercurrent illness or injury that occurred during the study regardless of relationship to the study medication.

The date of onset and the outcome (resolved, persisted, or unknown) were recorded for each adverse event. The severity of the adverse event was classified as marked (substantial impact on the subject's daily life), moderate (noticeable impact on the subject's daily life), or mild (minimal interference with the subject's daily life). Any adverse events persisting at the end of the study were to be followed until resolution, or until reaching a clinically stable endpoint. The investigator evaluated the relationship of each adverse event to study drug as not related, doubtful, possible, probable, or very likely. All measures taken for adverse event management and follow-up results were recorded on the CRF and in the source document.

A *treatment-emergent adverse event* was defined as an adverse event that was new in onset or aggravated in severity or frequency after administration of study medication. Subjects and/or caregivers were encouraged to report treatment-emergent adverse events spontaneously or in response to nondirected questioning throughout the study. All treatment-emergent adverse events were completely described and recorded on the subject's source document and CRF.

A *serious adverse event* was defined as an adverse event that was fatal, immediately life-threatening (i.e., presented an immediate risk of death at the time of the adverse event, not an adverse event that hypothetically might have caused death if it were more severe), required or prolonged inpatient hospitalization, was permanently or significantly incapacitating, or was a congenital anomaly or birth defect. Investigators were instructed to immediately report all serious adverse events to the sponsor. Serious unexpected adverse events were to have been immediately reported to the IRB by the investigator and to the local regulatory agencies by the sponsor in accordance with local laws and regulations.

Treatment-limiting adverse events were defined as adverse events that resulted in the subject discontinuing study medication.

5.5.16 Clinical laboratory evaluation

Clinical laboratory evaluations were made at baseline, at randomization (Day 1), after 3 weeks of titration, twice during stabilization (Days 71 and 127), at quarterly visits thereafter during the double-blind phase of the trial, and at the final visit. Clinical laboratory tests were performed at (b) (4) and at (b) (4) . Clinical laboratory tests included the following:

- Hematology: hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC), WBC differential, and platelet count.
- Chemistry: alkaline phosphatase, alanine transaminase (ALT or SGPT), aspartate transaminase (AST or SGOT), total bilirubin, calcium, bicarbonate, chloride, creatinine, GGT, glucose, LDH, phosphorus, potassium, total protein, sodium, blood urea nitrogen (BUN), and uric acid.

A serum pregnancy test for all females of childbearing potential was performed at the time of screening. A urine pregnancy test was preformed prior to randomization, and on the day of randomization (at Visits 2 and 3). A serum pregnancy test was performed at each quarterly visit during the stabilization phase and at the final visit. Urine pregnancy tests, followed where necessary by serum pregnancy tests, could be performed at any time during the study at the investigator's discretion.

A urine drug screen was performed at the screening visit.

5.5.17 Vital signs and body weights

The subject's vital signs (sitting pulse and blood pressure) were measured at baseline and at the final visit of the double-blind phase. Body weight was measured at the baseline visit, at the open-treatment visit (Day –7), at each of the visits during the double-blind phase, at each of the taper visits, and at the final visit of the double-blind phase. Height was measured at the baseline visit, at the quarterly visits, and at the final visit of the double-blind phase.

5.5.18 Physical and neurologic examinations

Physical and neurologic examinations were performed at the baseline visit (Day –21 to –8) and at the final visit of the double-blind phase. Abnormalities that were noted after baseline were reported as adverse events.

5.5.19 Protocol Amendments.

The study conduct was initiated based on the original study protocol dated August 13, 1999. The protocol was subsequently amended 6 times; the amendments contained various updates and clarifications to the protocol, as well as modifications to the inclusion/exclusion criteria, study evaluations, including additional laboratory tests, and statistical analysis. The key changes in study design and conduct were as follows.

- Protocol Amendment 1, dated January 21, 2000, contained the modified definition of the first seizure as only partial-onset or generalized tonic-clonic seizure and a modified procedure for dose reductions during double-blind phase that excluded the possibility of rechallenge (i.e., of upward titration following dose reduction). Entry criteria were modified so as to i) clarify that the diagnosis of epilepsy (to partial onset or generalized tonic clonic seizure) , as well as the seizures leading to that diagnosis, were to have occurred during the 3-month retrospective period, ii) exclude subjects with only myoclonic seizures, (The substitution changed the inclusion criteria from "and myoclonic seizures" to "with and without myoclonic seizures") and iii) removed clinically significant electrocardiographic abnormalities from the list of exclusion criteria. The purpose of the physical examinations and vital signs measurements at the final follow-up visit was clarified to indicate that they were intended only to follow up previously noted abnormalities. It was also clarified that visual field testing was to be performed only in subjects 12 years of age and older. At the time this amendment went into effect, 33 subjects were enrolled in the study. No patient with myoclonic seizures were included.

- Protocol Amendment 2, dated March 13, 2000, contained clarifications to the entry criteria such that prior use of an AED must have occurred only for emergency or temporary use, and that subjects who had uncontrolled epilepsy while taking AEDs were not eligible for enrollment. (Clinical Reviewer comment: these were clarifications to investigators regarding the study design.) It was also clarified that sample size calculation was based on the number of subjects with a failure event (108 subjects with a first seizure) needed to achieve sufficient power to demonstrate a significant difference between the treatment groups, and that randomization was to stop when 108 subjects experienced first seizures. The following laboratory tests were added to the chemistry panel: gamma glutamyl transferase (GGT), lactic dehydrogenase (LDH), phosphorus, and uric acid. At the time this amendment went into effect, 63 subjects were enrolled in the study.

- Protocol Amendment 3, dated 19 October 2000, increased the duration of the double-blind phase from 2 months to 4 months after the randomization of the last subject. At the time this amendment went into effect, 263 subjects were enrolled in the study.

- Protocol Amendment 4, dated 03 May 2001, changed the estimated sample size from approximately 330 to approximately 500 to 560. This estimate of the sample size required to yield 108 first seizures was updated for administrative reasons, based on the review of blinded seizure data showing that more subjects would have to be enrolled until 108 first seizures have occurred. At the time this amendment went into effect, 430 subjects were enrolled in the study.

- Protocol Amendment 5, dated 05 September 2001, increased the duration of the double-blind phase from 4 months to 6 months after the randomization of the last subject. This was motivated, in part, by the new European Union guidance document for AED trials. Analysis of the 6-month seizure-free rate was added to the statistical

analysis plan. In addition, quarterly visits for clinical laboratory tests (liver function tests) and serum pregnancy tests were added to the protocol at the request of the Division. At the time this amendment went into effect, all 487 subjects were enrolled in the study.

- Finally, Protocol Amendment 6, dated 04 October 2001, modified study evaluations by adding a chemistry panel at the third visit of the stabilization phase (Visit 8).

6. Sponsors Study and Efficacy Results

6.1 Study 106 - Pivotal Study

- Of a total of 487 subjects enrolled, 16 withdrew leaving 471 subjects. Of these, 470 were included in the intent to treat analysis. 1 was lost to follow up.

The demographic and baseline characteristics for the subjects in Study 106 are as follows. Of the 470 subjects in the intent-to-treat population, 233 (50%) were men, and 413 (88%) were white. The median age was 22 years (range, 6 to 83 years); 151 subjects (32%) were 15 years of age or younger (including 14 subjects (3%) who were 7 years of age or younger); 25 subjects (5%) were 65 years or older. The median weight was 64.0 kg (range, 22.3 to 154.5 kg); 192 subjects (41%) had a body weight not exceeding 60 kg, and 96 subjects (20%) weighed more than 85 kg. The treatment groups were well matched with regard to sex, race, age, body weight, and height. This is illustrated in Sponsor Table 9a reproduced below.

Table 9a: Demographic and Baseline Characteristics:
Sex, Race, Age, Weight and Height
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

	TPM 50 (N=234)		TPM 400 (N=236)		Total (N=470)	
Sex: n, %						
Male	110	47	123	52	233	50
Female	124	53	113	48	237	50
Race: n, %						
White	203	87	210	89	413	88
Black	13	6	15	6	28	6
Asian	2	1	1	<1	3	1
Other[a]	16	7	10	4	26	6
Age (years): n, %						
≤7	8	3	6	3	14	3
8-11	24	10	31	13	55	12
12-15	42	18	40	17	82	17
16-24	61	26	44	19	105	22
25-34	35	15	41	17	76	16
35-44	27	12	34	14	61	13
45-64	22	9	30	13	52	11
≥65	15	6	10	4	25	5
N	234		236		470	
Mean	27.3		27.9		27.6	
SD	17.79		17.19		17.48	
Median	21.0		24.0		22.0	
Range	6.0 - 83.0		6.0 - 78.0		6.0 - 83.0	
Weight (kg): n, %						
<60	89	38	103	44	192	41
≥60 - ≤85	96	41	86	36	182	39
>85	49	21	47	20	96	20
N	234		236		470	
Mean	67.3		65.2		66.2	
SD	24.31		22.90		23.61	
Median	65.0		62.0		64.0	
Range	22.3 - 154.5		25.0 - 142.7		22.3 – 154.5	
Height (cm)						
N	234		235		469	
Mean	163.4		161.7		162.6	
SD	15.71		15.04		15.39	
Median	167.0		163.0		165.1	
Range	115.0 - 195.6		115.0 - 188.0		115.0 – 195.6	

[a] "Other" included Hispanic, Hispanic/Caucasian, and East Indian.

Both treatment groups were well balanced with respect to all background disease characteristics, i.e., duration of epilepsy, distribution of seizure counts and types during the 3-month retrospective baseline phase, and number and type of AEDs used before randomization.

All subjects in the intent-to-treat population had experienced either 1 or 2 seizures during the 3-month retrospective baseline phase, as specified in the protocol. The majority of subjects (63%) had only 1 seizure (Table 9b below). One or 2 partial onset seizures were reported for 56% of the subjects, compared to 42% subjects with either 1 or 2 generalized seizures. Only 2% of all subjects experienced 2 seizures of different types. The distribution of seizure types and seizure counts was very similar for the 2 topiramate dose groups.

Approximately one-half of the subjects in the intent-to-treat population (53% in TPM 50 group and 50% in TPM 400 group) used an AED before enrollment. The types of AEDs used before randomization were comparable between the 2 treatment groups. AEDs used before randomization by more than 5% of subjects in the intent-to-treat population were phenytoin (20%), valproic acid (10%), and carbamazepine (7%). Twelve subjects (6 subjects in each of the treatment groups) used more than 1 AED before randomization.

Table 9b: Demographic and Baseline Characteristics:
Duration of Epilepsy, Baseline Seizure Counts and AED Use Before Randomization
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

	TPM 50 (N=234)		TPM 400 (N=236)		Total (N=470)	
Time Since Diagnosis (mos.)						
N	233		236		469	
Mean	19.3		27.0		23.2	
SD	56.27		72.21		64.83	
Median	1.0		1.0		1.0	
Range	0.0 - 408.0		0.0 - 456.0		0.0 - 456.0	
Seizure Count during 3-month Baseline[c]: n,%						
1 Partial Onset[a]	81	35	78	33	159	34
1 Generalized[b]	67	29	69	29	136	29
2 Partial Onset[a]	45	19	58	25	103	22
2 Generalized[b]	34	15	29	12	63	13
1 Partial Onset[a] + 1 Generalized[b]	7	3	2	1	9	2
Number of AEDs Used Before Randomization: n,%						
0	109	47	119	50	228	49
1	118	50	111	47	229	49
≥2[e,f]	7[f]	3	6	3	13[f]	3
Most Common[d] AEDs Before Randomization: n,%						
Phenytoin	50	21	44	19	94	20
Valproic acid	21	9	28	12	49	10
Carbamazepine	16	7	17	7	33	7
Phenobarbital	9	4	8	3	17	4
Clonazepam	6	3	9	4	15	3
Clobazam	7	3	6	3	13	3
Lamotrigine[g]	6	3	4	2	10	2
Oxcarbazepine[g]	7	3	3	1	10	2
Other antiepileptics[h]	4	2	0		4	1

[a] Includes simple partial, complex partial and partial evolving into secondarily generalized seizures.
[b] Includes generalized tonic-clonic, tonic, and clonic seizures.
[c] Seizures experienced by the subjects during the 3-month retrospective baseline phase of the study.
[d] AEDs used by at least 1% of the subjects in either treatment group. AEDs used by less than 1% of the subjects included fosphenytoin, gabapentin, lorazepam, Comital-L (a combination of phenobarbital, phenytoin, and mephobarbital), and fluoride.
[e] Twelve subjects used more than 1 AED before randomization. Of these, only 1 subject (Subject 534001) used 3 AEDs; another subject, Subject 554003, used both AEDs concomitantly for 3 days; both cases are described in Section 4.4, Protocol Deviations. The remaining 10 subjects used their 2 AEDs sequentially, not concomitantly, and 1 of the 2 AEDs was used only for short-term treatment.
[f] In case of Subject 550001 in TPM 50 group, who received only 1 AED (fosphenytoin) at baseline, topiramate was also coded in error as a baseline AED, bringing the number of subjects using 2 or more AEDs in that group to 7 (Attachment 3.2).
[g] In 9 subjects receiving Trileptal (oxcarbazepine) at baseline, it was coded in error as lamotrigine. An erratum to that effect has been added to the clinical database.
[h] Levetiracetam (3 subjects) and valproate (1 subject).

Dosage reductions or temporary interruptions of study medication due to adverse events occurred in 56 subjects (24%) in the TPM 400 group and 20 subjects (9%) in TPM 50 group. Thus, the mean (SD) average daily dosages in each of the treatment groups were lower than the assigned dosages, namely, 42.5 (8.95) mg/day in the TPM 50 group and 275.3 (120.97) mg/day in the TPM 400 treatment group. Similarly, the mean (SD) final daily dosages were 42.8 (14.07) mg/day for subjects assigned to receive TPM 50 and 309.4 (128.90) mg/day for those randomized to TPM 400. This is summarized in Sponsor Table 11.

Table 11: Daily Dosage of Topiramate
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

	TPM 50 (N=234)	TPM 400 (N=236)
Average Daily Dose (mg/day)		
Mean	42.5	275.3
SD	8.95	120.97
Median	47.5	335.3
Range	17.0 - 61.7	27.4 - 399.1
Maximum Daily Dose (mg/day)		
Mean	48.5	339.7
SD	9.43	121.42
Median	50.0	400.0
Range	25.0 - 100.0	50.0 - 800.0
Final Daily Dose (mg/day)		
Mean	42.8	309.4
SD	14.07	128.90
Median	50.0	400.0
Range	0.0 - 50.0	0.0 - 450.0

Cross-reference: Attachment 4.1.1

A total of 217 subjects (46% of the intent-to-treat population) completed the double-blind phase of the study at the time of its termination. The cumulative distribution of subjects by duration of therapy in the range from at least 1 day to more than 630. The median duration of exposure for all subjects in the intent-to-treat population was approximately 9 months (266 days; range, 9 to 786 days).

Of the 470 subjects in the intent-to-treat population, 294 (63%) received the double-blind study medication for at least 6 months, and approximately one-third (166 subjects; 35%) were treated for at least 360 days. Treatment durations are summarized in sponsor Table 12 below

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Table 12: Cumulative Distribution of Subjects by Duration of Therapy
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

Duration of Therapy	TPM 50		TPM 400		Total	
(Days)	N	%	n	%	N	%
≥ 1	234	100	236	100	470	100
≥ 15	225	96	224	95	449	96
≥ 30	204	87	203	86	407	87
≥ 90	159	68	171	72	330	70
≥180	145	62	149	63	294	63
≥270	115	49	117	50	232	49
≥360	79	34	87	37	166	35
≥450	58	25	67	28	125	27
≥540	33	14	33	14	66	14
> 630	13	6	13	6	26	6
N	234		236		470	
Mean	276.0		287.4		281.7	
SD	208.92		214.87		211.78	
Median	266.0		266.5		266.0	
Range	9 – 763		9 - 786		9 - 786	

Cross-reference: Attachment 4.2

Study completion/discontinuation information is reproduces as follows.

Table 8: Study Completion/Discontinuation Information
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

	TPM 50 (N=234)		TPM 400 (N =236)		Total (N=470)	
Completion Status	n	%	n	%	n	%
Completed	**195**	**83**	**161**	**68**	**356**	**76**
Completed at DB phase termination[a]	105	45	112	47	217	46
Completed by having a seizure	90	38	49	21	139	30
Withdrew	**39**	**17**	**75**	**32**	**114**	**24**
Adverse event	13	6	40	17	53	11
Subject choice	9	4	13	6	22	5
Lost to follow-up	9	4	10	4	19	4
Other	8	3	12	5	20	4

[a] Subjects who were active in the study at the time of termination of the double-blind (DB) phase, i.e., 6 months after randomization of the last subject.

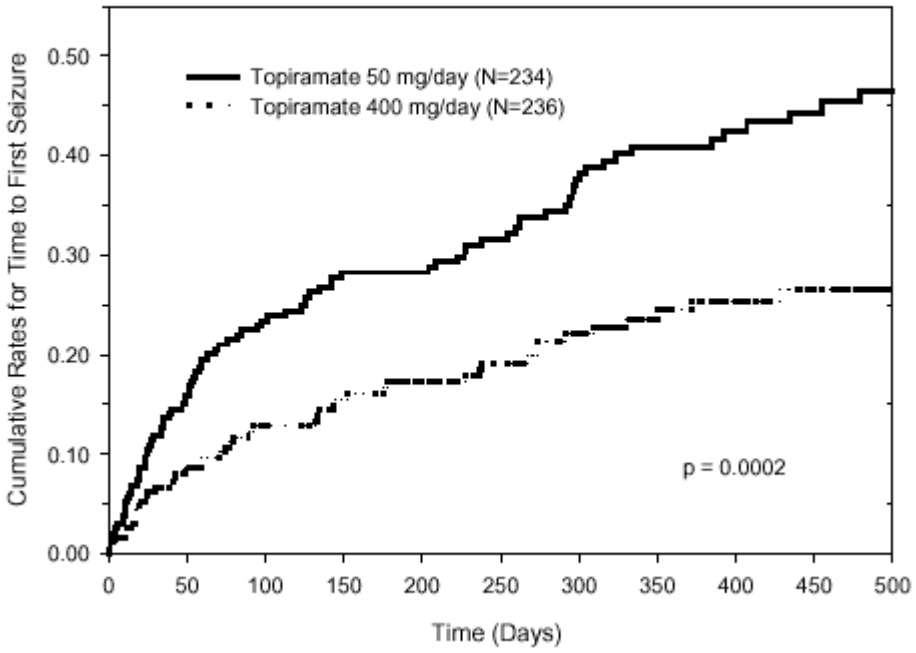
6.1.1 Sponsor's Efficacy Results for Study 106

- **The primary efficacy endpoint, comparison of the Kaplan-Meier survival curves of time to first seizure, favored topiramate 400 mg/day over topiramate 50 mg/day (p=0.0002; 2-sided log-rank test).**

- The separation between the groups in favor of the higher dose group occurred early in the titration phase and was statistically significant as early as 2 weeks post randomization (p = 0.046; 2-sided log-rank test), when, by following the weekly

titration schedule, the subjects in the higher dose group achieved the maximum topiramate dose of 100 mg/day.

Figure 3: Plot of Kaplan-Meier Estimates of Cumulative Rates for Time to First Seizure (Intent-to-Treat Population; Study TOPMAT-EPMN-106)



- The separation between the groups continued to increase for the duration of the double-blind phase; between-group comparisons using truncation of the follow-up duration on Day 14 favored topiramate 100 mg/day over topiramate 25 mg/day (p = 0.046; 2-sided log-rank test); on Day 21 (at the end of the third week, when the dose was titrated upwards in both groups), this comparison showed a trend for significance (p = 0.071; 2-sided log-rank test) in favor of topiramate 150 mg/day vs. topiramate 50 mg/day. Between-group pointwise comparisons were significant at all other time points examined for the remainder of the study.

- The higher dose group was superior to the lower dose group with respect to the estimated proportion of subjects who remained seizure-free for a minimum of 6 months of therapy (82.9% vs. 71.4%; p = 0.005, t-test), and for a minimum of 1 year of therapy (75.7% vs. 58.8%, p = 0.001, t-test).

Table 13: Kaplan-Meier Estimates of Cumulative Rates for Time to First Seizure (Intent-to-Treat Population; Study TOPMAT-EPMN-106)

	TPM 50 (N=234)		TPM 400 (N=236)		
Study Day	n	Estimate, %	n	Estimate, %	p value[a]
14	214	6.5	218	2.6	0.046
21	206	9.1	207	4.8	0.071
28	196	11.8	200	6.2	0.039
42	187	15.0	190	7.7	0.015
56	178	18.6	182	8.6	0.003
90	162	22.8	170	11.7	0.002
112	159	24.2	166	12.8	0.002
180	145	28.6	148	17.1	0.003
270	112	34.2	113	19.8	0.001
365	77	41.2	84	24.3	<0.001
455	53	44.6	62	26.3	<0.001

[a] p value for the difference between treatment groups at each time point, obtained using a log-rank test for Kaplan-Meier curves from each of the data sets that were truncated at these time points.

Covariate analysis

Based on the Cox proportional hazards model, the treatment effects with respect to time to first seizure were also consistent across the subgroups. Supportive of the subgroup analyses, adjustment of the model for each of the covariates (age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use) did not affect the comparison between topiramate dose groups. This is illustrated in Sponsor Table 15 reproduced below. The estimated hazard ratio of 0.525 was used in calculating the sample size. The upper bounds of the 95% confidence intervals for the ratio of hazard rates were below 1 relating that topiramate 400mg was superior to topiramate 50mg

Table 15: Cox Proportional Hazards Model for Time to First Seizure (Study TOPMAT-EPMN-106; Intent-to-Treat Population)

Covariates Included in the Model	p value for the Treatment-by-Covariate Interaction	Estimated Ratio of Hazard Rates[a]	95% Confidence Interval[b]
No Covariate	N/A	0.516	(0.364, 0.733)
Covariates[c]			
Sex	0.196	0.524	(0.369, 0.746)
Age	0.490	0.523	(0.369, 0.743)
Region	0.960	0.520	(0.367, 0.739)
Baseline weight	0.659	0.517	(0.364, 0.735)
Baseline seizure type	0.514	0.515	(0.362, 0.730)
Baseline AED use	0.979	0.521	(0.367, 0.739)
Time since the diagnosis of epilepsy	0.466	0.520	(0.366, 0.739)

[a] The ratio of estimated rates for time to first seizure in the TPM 50 mg/day group to the corresponding rates in TPM 400 mg/day group.
[b] Confidence interval for the estimated ratio of hazard rates with adjustment for the covariate.
[c] The covariates were grouped as follows: sex, male/female; age, 6-15, 16-44, >45 years; baseline weight, <60, 60-≤85, >85 kg; baseline seizure type, at least 1 POS seizure/GTC only; baseline AED use, yes/no; geographic region, North America/South America/others; time since the diagnosis of epilepsy, <=24 months/>24 months.

- Kaplan Meier survival curves for the subgroups are reproduced in Appendix 1 Section 12 at the end of this report.

- The higher dose group was superior to the lower dose group with respect to the estimated proportion of subjects who remained seizure-free for a minimum of 6 months of therapy (82.9% vs. 71.4%; p = 0.005, t-test), and for a minimum of 1 year of therapy (75.7% vs. 58.8%, p = 0.001, t-test). This is summarized in Sponsor Table 14.

Table 14: Differences Between Topiramate 50 mg/day and Topiramate 400 mg in Kaplan-Meier Estimates of Seizure-Free Rates (Intent-to-Treat Population; Study TOPMAT-EPMN-106)

Study Day	TPM 50 (N=234)		TPM 400 (N=236)			
	n[a]	Estimate[b]	n[a]	Estimate[b]	Difference[c]	p valu
180	145	0.714	148	0.829	-0.114	0.005
365	77	0.588	84	0.757	-0.168	0.001

[a] The number of subjects left in the study after the day indicated.
[b] The percentage of subjects who would be seizure free by the day indicated.
[c] Between-group difference in seizure-free rates on the day indicated (TPM 50 minus TPM

- The efficacy of topiramate monotherapy was examined as a function of plasma topiramate concentration data obtained on or after Day 36, at the time when subjects in the higher dose group have reached their target dose of topiramate. There was a statistically significant difference (log-rank test; p=0.029) among the 3 plasma topiramate concentration strata (<2 µg/mL, 2 to <10 µg/mL, and =10 µg/mL) in favor of the higher concentration strata with regard to the time to first seizure.

Overall, Study 106 demonstrated that monotherapy with topiramate 400mg was superior to topiramate 50mg with respect to efficacy in preventing the occurrence of seizures among adults and children (6 years of age and older with newly diagnosed or recurrent epilepsy.

6.2 Study YI – Supportive Study

48 subjects entered the double blind phase of the trial and were included in the efficacy analysis. 24 subjects received 100 mg/day topiramate and 24 received 1,000 mg/day topiramate. In the topiramate 1,000 mg/day dosage group, 13 (54%) of 24 subjects were successes (completed the double blind phase without meeting any exit criteria) compared with four (17%) of 24 subjects in the 100 mg/day dosage group (p=0.002).

The primary efficacy endpoint, time to exit, was statistically significantly greater for the topiramate 1,000 mg/day dosage group compared with the topiramate 100 mg/day dosage group (p=0.002).

When dropouts were excluded from the analysis, the proportion of subjects meeting an exit criterion was statistically significantly less (Fisher's exact test; p=0.005) in the 1,000 mg/day group (9/22 = 41%) than in the 100 mg/day group (20/24 = 83%). For a "worst case" analysis counting the two topiramate 1,000 mg/day group subjects who withdrew from double-blind therapy (no patients withdrew from the 100mg/day group) as having exited (failures), the difference between the dosage groups remains statistically significant (Fisher's exact test; p=0.015).

Among subjects who successfully completed double-blind therapy, a **reduction in seizure rate of 50% or greater from baseline** to the end of double-blind therapy was observed for 11 subjects in the 1,000 mg/day group (46%) compared to three subjects in the 100 mg/day group (13%). Among subjects in the 1,000 mg/day dosage group, six (25%) had a reduction of 75% or greater and three were seizure free during the entire double-blind phase.

Overall result from Study YI indicated that topiramate monotherapy at 1000mg daily was statistically superior to 100mg and was effective in the treatment of refractory partial epilepsy with or without secondarily generalized seizures.

6.3 Study 104 – Supportive Study

252 patients were randomized and received double blind topiramate treatment, 127 in the high dose group and 125 in the high dose group. Study results are listed in the following table relating to the primary efficacy variable, time to exit.

Table 9: Number of Subjects Meeting Exit Criteria
(Intent-to-Treat Population; Protocol TOPMAT-EPMN-104)

		Low-dose TPM 25 or 50 mg/day (N=125)		High-dose TPM 200 or 500 mg/day (N=127)	
Exit Criterion[a]		No.	%	No.	%
1	2 partial onset seizures, with or without a secondarily generalized component	53	42	49	39
2	a single generalized seizure if none occurred before randomization	4	3	1	1
3	a single episode status epilepticus	0	0	2	2
Total Exiting		57	46	52	41
	Number exiting after one seizure	3	2	1	1
	Number exiting after two seizures	54[b]	43	51[b]	40
Total Completing without Exiting		42	34	41	32
Total Dropouts		26	21	34	27

[a] Subjects could reach multiple exit criteria on the same day.
[b] One subject in the low-dose topiramate group and two in the high-dose topiramate group had a first seizure prior to the generalized seizure or status epilepticus episode that caused the exit.

Forty-one subjects (32%) of the 127 subjects in the high dose group and 42 (34%) of the 125 subjects in the low dose group completed the study without exiting.

Primary efficacy endpoint - The difference in the time to first seizure between the two treatment groups approached statistical significance (p=0.062). However, the study failed to demonstrate a difference between the dosage groups with respect to the pre-specified primary endpoint, time to exit which was, essentially, equivalent to the time to second seizure, (log-rank test; p=0.781).

Significant differences in favor of the high dose were reported with respect to seizure frequency and to the proportion of subjects who were seizure-free during the double-blind phase. The median time to first seizure during the double blind treatment was 317 days in the high dose group compared to 108 days in the low dose group. The median time to second seizure was also greater in the high dose group versus the low dose group (422 days versus 293 days), but the univariate statistical comparison was not statistically significant (log-rank test; p=0.781). A bivariate analysis was performed that took into consideration all efficacy data in comparing the two topiramate dosage groups. Results of this analysis indicated a statistically significant difference in the occurrence of seizures during the double-blind phase in favor of the high dose group (p=0.010).

Covariate analyses were performed with regards to treatment and age, baseline AED use, study center region, generalized tonic clonic seizures at baseline, and time since diagnosis of epilepsy. All yielded statistically significant differences in favor or the high dose topiramate group. Analyses indicated that efficacy of topiramate monotherapy at a dose of 200 to 500mg/day was enhanced among subjects with newer onset seizures (diagnosis within 6 months before study entry) or milder disease (those reporting one or two partial onset seizures at baseline compared to those reporting three or more and among subjects not receiving AED therapy during the baseline phase vs. those receiving a background AED.

There was a statistically significant difference (log rank test p=0.015) in the time to first seizure across three plasma topiramate concentration strata.

Overall conclusions from Study 104 demonstrated the efficacy of topiramate monotherapy at a dose of 200 or 500mg/day in adults and children with recently diagnosed partial onset seizures with or without secondary generalized seizures. The study failed to demonstrate a difference between dosing groups regarding time to second seizure, and approached statistical significance regarding time to first seizure.

6.4 Study 105 – Supportive Study

Of the 621 subjects randomly assigned to one of the treatment groups, 613 (98.7%) received the study medication and provided efficacy information during the double-blind phase; these subjects were included in the intent-to-treat population. Of these, the 390 subjects in the carbamazepine branch received topiramate 100 mg/day (136 subjects), topiramate 200 mg/day (128 subjects), or carbamazepine (126 subjects); the 223 subjects in the valproate branch were treated with topiramate 100 mg/day (74 subjects),

topiramate 200 mg/day (71 subjects), or valproate (78 subjects). Subject completion and withdrawal information are summarized in the following sponsor table:

Table 9: Study Completion and Withdrawal Information
(Study TOPMAT-EPMN-105: Intent-to-Treat Population)

	CBZ Branch						VPA Branch						Total	
	TPM 100 (N=136)		TPM 200 (N=128)		CBZ (N=126)		TPM 100 (N= 74)		TPM 200 (N= 71)		VPA (N= 78)		(N=613)	
Completion Status	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Did Not Exit	**74**	**54**	**74**	**58**	**70**	**56**	**45**	**61**	**30**	**42**	**35**	**45**	**328**	**54**
Completed[a]	64	47	66	52	63	50	41	55	21	30	30	38	285	46
Withdrawn[b]	10	7	8	6	7	6	4	5	9	13	5	6	43	7
Exited per protocol	**62**	**46**	**54**	**42**	**56**	**44**	**29**	**39**	**41**	**58**	**43**	**55**	**285**	**46**
Adverse Event	27	20	31	24	32	25	13	18	24	34	18	23	145	24
Ineffective Treatment	18	13	13	10	10	8	5	7	5	7	9	12	60	10
Subject Choice	10	7	6	5	7	6	8	11	10	14	9	12	50	8
Lost To Follow-Up	6	4	3	2	7	6	2	3	2	3	6	8	26	4
Other	1	1	1	1	0	-	1	1	0	-	1	1	4	1

[a] Completed at the time of the planned study termination (six months after the last subject was randomized).
[b] Withdrawn for protocol violations.

The percentage of subjects who exited the study was highest in the valproate group. The percentage of subjects who experienced treatment limiting adverse events was lowest in the topiramate 100 group.

Regarding the primary efficacy analysis, the difference between topiramate 100 mg/day and topiramate 200 mg/day in time to first seizure from Day 15 was not statistically significant (log-rank test stratified by branch; p=0.171). In the carbamazepine branch, the median time to the first seizure from Day 15 was longer among the subjects treated with topiramate 200 mg/day (323 days) than among those treated with topiramate 100 mg/day (225 days). In the valproate branch, the median time to the first seizure from Day 15 was shorter in the topiramate 200 mg/day group (179 days) than in the topiramate 100 mg/day group (373 days).

The log rank test stratified by branch did not detect a difference between topiramate treatment and standard treatment with respect to time to exit. (p=0.532).

Based on 95% confidence intervals, topiramate monotherapy was shown to be at least as effective as the physician's preferred AEDs in reducing seizures. This is illustrated in sponsor table 13 below.

Table 13: Differences Between Topiramate Treatment and Standard Treatment in Kaplan-Meier Estimates of Cumulative Rates[a] for Time to Exit (Study TOPMAT-EPMN-105: Intent-to-Treat Population)

Study Day	CBZ Branch		VPA Branch		P-value for Homogeneity	Overall[c]		95% Confidence Interval[c]
	N	Difference[b]	N	Difference[b]		N	Difference[b]	
90	290	-0.031	164	-0.030	0.987	454	-0.031	(-0.103, 0.042)
180	243	-0.016	140	-0.035	0.825	383	-0.024	(-0.104, 0.057)
270	171	0.010	105	-0.043	0.551	276	-0.010	(-0.095, 0.076)
365	113	-0.012	71	-0.061	0.612	184	-0.030	(-0.121, 0.061)

[a] The percentage of subjects who would exit by the day indicated.
[b] Difference of cumulative rates of time to exit (TPM 100/200 minus CBZ/VPA).
[c] For the overall difference in cumulative rates (pooling the two branches).

Topiramate treatment and standard treatment were similar with respect to all endpoints, i.e., time to exit, remission of seizures during the last 6 months of the double-blind phase, and time to first seizure. Treatment effects were consistent with respect to the primary efficacy or clinical utility endpoints across all subgroups including treatment and sex, age, baseline seizure count, and baseline AED use.

Overall, Study 105 demonstrated that topiramate, administered as monotherapy at the doses of 100 or 200mg/day was efficacious in the treatment of adults and children with newly diagnosed epilepsy. The global clinical utility and efficacy of topiramate were at least as good as those of the physician's treatment of choice in a broad range of epilepsy syndromes.

7. Reviewer's Analysis of Efficacy

The sponsor utilized a single trial (Study 106) and three supportive trials (Studies YI, 104 and 105) to gain approval for topiramate for monotherapy in epilepsy. Initially, the sponsor showed compelling data in Study 106 that on face value related statistical significance in separation of Kaplan Meier curves when comparing cumulative rates for time to first seizure between the low dose (50mg) and the high dose (400mg) groups.

This is illustrated in the flow chart provided earlier in the review of Study 106, the pivotal study. For brevity, this is summarized in the following chart:

	TPM 50	TPM 400
Intent to treat (N)	234	236
Withdrawals	39 (17%)	75 (32%)
Adverse event	13(6%)	40 (17%)
Subject choice	9(4%)	13 (6%)
Lost to follow up	9(4%)	10 (4%)
Other	8(3%)	12(5%)
Completed DB phase	195 (83% of ITT)	161 (68% of ITT)
Experienced 1st Seizure	90 (38% of ITT, 46% of	49 (21% of ITT, 30% of

(failures)	completers)	completers)
Completed at Termination	105(45% of ITT, 54% of completers	112 (47% of ITT, 70% of completers)

The problem with the sponsor's analysis is that the number of dropouts in the higher dose group for adverse events were much greater compared to the lower dose group. Dropouts due to adverse events were almost three times higher in the TPM 400 group compared to the TPM 50 group. We assume that an increased adverse event profile of the higher dose group led to fewer seizure events in the remaining population.

According to Division statisticians, if all withdrawals were considered treatment failures, regardless of the reason they withdrew, then in an all cause analysis (worst case analysis) adding back the withdrawals (as additional failures) to those who experienced first seizures (failures) raises the number of total failures as follows:

	TPM 50 (ITT=234)	TPM 400 (ITT=236)
Withdrawals	39	75
Failures	90	49
Totals	129	124
% of ITT	55%	52.5%

The all cause analysis shows no significant difference between the two treatment groups. (log-rank test, p=0.57)

7.1 Teleconference June 18, 2003

The Division had a teleconference with the sponsor on June 18, 2003 due to statistician concerns regarding the all cause analysis as it related to the lack of a statistical significant difference between the high and low dose groups. Particularly, the Division expressed concern that the overall dropout rate and large differential in dropouts due to adverse events between the topiramate 400mg/day group and the topiramate 50mg/day group may have introduced bias making the efficacy results difficult to interpret. The Division also questioned the interpretation of the log-rank test for time to first seizure given the amount of missing seizure event data from the subjects who withdrew.

Records in the Division, (as previously described above in Section 3, Regulatory History), included a "Memorandum of Understanding from Sponsor to Division"(dated April 14, 2000 and relating to a February 23, 2000 teleconference) noting that there might be a potential problem with a high number of dropouts. RWJPRI noted in response to Division concerns at that time, "…we do not foresee this as being an issue. Based on the results of previously conducted monotherapy trials, we do not expect to see a high number of dropouts."

RWJPRI sent a response dated July 31, 2003 attending to the teleconference and the major problem with efficacy. Division statistician, Kun He, related that the submitted response was not acceptable. He felt strongly that the sponsor was "computer modeling" the data to make it fit the necessary conclusion rather than relying on the actual data from the clinical trials. This reviewer agrees with that assessment and offers the following as a discussion. The next section contains a summary of the sponsor's response followed by a review of that response.

7.2 Sponsors submitted "Discussion and Conclusions" related to efficacy questions

The following is reproduced from the Sponsor's submission dated July 31, 2003.

A fundamental issue inherent to clinical trials is potential bias because of missing data due to withdrawals. This issue has been examined in detail for Study TOPMAT-EPMN-106 by addressing 3 key topics:

1) Study population:

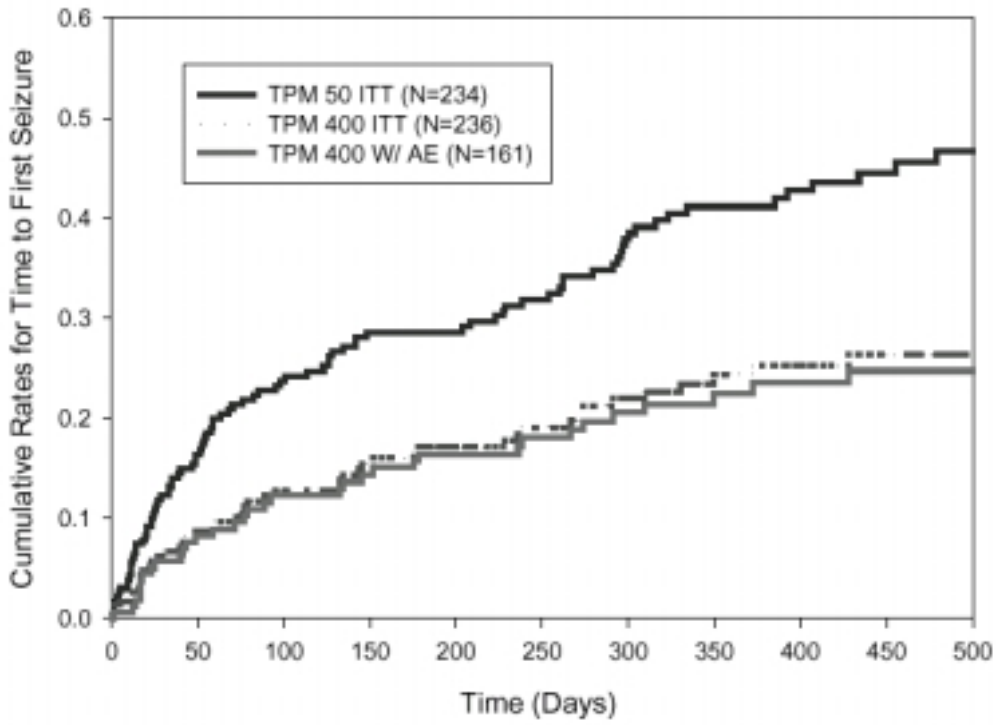
The population recruited for Study TOPMAT-EPMN-106 fulfilled the goals to homogenize the population, to study subjects with more reliably measured seizure events and to study subjects with infrequent seizures that were likely to respond to therapy.

2) Withdrawal population and potential impact on introduction of bias:

Cumulative rates of withdrawal in Study TOPMAT-EPMN-106 were not excessively high considering the prolonged duration of the study compared to prior epilepsy studies. The key factor in producing a differential rate of withdrawal between TOPMAT-EPMN-106 higher and lower dose groups was treatment-limiting adverse events and these occurred predominantly in the early titration phases of the study.

The characteristics of the adverse event withdrawal population do not appear to be greatly different from those of subjects who remained in the study. In addition, the adverse events reported by the adverse event withdrawal population are similar in quality and severity to the known topiramate related adverse events and to the adverse events reported by in subjects who remained in the study. The Kaplan-Meier survival curve for time to first seizure for the TPM 400 subjects with adverse events who remained in the study was similar to the intent-to-treat TPM 400 group and greater than that of the intent-to-treat TPM 50 group. (See Sponsor Figure 1 below.) There were no readily apparent factors identified to indicate that the time to first seizure among subjects with limiting adverse events would be different from what was observed in those who remained in the study.

Figure 1: Plot of Cumulative Rates for Time to First Seizure Comparing the Intent-to-Treat TPM 50 and TPM 400 Groups and Subjects in the TPM 400 Group Who Had Adverse Events But Did Not Withdraw Due to Adverse Events
(Study TOPMAT-EPMN-106)



3) Imputation and population analyses: Alternative sensitivity analyses presented in this document address concerns around the potential introduction of bias in the primary efficacy analysis. The following outcomes were found:

> Imputations replacing censored data from the TPM 400 group with randomly selected data from various subpopulations provided strong evidence that the TPM 400 group was superior to the TPM 50 group (median p value <0.0019). Of the 1,000 simulations conducted for each subpopulation, 100% showed statistical significance favoring the TPM 400 group. The imputations relied on a conservative approach that assumed subjects who withdrew due to adverse events in the TPM 400 group had similar seizure rates as the TPM 50 group and maximally extended the seizure-free time of the 13 subjects who withdrew due to adverse events in the TPM 50 group. These analyses consistently supported the efficacy of TPM 400.

Simulations replacing all censored data from the 114 subjects who withdrew and the 53 subjects who withdrew due to adverse events favored the TPM 400 group over the TPM 50 group, assuming the probability of a first seizure by Day 500 was 50% for all subjects who withdrew from the study (p=0.0296) and 90% for all subjects who withdrew due to an adverse event (p=0.0369). (this is illustrated in Tables 3a and 3b below)

Table 3a: Summary of Simulations: Simulating Data for 114 Subjects Who Withdrew (Study TOPMAT-EPMN-106; Double-Blind Phase)

Assumed seizure rate at Day 500	Number of 1st seizures for TPM 50 (N=234)	Number of 1st seizures for TPM 400 (N=236)	p value from one simulation
1%	90	48	0.0001
5%	91	51	0.0001
10%	92	55	0.0001
15%	93	58	0.0002
20%	95	59	0.0002
25%	96	63	0.0005
30%	96	66	0.0013
35%	98	69	0.0018
40%	98	73	0.0057
45%	99	77	0.0116
50%	100	82	0.0296
55%	101	86	0.0509
60%	101	90	0.0996
65%	101	91	0.1300
70%	107	94	0.0899
75%	110	98	0.1249
80%	111	100	0.1480
85%	112	105	0.2294
90%	117	108	0.2053
95%	120	112	0.2596
99%	122	116	0.3665

A similar analysis conducted by replacing only the data of those 53 subjects (40 and 13 from the TPM 400 and 50 groups, respectively) who withdrew due to adverse events (D) with computer-generated pseudo-random numbers showed that TPM 400 was superior to TPM 50, assuming an up to 90% (p=0.0369) probability that subjects would have a first seizure by Day 500. The summary of the p values using this approach is provided in Table 3b.

Table 3b: Summary of Simulations: Simulating Data for 53 Subjects Who Withdrew Due to Adverse Events
(Study TOPMAT-EPMN-106; Double-Blind Phase)

Assumed seizure rate at Day 500	Number of 1st seizures for TPM 50 (N=234)	Number of 1st seizures for TPM 400 (N=236)	p value from one simulation
1%	90	48	0.0001
5%	90	48	0.0001
10%	92	50	0.0001
15%	93	51	0.0001
20%	93	52	0.0001
25%	93	52	0.0001
30%	93	54	0.0001
35%	93	56	0.0001
40%	94	59	0.0003
45%	94	62	0.0007
50%	94	64	0.0013
55%	96	68	0.0023
60%	97	69	0.0029
65%	97	70	0.0041
70%	97	71	0.0052
75%	97	72	0.0080
80%	97	72	0.0086
85%	98	74	0.0119
90%	98	79	0.0369
95%	99	81	0.0517
99%	100	83	0.0735

- Comparison of time to first seizure from the start of the stabilization period for subjects who entered stabilization favored the TPM 400 over the TPM 50 group (p=0.0015; 2-sided log-rank test).

In conclusion, the data support the assumption that subjects who withdrew early due to adverse event were not at increased seizure risk. Sensitivity analyses under a variety of models demonstrated the robustness of the results of Study TOPMAT-EPMN-106 and showed that the impact of the withdrawals likely was not a significant source of bias in the primary efficacy analysis. Thus, the trial supports the efficacy of topiramate as monotherapy for newly diagnosed patients with epilepsy.

7.3 Reviewer Comments on sponsors submission dated July 31, 2003

The sponsor suggests that the main reason to explain the difference in withdrawal rates between the two dose groups was due to the duration of the trial, which was "substantially longer" than other studies. The following table compares the median durations of each trial.

Study Name	Study duration median	comments
Study 104	Low dose group – 158 days High dose group – 141 days	Range is 8-809 days

Study 105	244 days for ITT population	Range is 2-806 days
Study 106	266 days for ITT population	Range is 9-786 days

It is difficult to even make such a comparison, as each study was substantially different in design. Still despite differences in median duration of treatment, the range of treatment durations was about equal for all trials.

The sponsor noted that the majority of withdrawals occurred early in the TPM 400 group and that the primary reason for withdrawals was adverse events. Per the sponsor, these occurred early in the study, either in the titration or stabilization period of the Double Blind Phase. From Days 22 to 42, there was a fixed titration schedule with limited dose reductions. The early withdrawal of patients due to adverse events especially in the higher dose group was the concern of the Division as well. The sponsor did not give an explanation for this differential, just that it occurred, perhaps because of the higher dose titration schedule. This reviewer agrees that the higher dose was not well tolerated by this group given the fixed titration schedule. The sponsor was trying to maximize dose separation and in doing so, forced many patients to take higher doses than they could tolerate, causing an increased dropout rate. This occurred despite an ability to lower the dose by up to 100 mg (two 50mg reductions) in this group.

The duration of the trial would have very little to do with this phenomenon if the majority of dropouts due to adverse events were early in the trial! Also, those who stayed in the trial were able to tolerate the drug better overall. They also had fewer seizure events, thus creating the very bias that Division statisticians were concerned about.

According to the sponsor, the TPM 50 and TPM 400 treated patients in their respective groups who experienced treatment limiting adverse events showed no demographic differences that could explain a differential response to therapy. The only remaining difference then is the dose exposure, again relating that adverse events were more likely to be dose limiting with more events and more dropouts in the higher dose group. This relates also to this reviewer's safety concern that the 400mg dose is not well tolerated overall and certainly not with the forced titration schedule used in the trial.

Per the sponsor, seizure data was not collected for those patients who discontinued from the study. Follow up information was only provided after a subject had a serious adverse event or a persistent adverse event. However, some information was available for 42 of the 114 subjects who withdrew, with 3 patients reporting a seizure. The overall seizure rates of the subjects were felt to be low to the sponsors, indicating that the majority of those who withdrew from the study for any reason would also be low. There is no specific data on the number of seizures of those who withdrew for adverse events. This makes it difficult to ascertain any meaning from the available data in order to ascertain the difference in withdrawal rates in both groups and to ascertain the possible seizure rates after withdrawal.

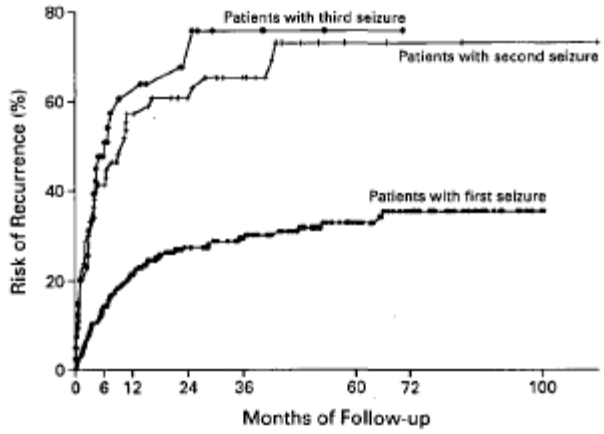
The sponsors performed alternative sensitivity analyses via imputation by replacing censored data from the TPM 400 group with randomly selected data from various subpopulations. Although the Sponsors were conservative with their presumed seizure rates, making them no higher than the TPM 50 group, this is erroneous and presumes a great deal. Division statistician, Kun He feels this is tantamount to computer modeling the data to fit the sponsor's assumptions. Further, he extends this as poor precedent, as future clinical studies could be done with small groups of patients and then computer extrapolated to provide more data.

Per the sponsor, had the subjects who withdrew early in the study remained in the double blind phase, their predicted seizure rate would not be any greater that that observed for the rest of the population.

Two representative articles from the literature provided by the sponsor, report that the probability of remaining seizure-free during treatment in a clinical practice setting 6 and 12 months after diagnosis of epilepsy is about 60% and 40%, respectively. One study found that 73% of patients who experienced 2 or 3 unprovoked seizures would have further seizures within 4 years with or without treatment.[3] The following graph was reproduced from that article illustrating that the risk of reoccurrence of seizures increases with the number of background events with rates anywhere from 40-80% in the first 24 months after an initial seizure event.

APPEARS THIS WAY IN ORIGINAL

[3] Hauser WA et al. Risk of recurrent seizures after two unprovoked seizures. NEJM, 1998;338:429-434.



PATIENTS AT RISK

With first seizure	204	176	153	117	100	60	42
With second seizure	63	36	24	19	13		
With third seizure	41	18	12	8	4		

Figure 1. Risk of a Second, Third, and Fourth Unprovoked Seizure after a First, Second, and Third Unprovoked Seizure.

P<0.001 for the comparison of the risk after one seizure with the risk after two seizures. P=0.47 for the comparison of the risk after two seizures with that after three seizures. The numbers below the figure show the numbers of patients remaining alive and free of seizures.

In another article supplied by the sponsor regarding seizure rates in children after a first unprovoked seizure, the risk of subsequent seizures after a second seizure (first reoccurrence) is anywhere from 40-65% within one year.[4] These rates are significant and apply directly to the intent to treat population.

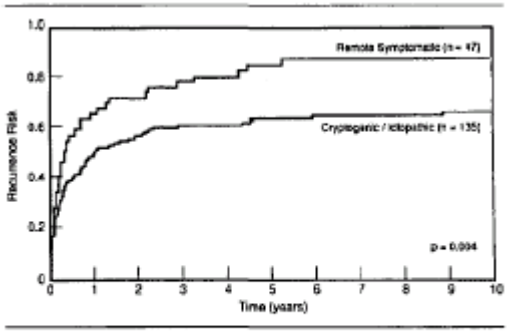


Fig 3. Probability of subsequent seizure recurrences after a second seizure in children with cryptogenic/idiopathic and remote symptomatic seizures (N = 182). Kaplan-Meier curves.

Using the sponsor own supplied data, if we assume seizure rates of all withdrawals (N=114 refer to table 3a) of at least 50% then any seizure rate above this would make the comparison not statistically significant. (p>0.05). However, according to the sponsor

[4] Shinnar S, et al. Predictors of multiple seizures in a cohort of children followed from the time of their first unprovoked seizure.

supplied articles, the real background seizure rate in this population is anywhere from 40-73%. Using Table 3b, replacing only patients who withdrew due to adverse events (N=54), any seizure rate above 90% would make the comparison not statistically significant, yet in the worst case analysis, the rate is set at 100% for that very reason. The data is not robust enough to accept this possibility.

The Sponsor assumes the much lower inherent rate of seizures in the newly diagnosed population (20-40%) vs. the higher inherent rate of seizures in those who have already had two or more events (40-80%). This is erroneous. Inclusion criteria for Study 106 maintained, "A new diagnosis of epilepsy within 3 months prior to study entry, or a recurrence of epilepsy while off of AEDs, including 1 or 2 (but no more than 2) documented seizures within the 3 months before enrollment." All patients in Study 106 would have had 1 or 2 seizures in the 3 months baseline phase prior to enrollment and at least 1 or 2 seizures before the baseline screening period to be identified as a patient with epilepsy. So therefore, in being enrolled in the study, each patient would have had at least 2 or more lifetime seizures (a minimum of one seizure for diagnosis and one seizure during the baseline phase). Therefore, the patients in Study 106 would have had a higher rate of recurrent seizures than patients with newly diagnosed epilepsy with a single seizure.

7.4 Reviewers Overall Efficacy Conclusions

Due to the lack of scientific evidence, the application for topiramate 400mg for initial monotherapy in epilepsy is not approvable based on the data reviewed.

Overall Study 106 as the pivotal trial failed to prove that topiramate at a dose of 400mg was superior to topiramate at a dose of 50mg regarding time to first seizure in the treatment of epilepsy as monotherapy.

The efficacy results seen in the supportive trials were promising, but also failed to prove that TPM at a dose of 400mg daily was efficacious as monotherapy for the treatment of partial seizures with or without secondary generalization.

- In Study YI, the sponsors did prove the superiority of TPM 1000 over TPM regarding time to exit and in reduction in seizure rates in patients with refractory seizures.

- In Study 104, the sponsors failed to prove a statistically significant difference in time to first seizure between the two treatment groups. The data for time to second seizure was much worse. Covariate analyses indicated that efficacy of topiramate monotherapy at a dose of 200 to 500mg/day was enhanced among subjects with newer onset seizures (diagnosis within 6 months before study entry) or milder disease (those reporting one or two partial onset seizures at baseline compared to those reporting three or more and among subjects not receiving AED therapy during the baseline phase vs. those receiving a background AED).

- In Study 105, the sponsors failed to prove a difference between TPM 100 and 200mg/day in regards to time to first seizure. Topiramate monotherapy at these doses was shown to be at least as effective as those of the physician's treatment of choice (carbamazepine or valproate). However, this study was an active control trial making it difficult to draw conclusions.

8. Safety Evaluation –Sponsor information

Overall Safety Conclusions from Study 106

Per the sponsor, topiramate administered as monotherapy in dosages of 50mg/day or 400mg/day was well tolerated in subjects with newly diagnosed or recurrent epilepsy. The overall adverse event profile was consistent with previous add on clinical experience. No significant hematologic, renal or liver toxicity was clearly attributable to the study drug.

8.1 TOPMAT-EPMN-106 (Study 106)

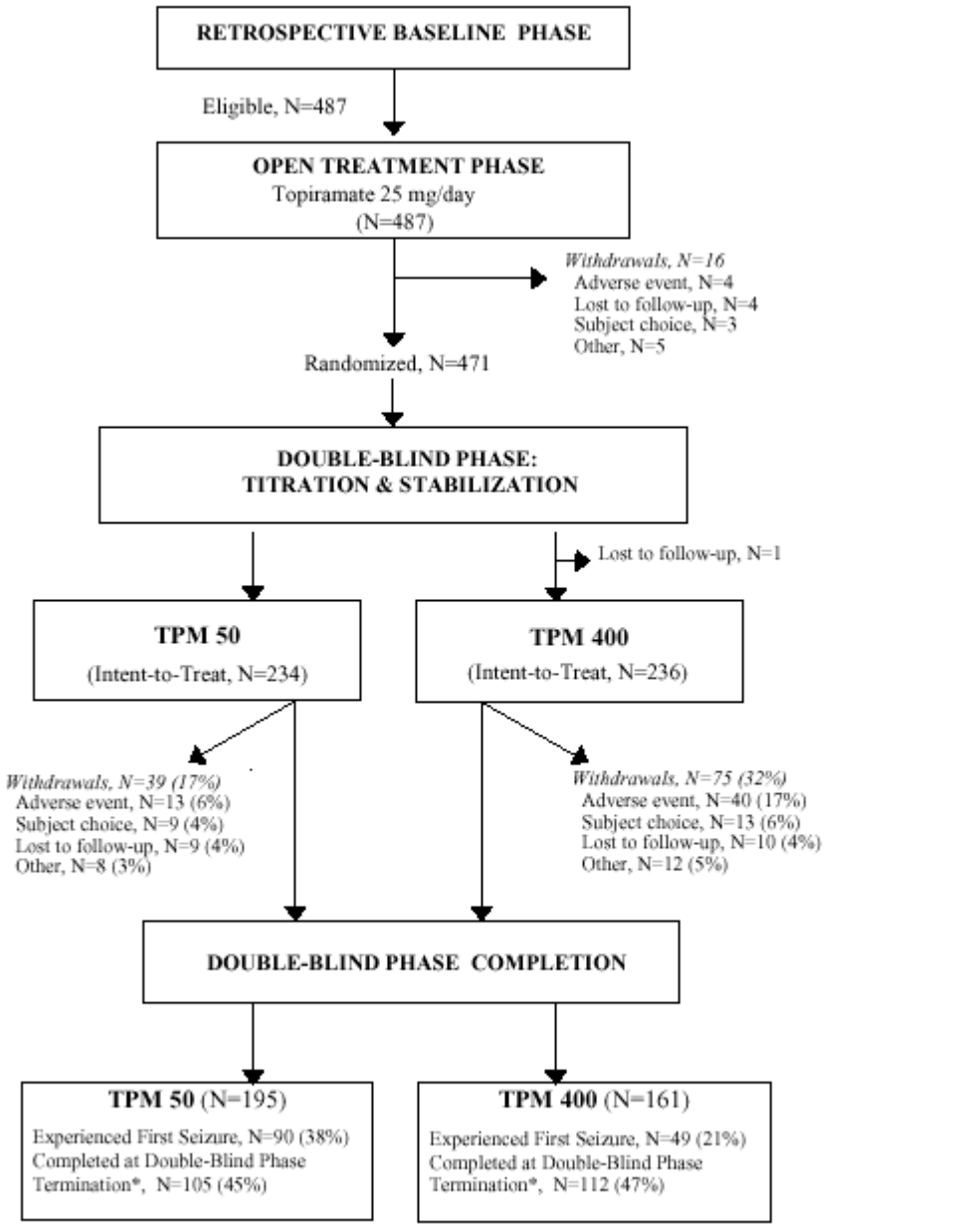
Per the sponsor, safety evaluation in Study 106 was based on the safety population, defined as all subjects who received topiramate during the study, including subjects who received open-label medication but were not randomized. Summaries and analyses of safety variables were based on data from the intent-to-treat population. Data for subjects who received only open-label treatment were listed. Safety assessments were based on the data from start of the study medication to the end of the double-blind phase, including taper.

The adverse event summaries were based on treatment-emergent adverse events, that is, adverse events that were new in onset or aggravated in severity following treatment. For this study, reports of adverse events were not collected during the baseline phase and were collected only during topiramate treatment; hence, all adverse events were considered treatment-emergent.

Treatment-emergent adverse events were coded in accordance with a modified World Health Organization Reporting Terminology (WHOART) dictionary maintained by the sponsor, where an included term is the description most closely related to the investigator's terminology, the preferred term is a group of closely related included terms, and the body system is a broad category including related preferred terms. Dropouts/withdrawals, discontinuations.

The flow of patients is illustrated in Sponsor Figure 2 below.

Figure 2. Study Discontinuation and Completion Information



* At the time of planned double-blind phase termination (6 months after randomization of the last subject)

8.1.1 Withdrawals

Open treatment phase

Of the 487 subjects who entered the trial, a total of 16 subjects withdrew from the open-treatment phase of the study prior to randomization. Of these, 5 subjects were dispensed the study medication, but did not provide any dosing information. Four of these subjects were lost to follow-up, and 1 withdrew due to subject choice. Of those subjects who received topiramate 25 mg/day (duration of exposure ranging between 3 and 10 days), 4 withdrew due to adverse events and 2 withdrew due to subject choice; 5 subjects were withdrawn for other reasons, including seizures that did not satisfy the protocol-specified eligibility criteria (3 subjects), as well as worsening epilepsy and noncompliance (1 subject each).

Double blind phase

A total of 114 subjects (24%) withdrew from the study for the protocol-specified reasons that included adverse events (53 subjects; 11%), subject choice (22 subjects; 5%), lost to follow-up (19 subjects; 4%), and other reasons (20 subjects; 4%). Adverse events were reported as the reason for withdrawal for more subjects in TPM 400 group (17%), compared to the TPM 50 group (6%). [5]

Table 8: Study Completion/Discontinuation Information
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

	TPM 50 (N=234)		TPM 400 (N =236)		Total (N=470)	
Completion Status	n	%	n	%	n	%
Completed	**195**	**83**	**161**	**68**	**356**	**76**
Completed at DB phase termination[a]	105	45	112	47	217	46
Completed by having a seizure	90	38	49	21	139	30
Withdrew	**39**	**17**	**75**	**32**	**114**	**24**
Adverse event	13	6	40	17	53	11
Subject choice	9	4	13	6	22	5
Lost to follow-up	9	4	10	4	19	4
Other	8	3	12	5	20	4

[a] Subjects who were active in the study at the time of termination of the double-blind (DB) phase, i.e., 6 months after randomization of the last subject.

8.1.2 Deaths

No Deaths were reported during the double blind phase of the study.

8.1.3 Serious adverse events

At least 1 serious adverse event was reported for 14 subjects (6%) in topiramate 400 mg/day group and for 10 subjects (4%) in topiramate 50 mg/day group. Only 2 of these

[5] This increased dropout rate due to adverse events in the higher dose group (TPM 400) was of major concern to Division statisticians who felt that this would falsely increase the success rate of the higher dose (TPM 400) group. See further discussion of efficacy under Reviewer's Analysis.

24 subjects were younger than 16 years of age. Subjects who experienced serious adverse events are listed in Sponsor Table 17.

Serious adverse events that primarily reflected increased seizure activity or status epilepticus, such as convulsions or grand mal convulsions, were reported in 1 subject treated with topiramate 50 mg/day (on Study Day 19) and in 2 subjects treated with topiramate 400 mg/day (on Study Days 134 and 237). These events were judged by the investigators as not related to the study medication. Both cases of status epilepticus, 1 in each treatment group, resulted in discontinuation of the study treatment. No seizure-related serious adverse events were reported during the open treatment phase. The only other serious adverse events reported in more than 1 subject across the treatment groups included infection (3 subjects) and abdominal pain (2 subjects).

All serious adverse events, with the exception of gastrointestinal symptoms (gastritis, abdominal pain, nausea, and vomiting) reported for Subject 536006 and kidney stone reported for Subject 571005, both in topiramate 400 mg/day treatment group, were considered by the investigators to be of either doubtful or no relationship to topiramate therapy. Most serious adverse events resolved as of the final study visit.

No abnormal laboratory test values, vital sign measurements, or physical or neurologic examination results were listed as serious adverse events.

Six subjects discontinued the study therapy due to the serious adverse events. In topiramate 50 mg/day group, these included i) myocardial infarction and ii) status epilepticus; in topiramate 400 mg/day group, these events were i) nausea and vomiting; ii) kidney stone; iii) status epilepticus; and iv) hospitalization for a neurologic work-up in a subject who discontinued study medication without consulting the investigator (Table 17). The latter case represented a protocol deviation. No consistent pattern of adverse events or clinically remarkable new event was observed in either of the treatment groups.

Table 17: Subjects with Serious Adverse Events
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

Investigator Subject No.	Age Sex	Preferred Term Investigator Term	Day of AE Onset/ Dosage at AE Onset (mg/day)	Total Days of Therapy[a]/Final Dosage (mg/day)[b]	Severity/ Relationship	Outcome/ Duration (Days)
Treatment Group: Topiramate 50 mg/day						
Leung 527002[d]	72 F	Myocardial Infarction[c] Myocardial Infarction	630/ 25	637/ 25	Marked Not Related	Resolved 7
Nash 531018	60 F	Adverse Event Surgical Repair C-Spine	33/ 50	320/ 50	Marked Not Related	Resolved 2
Ziman 552003	73 M	Withdrawal Syndrome Alcohol Withdrawal	477/ 25	492/ 0	Marked Not Related	Resolved 5
Pouyet 572001[d]	76 F	Cataract Cataract - Right Eye	120/ 25	317/ 25	Marked Not Related	Resolved 1
Bruggen 601005	59 M	Convulsions Grand Mal[c] Status Epilepticus	19/ 25	25/ 25	Marked Not Related	Resolved 1
Serrano 622005	57 F	Diabetes Mellitus Aggravated Hospitalization for Glycemia	91/ 50	608/ 50	Mild Not Related	Resolved 1
Guzman 640005	66 M	Arthritis Arthritis	8/ 25	139/ 50	Moderate Not Related	Resolved 36
Pasteris 646001	7 M	Testis Disorder Testicular Torsion	352/ 50	544/ 50	Moderate Not Related	Resolved 20
Jackel 652002	26 F	Muscle Weakness Bilateral Lower Leg Weakness	410/ 50	490/ 50	Marked Not Related	Persisted
Kramer 653002[d]	35 F	Thrombophlebitis Deep Left Leg DVT	189/ 50	398/ 25	Moderate Doubtful	Resolved 199
Treatment Group: Topiramate 400 mg/day						
Perkins 536006[d]	29 F	Suicide Attempt Suicidal Ideation Gastritis Gastritis Abdominal Pain Abdominal Pain Nausea[c] Nausea Vomiting[c] Vomiting Gastritis Gastritis	93/ 400[e] 99/ 400[e] 107/ 400 107/ 400 107/ 400 224/ 400	261/ 400	Moderate Doubtful Moderate Possible Moderate Possible Moderate Possible Moderate Possible Moderate Probable	Resolved 23 Resolved 5 Resolved 9 Resolved 9 Resolved 9 Persisted
Todorov 546007[d]	18 F	Placental Disorder Placenta Previa Vaginal Haemorrhage Vaginal Bleeding Abdominal Pain Abdominal Cramps	198/ 400 198/ 400 206/ 300	210/ 200	Moderate Not Related Moderate Not Related Moderate Not Related	Persisted Persisted Persisted
Truax 547005[d]	28 F	Pregnancy Ectopic Ectopic Pregnancy Ovarian Cyst Ovarian Cyst	299/ 400 309/ 400	474/ 400	Marked Not Related Marked Not Related	Resolved 11 Resolved 1

[a] Dosages are given in mg/day.
[b] Based on the investigator's assessment at the time of the occurrence of the adverse event.
[c] This adverse event was cited as a reason for discontinuing the study medication
[d] A narrative description of the adverse events reported for this subject is provided in Section 6.2.2.2
[e] In error, no dosing information was recorded for this subject in the clinical database at the time of these events.

Table 17: Subjects with Serious Adverse Events
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

Investigator Subject No.	Age Sex	Preferred Term Investigator Term	Day of AE Onset/ Dosage at AE Onset (mg/day)	Total Days of Therapy[a]/ Final Dosage (mg/day)[b]	Severity/ Relationship	Outcome/ Duration (Days)
Vossler	37	Chest Pain	6/	11/	Moderate	Resolved
550002	M	Chest Pain		25	Doubtful	1
Ryvlin	17	Renal Calculus[c]	447/	458/	Marked	Resolved
571005	M	Kidney Lithiasis	300	300	Very Likely	5
Schiller	17	Infection	292/	351/	Marked	Resolved
581003	M	Infected Rt Leg Hematoma	400	400	Not Related	13
Bruggen	46	Infection	282/	610/	Marked	Resolved
601001	M	Hospitalized For Appendicitis	0	400	Not Related	4
Aurlien	34	Pneumothorax	2/	29/	Marked	Resolved
612004	M	Pneumothorax	50	150	Doubtful	7
Fernandez	68	Angina Pectoris	5/	147/	Moderate	Resolved
625003	M	Angina Pectoris	50	200	Not Related	11
		Convulsions	134/		Moderate	Resolved
		Partial Evolving	200		Not Related	1
Arbelaiz	19	Abortion	111/	107/	Moderate	Resolved
636005[d]	F	Spontaneous Abortion		400	Not Related	1
Blasi	28	Convulsions Grand Mal[c]	237/	243/	Marked	Resolved
637006	F	Status Epilepticus		400	Not Related	2
Blasi	15	Infection	185/	453/	Moderate	Resolved
637007	M	Acute Appendicitis	400	400	Doubtful	6
Jackel	53	Cerebrovascular Disorder	139/	362/	Moderate	Resolved
652005[d]	M	Transient Ischemic Attack	150	150	Not Related	2
Kramer	32	Adverse Event[c]	179/	186/	Mild	Resolved
653001[f]	F	Hospitalization Neuro Work Up	150	150	Not Related	4

[a] Dosages are given in mg/day.
[b] Based on the investigator's assessment at the time of the occurrence of the adverse event.
[c] This adverse event was cited as a reason for discontinuing the study medication
[d] A narrative description of the adverse events reported for this subject is provided in Section 6.2.2.2.
[f] The subject stopped her medication abruptly without consulting the investigator and entered a different hospital for a neurologic work-up. This hospitalization was reported as a serious adverse event. This case is described in Section 4.5, Treatment Compliance.

Noteworthy serious adverse events reported for the subjects treated with topiramate are reproduced below from the sponsor's submission. In the topiramate 50 mg/day group, these events included myocardial infarction (Subject 527002), cataract (Subject 572001), and deep thrombophlebitis (Subject 653002); in the topiramate 400 mg/day group, these events included suicidal ideation (Subject 536006), placenta previa (Subject 546007), ectopic pregnancy (Subject 547005), spontaneous abortion (Subject 636005), and transient ischemic attack (Subject 652005).

Treatment Group: Topiramate 50 mg/day

Subject 527002 (Study TOPMAT-EPMN-106; topiramate dosage at onset of event: **25 mg/day**; serious adverse event: **myocardial infarction**). This 72-year-old, 55 kg woman was randomly assigned to the topiramate 50 mg/day treatment group.. On Day 526, mild heart disease, mild hypercholesterolemia, and markedly severe coronary artery disease were reported. These events, judged by the investigator as being of either doubtful or no relationship to topiramate, persisted through the end of the study. The drug was stopped temporarily as a result of the coronary artery disease, and nifedipine was discontinued by the investigator due to the onset of this condition. The subject was treated with niacin, lisonopril, furosemide, hydrocodone, and nicotinic acid for heart disease, and with simvastatin and atorvastatin for hypercholesterolemia. On Day 630, the subject was hospitalized for a myocardial infarction; study therapy was discontinued immediately. On that day, the subject received topiramate 25 mg. Her creatinine levels exceeded 3.5 mEq/L. Concomitant medications at that time included simvastatin, acetaminophen, lisinopril /hydrochlorothiazide, clopidogrel bisulfate (Plavix), metoprolol, and niacin. The subject recovered and was discharged from the hospital 6 days later. This event, judged by the investigator as not related to topiramate, was cited as the reason for the subject's withdrawal from the study.

Subject 572001 (Study TOPMAT-EPMN-106; topiramate dosage at onset of event: **25 mg/day**; serious adverse event: **cataract of the right eye**). This 76-year-old, 72 kg woman was randomly assigned to the topiramate 50 mg/day group. On Day 120, while receiving topiramate 25 mg/day, the subject was hospitalized for the surgical removal of a right cataract; the subject recovered from surgery without sequelae. The investigator considered this event to be unrelated to topiramate. On Day 159, mild glaucoma of the left eye, but not the right eye, was reported while the subject was taking topiramate 25 mg/day. This event, judged by the investigator as unrelated to topiramate, resolved in 2 days following treatment with latanoprost 0.005%. The subject was withdrawn from the study on Day 329 due to lack of compliance.

Subject 653002 (Study TOPMAT-EPMN-106; topiramate dosage at onset of event: **50 mg/day**; serious adverse event: **deep vein thrombosis**). This 35-year-old, 60 kg woman was randomly assigned to the topiramate 50 mg/day treatment group. She was not a smoker and was not using oral contraceptives. There was no family history of thrombosis.. On Day 185, the subject noted moderately severe pain in the left leg while taking topiramate 50 mg/day. On Day 189, the subject was hospitalized with a blood clot in her left leg that was diagnosed by an arteriogram as deep vein thrombosis (DVT) of the calf vein with extension into the popliteal vein. At the time of the event, the subject was taking tetracycline, naproxen, ibuprofen, and loratadine. This serious adverse event was treated immediately with enoxaparin 120 mg/day and warfarin 5 mg/day. A hypercoagulable evaluation, including a complete blood count, prothrombin time, partial thromboplastin time, Protein C, Protein S, activated protein C resistance, antithrombin 3, homocystine, and genotype for prothrombin, was performed; the results were unremarkable. Study medication continued uninterrupted, and the subject was discharged the next day. The DVT was thought by the investigator to be of doubtful relationship to topiramateOn Day 387, the subject was considered by the investigator to have recovered without sequelae. The subject

completed the study on Day 392. Warfarin was discontinued the next day. Approximately 2 months later, while taking commercial topiramate 350 mg/day, she experienced a second episode of DVT in the peroneal and posterior tibial vein in the right calf without DVT between knee and groin. The patient was reportedly complaining of nonspecific intermittent musculoskeletal pain in arms and legs. Topiramate was tapered off starting approximately 2 months after the event; treatment was completely discontinued within a month. A repeat of the previous hypercoagulable panel was unremarkable. A more comprehensive hypercoagulable workup revealed the presence of a low-titer cardiolipin antibody IgG at 17 g/dL (normal, <10 g/dL; low positive, 10-19 g/dL). Antinuclear antibody was evaluated to rule out autoimmune diseases; it was negative. C-reactive protein was under 0.1. The lupus anticoagulant was not detected. The platelet function studies did not support the presence of a sticky platelet syndrome. Based on the clinical history and on the presence of low-titer IgG, it was suggested by the hematologist that the patient could have an antiphospholipid antibody syndrome;. In addition, an alternative diagnosis of fibromyalgia was proposed for the pain in upper extremities; rheumatological evaluation was suggested. Coumadin therapy continued.

Treatment Group: Topiramate 400 mg/day

Subject 536006 (Study TOPMAT-EPMN-106; topiramate dosage at onset of event: **400 mg/day**; serious adverse event: **suicidal ideation**). This 29-year-old, 122 kg woman with partial onset seizures evolving to secondary generalized seizures was randomly assigned to the topiramate 400 mg/day treatment group.. On Day 93, the subject was reported as having suicidal ideation (WHOART preferred term: “suicide attempt”). On Day 99, the subject presented at an emergency room with complaints of vomiting and coughing up small amounts of blood. While in the emergency room, the subject expressed suicidal ideations and appeared depressed. At the time of these events, the subject was taking albuterol for asthma, lansoprazole and simethicone sorbitol for gastritis and esophagitis, paroxetine for situational depression, a combination of butalbital, aspirin, and caffeine for migraines, and amitriptyline for sleep difficulties. She was admitted to the hospital and placed on suicide precautions. An endoscopy performed the next day revealed gastritis, judged by the investigator as moderate in severity and possibly related to the study medication; this event resolved in 5 days following treatment with lansoprazole and aluminum hydroxide/magnesium hydroxide. The subject was discharged from the hospital in 4 days. The suicidal ideation, judged by the investigator as moderate in severity and doubtfully related to topiramate, resolved in 23 days. Depression, judged by the investigator as moderate in severity and possibly related to topiramate, persisted through the remainder of the study. The symptoms were treated with paroxetine. Gastrointestinal complaints (gastritis, esophagitis, abdominal pain, nausea, vomiting) recurred at various points through the remainder of the study, while the subject was taking topiramate 400 mg/day. The subject withdrew from the study on Day 282, citing vomiting and nausea as the reasons for discontinuation. She completed the taper within a month.

Subject 546007 (Study TOPMAT-EPMN-106; topiramate dosages at onset of event: **300-400 mg/day**; serious adverse events: **placenta previa, vaginal bleeding, abdominal cramps**). This 18-year-old, 49 kg woman with complex partial seizures was randomly assigned to the topiramate 400 mg/day treatment group. Phenytoin was discontinued before randomization. No other medications, including oral contraceptives, were reported at Day 73 baseline. On Day 198, the subject was hospitalized due to heavy uterine bleeding. At that time, she was informed that she was pregnant and had placenta previa. These adverse events were judged by the investigator as being moderate in severity and not related to study medication. Taper of study medication was initiated. On Day 206, the subject was admitted to a local hospital for complaints of vaginal hemorrhage and abdominal cramping while on topiramate 300 mg/day. Examination indicated a viable fetus of 15 weeks and 1 day, and complete placenta previa. Following overnight hospitalization, the subject was discharged with instructions for limited physical activity. On Day 209, fever was reported while the subject was taking topiramate 300 mg/day; the fever, judged by the investigator as mild and not related to study medication, resolved within 2 days. The taper of study medication was completed by Day 231. The subject withdrew from the study on Day 242 due to placental previa and vaginal hemorrhage. Follow-up information indicated that the subject

delivered a full-term healthy 6 lb 15 oz baby via an uncomplicated vaginal delivery approximately 5 months later.

Subject 547005 (Study TOPMAT-EPMN-106; topiramate dosage at onset of event: **400 mg/day**; serious adverse events: ectopic pregnancy, ovarian cyst; adverse event of interest: **elevated GGT**). This 28-year-old, 77 kg woman with partial onset seizures was randomly assigned to the topiramate 400 mg/day treatment group. Relevant medical history included cholelithiasis and cholecystectomy, elevated GGT, insomnia, depression, and anxiety. Baseline medications included cetirizine for seasonal allergies, a combination of hydrochlorothiazide and triamterene (Dyazide) for edema, valium for anxiety, trazadone for insomnia, famotidine for indigestion, ibuprofen and a combination of acetaminophen and propoxyphene napsylate (Darvocet N-100) for migraines, loratadine for sinusitis prophylaxis, and an oral contraceptive. Gabapentin was tapered off prior to randomization. A marked weight decrease was noted on Day 71, at the dose of 400 mg/day; this was judged by the investigator as very likely related to topiramate. Markedly abnormal elevated GGT levels were noted on Days 26, 218, 322, and 328. On Day 26, this laboratory abnormality was reported as "worsening of elevated GGT"; on Day 322, this event was reported as "elevated GGT". Laboratory analyte values for hepatic tests are shown in the table below.

An HCG pregnancy test performed during a routine study visit on Day 299 was found to be positive. Concomitant therapy in use at this time included cetirizine, trazadone, a combination of acetaminophen/propoxyphene napsylate, famotidine, ibuprofen, and an oral contraceptive. The physician reported that the pregnancy was not felt to be viable and would possibly result in a

Study Day	TPM Dosage (mg/day)	Alkaline Phosphatase (U/L)	GGT (U/L)	AST (U/L)	ALT (U/L)	Bilirubin (mg/dL)
Baseline	0	88	72	22	28	0.35
1	50	83	81	20	23	0.35
26	200	96	136 M+	24	41	0.35
218	400	75	168 M+	19	23	0.46
299	400	66	66	12	11	0.35
322	400	293 M+	534 M+	30	79	0.35
328	400	156	313 M+	16	33	0.35
389	400	64	76	22	18	0.35
467	400	73	77	12	11	0.23

M+ = Value exceeding markedly abnormal upper limits (>280 U/L for alkaline phosphatase and >120 U/L for GGT).

miscarriage or ectopic pregnancy. The subject therefore continued to receive topiramate. She was hospitalized and underwent laparoscopy that identified a left tubal pregnancy and left ovarian cyst on Study Day 309. The ectopic pregnancy and the cyst resolved and were judged by the investigator as unrelated to the study medication. The subject completed the trial on Day 467. (

Subject 652005 (Study TOPMAT-EPMN-106; topiramate dosage at onset of event: **150 mg/day;** serious adverse event: **transient ischemic attack**). This 53-year-old, 126 kg man with partial onset seizures was randomly assigned to the topiramate 400 mg/day treatment group. Relevant medical history included bilateral carotid artery occlusion, right parietal cerebral vascular accident, mild left hemiparesis, low flow of the right internal carotid artery, and Type 2 diabetes mellitus. Baseline medications were glyburide and metformin for diabetes and aspirin for coronary artery disease prophylaxis. Adverse events that occurred early in titration included anxiety, ataxia, headaches, increased forgetfulness, and emotional lability. On Day 29, while the subject was taking topiramate 175 mg/day, moderately severe hypertension was noted; it was judged by the investigator to be of doubtful relationship to the study medication and resolved in 2 days. On Day 103, while taking topiramate 150 mg/day, the subject reported intermittent visual disturbance, which he described as a cloud passing over the sun. The subject was treated with a combination of aspirin and dipyridamole. This event resolved within 5 days and was judged by the investigator as moderate in severity and unrelated to topiramate. On Day 139, the subject was hospitalized for a transient ischemic attack, although the exact etiology of the event was unclear

to the investigator. The event began with complaints of abnormal, uncoordinated movements of the right arm that spread to the face; the subject's right leg also became weak. During hospitalization, an MRI scan and MR angiogram revealed no change from the subject's previous studies. The limb weakness resolved within 2 days. The subject was treated with clopidogrel bisulfate, pravastatin sodium, and atenolol. Concomitant medications at the time of this event were glyburide, metformin, and aspirin/dipyridamole combination. No abnormalities in laboratory measurements or vital signs were noted during the study. The subject completed the study on Day 356 with no further vascular events reported.

Subject 636005 (Study TOPMAT-EPMN-106; serious adverse event: **spontaneous abortion**.) This 19-year-old, 51 kg woman was randomly assigned to the topiramate 400 mg/day treatment group. Her medical history was unremarkable. On Day 99, a positive pregnancy test indicated that the subject was pregnant and the subject was withdrawn from the study. On Day 111, the subject had a spontaneous abortion, which was judged by the investigator as unrelated to topiramate. No concomitant medications were being given at the time of this event.

8.1.4 Adverse events leading to discontinuation of medication

44 subjects (19%) in the topiramate 400 mg/day group and 16 subjects (7%) in topiramate 50 mg/day group experienced adverse events that resulted in permanent discontinuation of therapy (See Sponsor Table 18 below). *The discrepancy between this number and the number of subjects who withdrew from the study due to adverse events (40 subjects in topiramate 400 mg/day group and 13 in topiramate 50 mg/day group, according to Table 8) is due to the fact that 7 subjects (4 in topiramate 400 mg/day group and 3 in topiramate 50 mg/day group) completed the double-blind phase by having a first seizure, but also experienced treatment-limiting adverse events*. Due to these events, after the report of the first seizure, the decision was made to stop topiramate therapy in each of these cases; consequently, the subjects did not enter the open-label extension phase.

The incidence of adverse events that resulted in discontinuing the study medication in at least 1% of the subjects in either treatment group is presented in Table 18.

Table 18: Incidence of the Most Common[a] Limiting Adverse Events
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

Body System / Preferred Term	TPM 50 (N=234) n	%	TPM 400 (N=236) n	%	Total (N=470) n	%
Psychiatric						
Depression	3	1	5	2	8	2
Difficulty With Concentration/Attention	1	<1	5	2	6	1
Difficulty With Memory	0		6	3	6	1
Insomnia	2	1	4	2	6	1
Somnolence	1	<1	5	2	6	1
Cognitive Problems	1	<1	3	1	4	1
Psychomotor Slowing	1	<1	3	1	4	1
Confusion	1	<1	2	1	3	1
Anxiety	2	1	0		2	<1
Mood Problems	0		2	1	2	<1
Nervousness	0		2	1	2	<1
Central and Peripheral Nervous System						
Paraesthesia	1	<1	5	2	6	1
Dizziness	2	1	3	1	5	1
Language Problems	3	1	2	1	5	1
Ataxia	3	1	1	<1	4	1
Speech Disorders/Related Speech Problems	1	<1	2	1	3	1
Coordination Abnormal	2	1	0		2	<1
Body As A Whole						
Fatigue	0		5	2	5	1
Fever	0		3	1	3	1
Asthenia	0		2	1	2	<1
Gastrointestinal System						
Nausea	2	1	3	1	5	1
Abdominal Pain	0		2	1	2	<1
Urinary System						
Renal Calculus	0		2	1	2	<1
Metabolic and Nutritional						
Weight Decrease	0		3	1	3	1
Vascular Extracardiac						
Flushing	0		3	1	3	1
Other Special Senses						
Taste Perversion	0		2	1	2	<1
Reproductive, Female[b]						
Placental Disorder	0		1	1	1	<1
Vaginal Hemorrhage	0		1	1	1	<1
Any Adverse Event	**16**	**7**	**44**	**19**	**60**	**13**

[a] Adverse events that occurred in at least 1% of subjects in either of the treatment groups
[b] Percentage calculated based on the number of females (124 in TPM 50 and 113 in TPM 400).

Per the sponsor, "Neuropsychiatric adverse events (depression, difficulty with memory, difficulty with concentration/attention, insomnia, somnolence, paresthesia, dizziness, and language problems) were most likely to contribute to discontinuation of topiramate therapy in both treatment groups. Most of the limiting adverse events, with the exception of language problems, nausea, ataxia, anxiety, and abnormal coordination, were reported at a higher incidence in subjects assigned to topiramate 400 mg/day group, compared to those assigned to topiramate 50 mg/day group".

8.1.5 Adverse events requiring reduction of topiramate dosage or temporary interruption of treatment.

- A total of 56 subjects (24%) in topiramate 400 mg/day group and 20 subjects (9%) in topiramate 50 mg/day group experienced adverse events that resulted in reduction of topiramate dosage or temporary interruption of treatment (See Sponsor Table 19).

- Most of those subjects who experienced dose reductions or temporary interruptions of study treatment (11 out of 20 [55%] in the topiramate 50 mg/day group and 42 out of 56 [75%] in the topiramate 400 mg/day group) completed the study per protocol. (Clinical Reviewer comment: This implies that 45% of those who experienced dose reductions in the TPM 50 group and 25% of those in the TPM 400 group did not complete the study per protocol! This raises concerns for the tolerability of the goal dose of 400mg.)

- The adverse events leading to dose reductions or temporary interruption of treatment were later cited among the reasons for permanent discontinuation of study treatment in 4 of the 20 [20%] of subjects who experienced these events in the topiramate 50 mg/day group and in 6 of the 56 [11%] of subjects in the topiramate 400 mg/day group.

The incidence of adverse events that resulted in dosage reductions or temporary interruption of treatment in at least 1% of the subjects in either treatment group was consistent with that observed for treatment-limiting events (Sponsor Table 19).

Table 19: Incidence of the Most Common[a] Adverse Events Leading to a Dosage Reduction or Interruption of Study Medication
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

Body System / Preferred Term	TPM 50 (N=234) n	%	TPM 400 (N=236) n	%	Total (N=470) n	%
Psychiatric						
Difficulty With Concentration/Attention	4	2	12	5	16	3
Difficulty With Memory	3	1	7	3	10	2
Somnolence	3	1	7	3	10	2
Anorexia	0		9	4	9	2
Cognitive Problems	1	<1	5	2	6	1
Depression	0		4	2	4	1
Nervousness	1	<1	3	1	4	1
Insomnia	1	<1	2	1	3	1
Libido Decreased	0		3	1	3	1
Psychomotor Slowing	1	<1	2	1	3	1
Anxiety	0		2	1	2	<1
Mood Problems	0		2	1	2	<1
Central and Peripheral Nervous System						
Paraesthesia	3	1	17	7	20	4
Headache	2	1	4	2	6	1
Language Problems	2	1	3	1	5	1
Dizziness	1	<1	3	1	4	1
Ataxia	0		3	1	3	1
Speech Disorders/Related Speech Problems	1	<1	2	1	3	1
Body as a Whole						
Fatigue	3	1	7	3	10	2
Asthenia	2	1	2	1	4	1
Gastrointestinal System						
Nausea	3	1	4	2	7	1
Abdominal Pain	1	<1	3	1	4	1
Metabolic and Nutritional						
Weight Decrease	0		7	3	7	1
Vision Disorders						
Vision Abnormal	0		2	1	2	<1
Resistance Mechanism						
Infection	0		2	1	2	<1
Any Adverse Event	**20**	**9**	**56**	**24**	**76**	**16**

[a] Adverse events that occurred in at least 1% of subjects in either of the treatment groups

Neuropsychiatric adverse events (paresthesia, difficulty with concentration/attention, difficulty with memory, somnolence, anorexia, and fatigue) were most likely to contribute to dosage reductions or temporary interruption of treatment in either treatment group. Most of these adverse events were reported at a higher incidence in subjects assigned to topiramate 400 mg/day group, compared to those assigned to topiramate 50 mg/day group.

8.1.6 Common Adverse events

Treatment-emergent adverse events occurring at an incidence of at least 5% in subjects receiving either of the study treatments are summarized in Sponsor Table 16. Among the most common adverse events, those reported as marked in severity by at least 2% of the subjects in either treatment group included weight decrease, headache, paresthesia, and difficulty with concentration/attention.

The most common treatment-emergent adverse events reported in both treatment groups were neuropsychiatric in nature; many occurred at a less than 10% incidence at either dosage. Some neuropsychiatric events were experienced at similar rates by subjects receiving topiramate 400 mg/day and topiramate 50 mg/day, e.g., dizziness (12% vs. 13%), fatigue (11% in either group), difficulty with concentration/attention (8% vs. 7%), and insomnia (7% in either group). The incidence of headache was lower in the TPM 400 group (15%) than in the TPM 50 mg group (23%).

The most common among the events with at least twice the incidence in the TPM 400 group, compared to the TPM 50 group were paresthesia (31% vs. 15%), as well as anorexia (14% vs. 7%), weight decrease (16% vs. 6%), difficulty with memory (8% vs. 4%), mood problems (6% vs. 2%), and cognitive problems (5% vs 1%). These observations are consistent with the known side effect profile of topiramate.

Common adverse events in other body systems that occurred at similar rates across both groups included, among others, upper respiratory tract infection, nausea, injury, diarrhea, abdominal pain, viral infection, and dyspepsia. Most adverse events were reported as mild to moderate in severity and of either doubtful or possible in relationship to the study medication.

Table 16: Incidence of the Most Common[a] Treatment-Emergent Adverse Events (Intent-to-Treat Population; Study TOPMAT-EPMN-106)

Body System / Preferred Term	TPM 50 (N=234) n	%	TPM 400 (N=236) n	%	Total (N=470) n	%
Central and Peripheral Nervous System						
Paresthesia	36	15	73	31	109	23
Headache	53	23	35	15	88	19
Dizziness	30	13	29	12	59	13
Psychiatric						
Somnolence	24	10	33	14	57	12
Anorexia	16	7	32	14	48	10
Difficulty With Concentration/Attention	16	7	20	8	36	8
Insomnia	17	7	16	7	33	7
Depression	11	5	17	7	28	6
Difficulty With Memory	9	4	18	8	27	6
Mood Problems	4	2	14	6	18	4
Cognitive Problems	2	1	12	5	14	3
Gastrointestinal System						
Nausea	25	11	18	8	43	9
Abdominal Pain	19	8	16	7	35	7
Diarrhoea	14	6	17	7	31	7
Dyspepsia	13	6	11	5	24	5
Vomiting	12	5	9	4	21	4
Body as a Whole – General						
Fatigue	25	11	26	11	51	11
Injury	22	9	16	7	38	8
Asthenia	6	3	12	5	18	4
Fever	6	3	12	5	18	4
Respiratory System						
Upper Respiratory Tract Infection	38	16	35	15	73	16
Pharyngitis	23	10	10	4	33	7
Sinusitis	11	5	7	3	18	4
Rhinitis	6	3	11	5	17	4
Metabolic and Nutritional						
Weight Decrease	15	6	38	16	53	11
Resistance Mechanism						
Infection Viral	11	5	17	7	28	6

[a] Adverse events that occurred in at least 5% of subjects in either of the treatment groups.

NOTE: The median duration of double-blind therapy for all subjects in the intent-to-treat population was approximately 9 months (266 days; range, 9 to 786 days).
Cross-reference: Attachment 7.1.1.

8.1.7 Adverse events of interest

Per the sponsor, no evidence of encephalopathy[6], stupor, coma, EEG abnormality, or hyperammonemia were noted in the study. The sponsor highlighted the following.

8.1.8 Paresthesias

[6] This depends on how the Sponsor is coding the diagnosis of encephalopathy. This could be included within a number of alternate diagnoses such as "somnolence, difficulty with memory, difficulty with concentration/attention and cognitive problems". This is further discussed in the review of the ISS later in this document.

This was the single most common adverse effect reported in 15% of TPM 50 and 31% of subjects in the TPM 400 group. Per the sponsor, paresthesia was of mild to moderate severity and resulted as one of the reasons for discontinuation in 1 of the subjects in the TPM 50 and 5 subjects in the TPM 400 group.

8.1.9 Renal calculi

Renal calculi were reported in 4 subjects who were in the TPM 400 group. 2 cases were noted as marked in severity leading to discontinuation.

8.1.10 Delirium and confusion

Delirium was reported in one subject (601005) assigned to the TPM 50mg group the day after status epilepticus on treatment day 20.

Confusion was reported for 5 subjects in the TPM 50 group and 8 subjects in the TPM 400 group. One 76 year old woman experienced marked confusion (verbatim: disorientation) while on topiramate 400 mg/day; the event, which resolved without intervention, was considered by the investigator to be not related to topiramate; the subject continued in the study. Moderately severe confusion[7] was reported twice for Subject 520003, at topiramate dosages of 100 mg/day and then 400 mg/day; the event, considered by the investigator to be possibly related to topiramate, persisted. In the remaining 11 out of 13 cases, confusion was mild in severity and occurred in titration (during the first month of therapy in 9 subjects and on Day 43 in another 2 subjects). Most events resolved without intervention.

8.1.11 Eye pain

Abnormal vision (included terms: blurred vision; visual disturbance; vision decreased), judged by the investigators as mild in severity in the majority of cases, was reported for 7 subjects in each treatment group. Among these 14 cases were markedly severe decrease in visual acuity in Subject 622005 and a decrease in peripheral visual fields in Subject 533006. The first subject, a 57-year-old woman with a history of diabetes mellitus, experienced aggravated diabetes mellitus and diabetic retinopathy earlier in the study. The decrease in visual acuity was judged by the investigator as being of doubtful relationship to topiramate treatment. Decrease in peripheral visual fields was reported as a result of visual field examination in Subject 533006; review of the results of a follow-up visual field test by an independent expert ophthalmologist did not reveal any abnormalities in this subject's measurements. None of the cases of abnormal vision was serious or resulted in dose reductions or withdrawal from the study. No pattern of drug

[7] Reviewer comment: Again, although the sponsor relates that there were no instances of encephalopathy, I would consider that these cases of delirium and confusion would be consistent with mild forms of encephalopathy.

toxicity was detected in any of the visual field measurements by an independent expert ophthalmologist.

8.1.12 Hyperthermia and flushing

Hyperthermia and flushing, events potentially related to oligohydrosis, were reported in 3 pediatric subjects at the same investigational site in Spain (investigator Barrera), all assigned to the TPM 400 group. All 3 subjects were withdrawn from the study by the investigator due to these events; in 2 of these cases, potential infectious etiology could not be ruled out. In addition, topiramate dose was reduced due to decreased sweating in a 46-year-old man in the TPM 400 group. Moderately severe dehydration was reported in Subject 554006, who was in the TPM 50 group. This event, preceded by migraine and nausea, and accompanied by diarrhea, was judged by the investigator as not related to topiramate treatment and resolved in 2 days. Finally, mild flushing and fever were reported in a 35-year-old woman in the TPM 50 group. These events, judged by the investigator to be possibly related to topiramate, resolved; no symptoms or laboratory indicators of dehydration were reported during topiramate therapy. The subject continued her participation in the study.

8.1.13 Pregnancy

Four subjects, 1 assigned to the TPM 50 group (Subject 640003) and 3 to TPM 400 (Subjects 547005, 546007, and 636005) became pregnant during the double-blind phase of the study. Subject 640003 was withdrawn from the study upon confirmation of her pregnancy; she subsequently delivered a full-term healthy baby. Subject 546007, who experienced placenta previa and vaginal bleeding early in the course of her pregnancy subsequently delivered a normal healthy baby. Subject 636005, assigned to TPM 400 group, experienced a spontaneous abortion 10 days after having discontinued topiramate treatment. This event was judged by the investigator as not related to topiramate therapy. Finally, Subject 547005 experienced an ectopic pregnancy; she subsequently completed the study per protocol. This subject was taking an oral contraceptive (norethindrone acetate 1.5 mg/ethynyl estradiol 30 mg) at baseline; no information regarding birth control methods was available for the other subjects.

8.1.14 Headache and dizziness

Clinical Reviewer comment: Not noted by the sponsor, but of some concern to this reviewer is the incidence of headache and dizziness reported by those in the study. Per Sponsor Table 16, headache was noted in 53 of 234 (23%) patients in the TPM 50 group and in 35 of 236 (15%) patients in the TPM 400 group. Dizziness was reported by 30 (13%) of patients in the TPM 50 group and in 29 (12%) of the TPM 400 group.

8.1.15 Laboratory test abnormalities noted as adverse events

One or more laboratory test abnormalities were reported as adverse events in 26 subjects. Most of those abnormalities were transient and were judged by the investigators to be of doubtful or no relationship to the study therapy. No subjects exited the study or had their topiramate dosage reduced due to laboratory abnormalities. All hepatic laboratory abnormalities, with the exception of one case of markedly severe abnormal hepatic function (See narrative for subject 547005 28 year old female with ectopic pregnancy and increased GGT, where GGT was elevated to 534 U/L on study day 322, resolving by Day 389), were mild or moderate in severity. No abnormalities in bilirubin levels were reported as adverse events; in the 2 subjects who had markedly abnormal levels of bilirubin reported during the study, these abnormalities were not accompanied by elevated AST or ALT levels. One subject with a history of CREST (calcinosis cutis, Raynauds phenomena, esophageal dysmotility, scleroderma and telangiectasias) syndrome experienced markedly abnormal elevations in AST, ALT, and LDH levels on her last study visit; these events were attributed to acetaminophen.

Markedly abnormal values reported at an incidence of more than 3% included low CO2 levels, high GGT levels, high inorganic phosphorus, low neutrophils, and high lymphocytes.

Serum bicarbonate (CO2)

Serum CO2 showed a mean decrease of 1.95 mmol/L (mean percent change of –6.7%) in the topiramate 50 mg/day group and a mean decrease of 2.68 mmol/L (mean percent change of –9.6%) in the topiramate 400 mg/day group. This decrease in serum CO2 levels is consistent with the properties of topiramate as a carbonic anhydrase inhibitor. Chloride showed slight mean increases (2.4 mmol/L in the topiramate 50 mg/day group and 3.2 mmol/L in the topiramate 400 mg/day group).

Dr. Gerald Boehm, safety reviewer for the Division provided the following analysis regarding serum CO2

I analyzed the submitted lab data set for study 106 to examine low CO_2 outlier risks that occurred during this study. Following an open label introduction (all subjects received topiramate 25mg), subjects were randomized to topiramate 50mg or topiramate 400mg. Since the study allowed some downward dose titration, for the purpose of these analyses, I identify the two treatment groups as Topiramate 50mg and Topiramate high dose. I first selected those subjects who continued past the open label introduction (Topiramate 50 n=234, Topiramate high dose n=236). I then identified those subjects who had a baseline CO_2 lab result in the data set (Topiramate 50 n=223, Topiramate high dose n=225). I then performed separate analyses using those subjects with a CO_2 >=20mmol/L at baseline and then for subjects with a CO_2>=22mmol/L at baseline. For these groups, I identified the number of subjects who had one or more low CO_2 results meeting the following criteria: <20mmol/L, <17mmol/L, <15mmol/L, <12mmol/L. I present those results in the following table.

Subjects with baseline CO_2 >=20 and with one or more low CO_2 outliers during study 106

Low outlier	*Topiramate 50mg (n=219)*	*Topiramate high dose (n=219)*
Below 20mmol/L	*26.0% (n=57)*	*36.5% (n=80)*
Below 17mmol/L	*4.7% (n=10)*	*15.1% (n=33)*
Below 15mmol/L	*1.8% (n=4)*	*5.5% (n=12)*
Below 12mmol/L	*0.5% (n=1)*	*0.9% (n=2)*

Subjects with baseline CO_2 >=22 and with one or more low CO_2 outliers during study 106

Low outlier	*Topiramate 50mg (n=189)*	*Topiramate high dose (n=180)*
Below 20mmol/L	*28.6% (n=57)*	*37.8% (n=68)*
Below 17mmol/L	*5.3% (n=10)*	*15.0% (n=27)*
Below 15mmol/L	*2.1% (n=4)*	*4.4% (n=8)*
Below 12mmol/L	*0.5% (n=1)*	*0.6% (n=1)*

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Subjects ≤16 years old with baseline CO_2 >=20 and with one or more low CO_2 outliers during study 106

Low outlier	*Topiramate 50mg (n=74)*	*Topiramate high dose (n=77)*
Below 20mmol/L	*20.3% (n=15)*	*28.6% (n=22)*
Below 17mmol/L	*5.4% (n=4)*	*14.3% (n=11)*
Below 15mmol/L	*1.4% (n=1)*	*5.2% (n=4)*
Below 12mmol/L	*(n=0)*	*(n=0)*

Subjects ≤16 years old with baseline CO_2 >=22 and with one or more low CO_2 outliers during study 106

Low outlier	*Topiramate 50mg (n=57)*	*Topiramate high dose (n=56)*
Below 20mmol/L	*26.3% (n=15)*	*26.8% (n=15)*
Below 17mmol/L	*7.0% (n=4)*	*14.3% (n=8)*
Below 15mmol/L	*1.8% (n=1)*	*3.6% (n=2)*
Below 12mmol/L	*(n=0)*	*(n=0)*

Per the sponsor, The markedly low CO2 values (i.e., values below 18 mmol/L) in the topiramate-treated subjects may be associated with the properties of topiramate as a carbonic anhydrase inhibitor. For individual subjects, most of the markedly abnormal values were not lower than 16 mmol/L and were reported on single or occasional test dates. In 2 subjects in topiramate 400 mg/day treatment group, recurrent markedly low levels of CO2 did not resolve as of the last clinic visit. Subject 581005, a 17-year-old woman, had CO2 levels ranging between 17 and 11 mmol/L. Subject 583001, an 8-year-old boy, had CO2 levels ranging between 12 and 17 mmol/L while receiving topiramate 400 mg/day. In both cases, decreases in CO2 levels were accompanied by elevated chloride levels (109 to 112 mmol/L); no adverse events were reported for either subject, and both completed the study per protocol.

Inorganic phosphorus

Markedly abnormal increases in inorganic phosphorus were reported in 29 subjects, 26 of whom were children. The high incidence of markedly abnormal phosphorus levels is, at least in part, due to the fact that the markedly abnormal criteria for this analyte were not stratified by age. The high levels of phosphorus in the 26 pediatric patients wereattributable to developmental effects and do not represent clinically notable abnormalities.

8.1.16 Weight decrease

An adverse event of weight decrease was reported by 6% of subjects receiving topiramate 50 mg/day and 16% of subjects receiving topiramate 400 mg/day. In most cases, these events were mild to moderate in severity. Markedly severe weight decrease was reported for 4 adult subjects and 1 pediatric subject (a 15-year-old girl, whose BMI decreased from 24.1 at baseline to 21.8)) in the topiramate 400 mg/day group. Topiramate therapy was discontinued for 1 of these 4 adults and for 2 other adults in the same group who reported mild weight decreases together with other treatment-limiting events. The dose of topiramate was reduced in 7 subjects (3%) in topiramate 400 mg/day treatment group due to weight decreases.

Most of the 470 topiramate-treated subjects, (55% in topiramate 50 mg/day group and 69% in topiramate 400 mg/day group) experienced weight reductions. The majority of weight changes across the treatment groups were in the range from –9% to 9% (See Sponsor Table 22 below). Weight decreases of at least 10% were reported at a higher incidence in the subjects receiving topiramate 400 mg/day (16%), compared with those receiving topiramate 50 mg/day (4%). Weight changes of 20% or more were reported for 2 subjects in topiramate 50 mg/day group (both cases of weight gain) and 6 subjects in topiramate 400 mg/day group (5 cases of weight loss and 1 of weight gain).

Table 22: Changes from Baseline[a] to Final Visit in Body Weight
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

	TPM 50 (N=234)[b]		TPM 400 (N=236)[b]	
Weight (kg)				
Mean at Baseline	67.3		65.2	
Mean at Final	66.6		62.5	
Mean Change (SD)	-0.7 (4.11)		-2.7 (5.19)	
Mean Percent Change (SD)	-0.4 (6.18)		-3.5 (7.55)	
Incidence of Weight Changes (n,%)				
20-29% Increase	2	(1)	1	(0)
10-19% Increase	12	(5)	7	(3)
1-9% Increase	69	(29)	47	(20)
No Change	23	(10)	18	(8)
1-9% Decrease	119	(51)	125	(53)
10-19% Decrease	9	(4)	33	(14)
20-29% Decrease	0	(0)	5	(2)

[a] Baseline was defined as the last observation prior to the first topiramate dose.
[b] Includes only subjects with data available for both baseline and the final visit.

Among all subjects with weight decreases of 10% or more, 10 were pediatric subjects, including an 11-year-old and 9 subjects between 12 and 15 years of age. Of these 10 pediatric subjects, only 1 (the 11-year-old Subject 537003 in topiramate 400 mg/day group) had a BMI under the 5th percentile for his age at the final evaluation. Weight decrease was not reported as an adverse event for this subject, who discontinued the study due to micturition frequency (urinary urgency) on Day 42; his final dose of topiramate was 150 mg/day.

8.1.17 Vital signs

Seven subjects had 1 or more vital sign abnormalities reported as adverse events. All of these abnormalities were mild to moderate in severity; all but 1 were judged by the investigators as having a doubtful or no relationship to study treatment. None of those events were serious or resulted in discontinuation of treatment. In 1 case, the dose of topiramate was reduced in a subject reporting mild palpitation. All events resolved.

8.1.18 Visual Field examinations

Of the 48 subjects who had baseline visual field examinations on the Humphrey Perimeter, 46 subjects also had post baseline data available. The average duration of double-blind topiramate treatment for these 46 subjects was 285 days (median, 267 days; range, 16 to 729 days). These cases were reviewed in a blind fashion with regard to the topiramate dose by an independent expert ophthalmologist, (b) (4). Of the 46 cases, 40 were considered normal, while the remaining 6 showed some minimal deficits, which were considered by the expert to be associated with some technical problems such as eyelid impairment, loss of fixation, or nystagmus. The decrease in peripheral visual fields was reported as an adverse event following a visual field examination in Subject 533006; review of the results of a follow-up visual field test by the independent expert ophthalmologist did not reveal any abnormalities in this subject's measurements. No pattern of drug toxicity was detected in any of the visual field measurements in the expert review.

8.2 ISS Safety Review

Per the sponsor, safety data from 3 topiramate monotherapy studies conducted in pediatric and adult subjects with newly/recently diagnosed or recurrent epilepsy were pooled into 3 data sets. Data from these 3 studies provided the principal safety information related to the use of topiramate monotherapy in epilepsy. The 3 data sets included full safety data for subjects who received topiramate in the open-treatment, double-blind, and open-label extension phases of Studies TOPMAT-EPMN-104 (Study 104) and TOPMAT-EPMN-106 (Study 106), and the double-blind phase data from Study TOPMAT-EPMN-105 (Study 105). A cut-off date of February 15, 2002 was applied to the data from ongoing extension phases of Studies 104 and 106.

8.2.1 Study design differences per sponsor

Studies 104 and 106 included an open-treatment phase prior to randomization to double-blind treatment. In this phase, which was designed to assess the subject's ability to tolerate the study drug, subjects received topiramate 25 mg/day for 7 days. Only those

subjects who did not have unacceptable tolerability problems were randomly assigned to double-blind treatment. Study 105 did not include an open-treatment phase.

During the titration period of the double-blind phase of Studies 104 and 105, baseline AEDs used by the subjects were gradually tapered off concurrent with the upward titration of the double-blind study medication. In Study 106, baseline AEDs were discontinued **before** randomization.

The topiramate titration rates employed in the 3 studies differed. For example, the 500 mg/day target dose for the high-weight subjects in Study 104 was first administered on Day 36, the same day on which the 400 mg/day target dose in Study 106 was reached.

Study 104 permitted topiramate dose reductions during the stabilization period on up to 2 occasions. The dose reductions were to be temporary, **with subsequent retitration** to the target dose or the maximum tolerated dose, if possible. In Study 106, dose reductions were not permitted during the first 3 weeks of the titration period. Subjects who experienced unacceptable difficulty tolerating topiramate during this time were withdrawn from the study. A total of 2 50-mg dose reductions were allowed after Day 21 through the end of titration period. During stabilization, dose reductions were also allowed. Following dose reduction during the either study period, the topiramate dose was not to be increased (**no subsequent retitration**) Dose reductions for subjects randomized to the 400 mg/day dose group were to occur in 50 mg/day increments; the reduced dose could not be lower than the dose of the titration week prior to the maximum dose achieved during titration. One dose reduction of 25 mg/day was allowed for subjects randomized to the 50 mg/day dose group.

Unlike the other 2 studies, Study 105 did not permit dose reductions during the double-blind phase. Subjects who experienced unacceptable tolerability difficulties in Study 105 were withdrawn from the study.

The TPM 500 dose group in the Double-Blind Topiramate data set included subjects in the high-dose group of Study 104 who received target topiramate doses of 200 mg/day (subjects weighing 25-50 kg) or 500 mg/day (subjects weighing 50.1-110 kg). Thus, the actual topiramate doses received by many of the subjects in the TPM 500 group, including most pediatric subjects, were less than 500 mg/day. Additional differences between the actual and target dosages of the Double-Blind Topiramate treatment groups, in particular the TPM 400 and TPM 500 groups contributed to apparent associations between topiramate dose and safety results.

The duration of the double-blind phase of the 3 studies differed. The duration of therapy for subjects in Study 104, which contributed subjects to the lowest (TPM 50) and highest (TPM 500) treatment groups in the Double-Blind Topiramate data set, was shorter than the duration of therapy in the other 2 studies.

8.2.2 Monotherapy data sets

Sponsor Table 6 from the submission, outlines the basic treatment groups in the pooled monotherapy data. The data are presented with the numbers of exposures related to dosing in Sponsor Table 7.

Table 6: Topiramate Treatment Groups Used in the Principal Safety Analyses (Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

Data Set Topiramate Treatment Group	Composition of Treatment Groups
Data Set 1: Double-Blind Topiramate. Subjects who entered the double-blind phase of Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106	
TPM 50	Subjects randomized to 50 mg/day in TOPMAT-EPMN-106 or into the low-dose group (25 mg/day for subjects weighing 25-50 kg or 50 mg/day for subjects weighing 50.1-110 kg) in TOPMAT-EPMN-104
TPM 100	Subjects in TOPMAT-EPMN-105 randomized to 100 mg/day
TPM 200	Subjects in TOPMAT-EPMN-105 randomized to 200 mg/day
TPM 400	Subjects in TOPMAT-EPMN-106 randomized to 400 mg/day
TPM 500	Subjects in TOPMAT-EPMN-104 randomized into the high-dose group (200 mg/day for subjects weighing 25-50 kg or 500 mg/day for subjects weighing 50.1-110 kg)
Data Set 2: Open-Label Extension Topiramate. Subjects who entered the open-label extension phase of Studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106	
TPM 50/500	Subjects in TOPMAT-EPMN-104 who had been randomized to the low-dose regimen (25 mg/day for subjects weighing 25-50 kg or 50 mg/day for subjects weighing 50.1-110 kg) during the double-blind phase and were to receive 500 mg/day in the open-label extension phase
TPM 50/400	Subjects in TOPMAT-EPMN-106 who had been randomized to double-blind therapy with 50 mg/day; these subjects were to receive 400 mg/day in the open-label extension phase
TPM 400/400	Subjects in TOPMAT-EPMN-106 who had been randomized to double-blind therapy with 400 mg/day; these subjects were to receive 400 mg/day in the open-label extension phase
TPM 500/500	Subjects in TOPMAT-EPMN-104 who had been randomized to the high-dose regimen (200 mg/day for subjects weighing 25-50 kg or 500 mg/day for subjects weighing 50.1-110 kg) during the double-blind phase and were to receive 500 mg/day in the open-label extension phase
Data Set 3: Total Topiramate Monotherapy Exposure. Subjects who received topiramate monotherapy in the double-blind phase of Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106 or the open-label extension phase of Studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106	
TPM 1 to <100 mg/day	Subjects whose maximum dose of topiramate monotherapy was within this range
TPM 100 to <200 mg/day	Subjects whose maximum dose of topiramate monotherapy was within this range
TPM 200 to <300 mg/day	Subjects whose maximum dose of topiramate monotherapy was within this range
TPM 300 to <500 mg/day	Subjects whose maximum dose of topiramate monotherapy was within this range
TPM ≥500 mg/day	Subjects whose maximum dose of topiramate monotherapy was within this range

NOTE: The data from studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106 are included from the start of the open-treatment phase through the end of monotherapy, i.e., through either termination of treatment, addition of another AED allowed in the extension phase, or through the 15 February 2002 cut-off date.

Table 7: Principal Safety Data Sets in the ISS: Numbers of Subjects by Randomized Treatment and Study

Data Set / Study	Topiramate (TPM) treatment group (mg/day)					
Double-blind topiramate treatment (N=1,131)	**50**	**100**	**200**	**400**	**500**	**All doses**
TOPMAT-EPMN-104	125	0	0	0	127	252
TOPMAT-EPMN-105	0	210	199	0	0	409
TOPMAT-EPMN-106	234	0	0	236	0	470
Total	359	210	199	236	127	1,131[a]
Open-Label Extension Topiramate (N=432)	**50/500**	**50/400**	**400/400**	**500/500**		**All doses**
TOPMAT-EPMN-104	87	0	0	77		164
TOPMAT-EPMN-106	0	150	118	0		268
Total	87	150	118	77		432
Total Topiramate Monotherapy Exposure (N=1,127)	**<100**	**100-<200**	**200-<300**	**300-<500**	**≥500**	**All doses**
TOPMAT-EPMN-104	43	10	27	35	137	252
TOPMAT-EPMN-105	19	211	175	0	0	405[a]
TOPMAT-EPMN-106	102	90	23	244	11	470
Total	164	311	225	279	148	1,127[a]

[a] Four subjects randomized to receive topiramate in Study TOPMAT-EPMN-105 received treatment with another AED instead of their assigned topiramate treatment; thus, these subjects are included in data set 1 and excluded from data set 3.

8.2.3 Exposures

Per the sponsor, in terms of exposure,

- Of the 1131 patients in the double blind topiramate set, 245 (22%) were pediatric (6-15), 886 (78%) were adults including 93 (8%) elderly (equal or greater than age 65).
- Of the 432 patients in the open label extension, included was a somewhat higher proportion of pediatric subjects, 128 (30%).
- Overall, 1127 patients received topiramate monotherapy in the three studies (104, 105 and 106). This population included 584 male and 543 female patients ranging in age from 6-85 years.
- In all three data sets, the median time since the diagnosis of epilepsy was 1 or 2 months and approximately half of the subjects had received AEDs during the three months prior to the start of topiramate treatment.
- The average duration of exposure was 253 days in the double blind topiramate group and 360 days in the open label extension data set. The overall mean duration of exposure to topiramate monotherapy was 368 days.

- At all target doses of 400mg/day or lower, more than 300 subjects received at least six months of treatment and 100 patients received more than one year of treatment.

- The 1,131 subjects in the Double-Blind Topiramate data set received a total of 783.9 person-years of topiramate treatment, including a total exposure of 209.3 person-years among pediatric subjects and 574.6 person-years among adults.

- Total Topiramate Monotherapy Exposure: Among the 1,127 subjects who received topiramate monotherapy in Studies 104, 105, and 106, the mean duration of monotherapy was approximately 1 year (range, 3 days to 5.7 years). Overall, 455 (40%) of 1,127 subjects received topiramate monotherapy for at least 1 year, with 772 (69%) and 876 (78%) subjects receiving at least 6 months and 3 months of monotherapy, respectively.

8.2.4 Dosages and the exposures in each group by dose (Sponsor Table 29)

Table 29: Daily Dosage of Study Therapy: Double-Blind Topiramate
(Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

Treatment Group	N	Mean	SD	Median	Range
Average daily dosage (mg/day)					
TPM 50	359	42.9	9.08	47.4	17.0-78.1
TPM 100	209	88.4	17.14	95.9	6.7-100.0
TPM 200	196	162.0	45.48	184.9	25.0-195.9
TPM 400	236	275.3	120.98	335.3	27.4-399.1
TPM 500	127	283.6	141.39	306.0	38.3-480.6
Maximum daily dosage (mg/day)					
TPM 50	359	49.2	15.39	50.0	25.0-200.0
TPM 100	209	97.0	12.26	100.0	25.0-100.0
TPM 200	196	188.9	35.19	200.0	25.0-200.0
TPM 400	236	339.7	121.42	400.0	50.0-800.0
TPM 500	127	406.5	153.70	500.0	50.0-1,000.0
Final daily dosage (mg/day)					
TPM 50	358	45.3	15.57	50.0	0.0-200.0
TPM 100	209	96.5	13.31	100.0	25.0-100.0
TPM 200	196	188.8	35.29	200.0	25.0-200.0
TPM 400	236	313.0	126.35	400.0	0.0-450.0
TPM 500	127	366.5	158.56	450.0	50.0-500.0

Note: Treatment groups are defined in Table 6.

8.2.5 Differences in Topiramate Exposure and Administered Dosages

- The TPM 500 dose group in the Double-Blind Topiramate data set included subjects in the high-dose group of Study 104 who received target topiramate doses of 200 mg/day (subjects weighing 25-50 kg) or 500 mg/day (subjects weighing 50.1-110 kg). Thus, the actual topiramate doses received by many of the subjects in the TPM 500 group, including most pediatric subjects, *were less than* 500 mg/day.

- The duration of the double-blind phase of the 3 studies differed. The duration of therapy for subjects in Study 104, which contributed subjects to the lowest (TPM 50) and highest (TPM 500) treatment groups in the Double-Blind Topiramate data set, was *shorter* than the duration of therapy in the other 2 studies.

This is summarized in Sponsor Tables 25 and 30.

Table 25: Cumulative Distribution of Subjects by Duration of Therapy: Double-Blind Topiramate (Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

Duration of therapy (days)	TPM 50 (N=359) n (%)	TPM 100 (N=210) n (%)	TPM 200 (N=199) n (%)	TPM 400 (N=236) n (%)	TPM 500 (N=127) n (%)	Total (N=1,131) n (%)
≥1	359 (100)	210 (100)	199 (100)	236 (100)	127 (100)	1131 (100)
≥30	319 (89)	190 (90)	176 (88)	203 (86)	112 (88)	1000 (88)
≥90	237 (66)	160 (76)	141 (71)	171 (72)	80 (63)	789 (70)
≥180	203 (57)	141 (67)	116 (58)	149 (63)	54 (43)	663 (59)
≥365	87 (24)	67 (32)	56 (28)	86 (36)	17 (13)	313 (28)
N	359	210	199	236	127	1131
Mean	242.8	277.4	242.0	287.3	194.8	253.0
SD	195.63	194.35	183.37	214.87	176.03	197.11
Median	213.0	256.5	225.0	266.5	141.0	225.0
Range	(9-763)	(6-729)	(3-806)	(9-786)	(15-809)	(3-809)

Note: Treatment groups are defined in Table 6.

- Overall Exposure to Topiramate (Double-Blind + Open-Label): In Studies 104, 105, and 106, the average overall exposure to topiramate for all 1,131 topiramate-treated subjects (i.e., Double-Blind and Open-Label Extension data sets combined) was more than 1 year (390.6 days). The average duration of topiramate treatment was somewhat longer for the 245 pediatric subjects who received topiramate (423.5 days). Of the total population of topiramate-treated subjects, 478 (42%), 791 (70%), and 892 (79%) subjects received topiramate for at least 1 year, 6 months, and 3 months, respectively. The corresponding numbers and percentages for pediatric topiramate-treated subjects were 132 (54%), 211 (86%), and 221 (90%) subjects, respectively. This is illustrated in Sponsor Table 28.

Table 28: Cumulative Distribution of Subjects by Duration of Therapy: Total Topiramate Monotherapy Exposure
(Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

	Maximum TPM dose (mg/day)					
Duration of treatment (days)	1-<100 (N=164) n (%)	100-<200 (N=311) n (%)	200-<300 (N=225) n (%)	300-<500 (N=279) n (%)	≥500 (N=148) n (%)	Total (N=1,127) n (%)
≥1	164 (100)	311 (100)	225 (100)	279 (100)	148 (100)	1127 (100)
≥30	105 (64)	275 (88)	221 (98)	279 (100)	148 (100)	1028 (91)
≥90	72 (44)	236 (76)	181 (80)	251 (90)	136 (92)	876 (78)
≥180	63 (38)	211 (68)	153 (68)	229 (82)	116 (78)	772 (69)
≥365	32 (20)	113 (36)	83 (37)	140 (50)	87 (59)	455 (40)
N	164	311	225	279	148	1127
Mean	180.4	294.8	333.7	402.9	715.8	368.0
SD	206.24	207.99	310.97	293.92	617.73	362.62
Median	74.5	274.0	267.0	365.0	458.5	288.0
Range	(3-763)	(8-782)	(23-1695)	(30-1982)	(33-2086)	(3-2086)

Note: Treatment groups are defined in Table 6.

8.2.6 Discontinuations/double blind phase

Discontinuations by study were summarized separately in each study and summarized in the following sponsor tables (Tables 20-22).

Table 20: Study Completion/Discontinuation Information: Double-Blind Topiramate
(Study TOPMAT-EPMN-104)

	TPM 50 (N=125)		TPM 500 (N=127)	
Completion status	n	(%)	n	(%)
Completed[a]	**99**	**(79)**	**93**	**(73)**
Discontinued	**26**	**(21)**	**34**	**(27)**
Subject's choice	10	(8)	17	(13)
Lost to follow-up	5	(4)	2	(2)
Other	11	(9)	15	(12)

Note: Treatment groups are defined in Table 6.
[a] Includes subjects who completed by exiting the study according to criteria specified in the protocol and those who continued in the double-blind phase until it was terminated.

Table 21: Study Completion/Discontinuation Information: Double-Blind Topiramate (Study TOPMAT-EPMN-105)

	TPM 100 (N=210)		TPM 200 (N=199)		Total (N=409)	
Completion Status	n	(%)	n	(%)	n	(%)
Did Not Exit	**119**	**(57)**	**104**	**(52)**	**223**	**(55)**
Completed[a]	105	(50)	87	(44)	192	(47)
Withdrawn[b]	14	(7)	17	(9)	31	(8)
Exited per protocol	**91**	**(43)**	**95**	**(48)**	**186**	**(45)**
Adverse Event	40	(19)	55	(28)	95	(23)
Ineffective Treatment	23	(11)	18	(9)	41	(10)
Subject Choice	18	(9)	16	(8)	34	(8)
Lost to Follow-Up	8	(4)	5	(3)	13	(3)
Other	2	(1)	1	(1)	3	(1)

[a] Completed at the time of the planned study termination (6 months after the last subject was randomized.
[b] Withdrawn for protocol violations.

Table 22: Study Completion/Discontinuation Information: Double-Blind Topiramate (Study TOPMAT-EPMN-106)

	TPM 50 (N=234)		TPM 400 (N =236)		Total (N=470)	
Completion Status						
Completed, n (%)	**195**	**83**	**161**	**68**	**356**	**76**
Completed at DB phase termination[a]	105	45	112	47	217	46
Completed by experiencing a seizure	90	38	49	21	139	30
Withdrew, n(%)	**39**	**17**	**75**	**32**	**114**	**24**
Adverse event	13	6	40	17	53	11
Subject choice	9	4	13	6	22	5
Lost to follow-up	9	4	10	4	19	4
Other	8	3	12	5	20	4

[a] Subjects who were active in the study at the time of termination of the double-blind (DB) phase, i.e., 6 months after randomization of the last subject.

8.2.7 Discontinuations/open label extension

This is summarized in Sponsor Tables 23 and 24.

Table 23: Study Completion/Discontinuation Information: Open-Label Extension Topiramate (Study TOPMAT-EPMN-104)

	TPM 50/500 (N=87)	TPM 500/500 (N=77)	Total (N=164)
Status as of 15 February 2002			
Ongoing, n (%)	26 (30)	31 (40)	57 (35)
Discontinued, n (%)			
Lost to follow-up	3 (3)	2 (3)	5 (3)
Subject choice	14 (16)	13 (17)	27 (16)
Other	42 (48)	27 (35)	69 (42)
Death	2 (2)	4 (5)	6 (4)
Total discontinued	61 (70)	46 (60)	107 (65)

Note: Treatment groups are defined in Table 6.

Table 24: Study Completion/Discontinuation Information: Open-Label Extension Topiramate (Study TOPMAT-EPMN-106)

Status as of 15 February 2002	TPM 50/400 (N=150)	TPM 400/400 (N=118)	Total (N=268)
Ongoing, n (%)	125 (83)	106 (90)	231 (86)
Discontinued, n (%)			
Lost to follow-up	5 (3)	1 (1)	6 (2)
Adverse event	10 (7)	4 (3)	14 (5)
Subject choice	2 (1)	4 (3)	6 (2)
Other	8 (5)	3 (3)	11 (4)
Total discontinued	25 (17)	12 (10)	37 (14)

Clinical Reviewer comment: This reviewer notes the larger number of dropouts during the double blind phase due to adverse events seen in the higher dose groups. In Study 105, 19% of the TPM 100 group vs. 28% of the TPM 200 group dropped out. In Study 106 6% of the TPM 50 group vs. 17% of the TPM 400 group withdrew from the study. The reviewer also notes the large number of discontinuations in the extension phase of Study 104 at the 500 mg dose (65% overall) and in the extension phase of Study 106 at the 400mg dose (14% overall). This is concerning as adverse events leading to dropouts seems to be more significant in the higher dose groups, although this is difficult to compare across the different studies.

8.2.8 Treatment emergent Adverse events

Per the sponsor, the overall adverse event profile observed in the Double-Blind Topiramate, Open-Label Extension Topiramate, and the Total Topiramate Monotherapy Exposure data sets was consistent with the known safety profile of topiramate administered as adjunctive antiepileptic therapy.

Double Blind population (adults and children N=1131)

Adverse events related to dose groups for the double blind topiramate population (adults and pediatric are illustrated in Sponsor table 31.

Table 31: Subject Incidence of the Most Common[a] Adverse Events: Double-Blind Topiramate (Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

Body system Preferred term	TPM 50 (N=359) n (%)	TPM 100 (N=210) n (%)	TPM 200 (N=199) n (%)	TPM 400 (N=236) n (%)	TPM 500 (N=127) n (%)	Total (N=1131) n (%)
Central & peripheral nervous system						
Paresthesia	53 (15)	52 (25)	66 (33)	73 (31)	44 (35)	288 (25)
Headache	83 (23)	52 (25)	36 (18)	35 (15)	25 (20)	231 (20)
Dizziness	54 (15)	28 (13)	24 (12)	29 (12)	15 (12)	150 (13)
Hypoesthesia	12 (3)	10 (5)	9 (5)	8 (3)	14 (11)	53 (5)
Language problems	11 (3)	6 (3)	13 (7)	8 (3)	8 (6)	46 (4)
Ataxia	6 (2)	7 (3)	9 (5)	6 (3)	5 (4)	33 (3)
Psychiatric						
Somnolence	41 (11)	26 (12)	25 (13)	33 (14)	21 (17)	146 (13)
Anorexia	27 (8)	23 (11)	27 (14)	32 (14)	14 (11)	123 (11)
Insomnia	27 (8)	21 (10)	14 (7)	16 (7)	12 (9)	90 (8)
Difficulty with concentration/ attention	24 (7)	9 (4)	22 (11)	20 (8)	10 (8)	85 (8)
Difficulty with memory	14 (4)	17 (8)	17 (9)	18 (8)	12 (9)	78 (7)
Depression	14 (4)	16 (8)	21 (11)	17 (7)	5 (4)	73 (6)
Nervousness	19 (5)	15 (7)	18 (9)	10 (4)	9 (7)	71 (6)
Mood problems	9 (3)	14 (7)	14 (7)	14 (6)	5 (4)	56 (5)
Anxiety	11 (3)	9 (4)	11 (6)	10 (4)	6 (5)	47 (4)
Psychomotor slowing	7 (2)	8 (4)	11 (6)	10 (4)	9 (7)	45 (4)
Confusion	11 (3)	6 (3)	11 (6)	8 (3)	8 (6)	44 (4)
Cognitive problems	3 (1)	6 (3)	4 (2)	12 (5)	3 (2)	28 (2)
Body as a whole – general						
Fatigue	46 (13)	43 (20)	45 (23)	26 (11)	23 (18)	183 (16)
Injury	29 (8)	14 (7)	11 (6)	16 (7)	6 (5)	76 (7)
Asthenia	10 (3)	8 (4)	7 (4)	12 (5)	5 (4)	42 (4)
Fever	6 (2)	3 (1)	6 (3)	12 (5)	4 (3)	31 (3)
Back pain	12 (3)	3 (1)	6 (3)	3 (1)	6 (5)	30 (3)
Pain	8 (2)	5 (2)	4 (2)	3 (1)	6 (5)	26 (2)
Gastrointestinal						
Nausea	38 (11)	15 (7)	28 (14)	18 (8)	16 (13)	115 (10)
Diarrhea	21 (6)	18 (9)	17 (9)	17 (7)	15 (12)	88 (8)
Abdominal pain	27 (8)	7 (3)	14 (7)	16 (7)	10 (8)	74 (7)
Vomiting	19 (5)	10 (5)	8 (4)	9 (4)	4 (3)	50 (4)
Dyspepsia	16 (4)	8 (4)	6 (3)	11 (5)	4 (3)	45 (4)
Mouth dry	1 (<1)	5 (2)	2 (1)	4 (2)	7 (6)	19 (2)
Respiratory						
Upper resp. tract infection	63 (18)	37 (18)	34 (17)	35 (15)	14 (11)	183 (16)
Pharyngitis	24 (7)	10 (5)	11 (6)	10 (4)	5 (4)	60 (5)
Sinusitis	14 (4)	5 (2)	11 (6)	7 (3)	9 (7)	46 (4)
Rhinitis	9 (3)	10 (5)	5 (3)	11 (5)	9 (7)	44 (4)
Metabolic and nutritional						
Weight decrease	26 (7)	20 (10)	24 (12)	38 (16)	20 (16)	128 (11)

Note: Treatment groups are defined in Table 6.
[a] Adverse events that occurred in at least 5% of the subjects in any treatment group.

Table 31: Subject Incidence of the Most Common[a] Adverse Events: Double-Blind Topiramate (Continued)
(Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

Body system Preferred term	TPM 50 (N=359) n (%)	TPM 100 (N=210) n (%)	TPM 200 (N=199) n (%)	TPM 400 (N=236) n (%)	TPM 500 (N=127) n (%)	Total (N=1131) n (%)
Skin and appendages						
Rash	4 (1)	13 (6)	7 (4)	10 (4)	6 (5)	40 (4)
Resistance mechanism						
Infection viral	15 (4)	13 (6)	20 (10)	17 (7)	8 (6)	73 (6)
Urinary						
Urinary tract infection	6 (2)	3 (1)	4 (2)	3 (1)	6 (5)	22 (2)
Musculoskeletal						
Arthralgia	6 (2)	7 (3)	9 (5)	6 (3)	5 (4)	33 (3)
Reproductive, female[b]						
Menstrual disorder	4 (2)	2 (2)	1 (1)	0	4 (7)	11 (2)
Special senses other						
Taste perversion	6 (2)	6 (3)	7 (4)	8 (3)	7 (6)	34 (3)
Any adverse event	**298 (83)**	**189 (90)**	**176 (88)**	**201 (85)**	**118 (93)**	**982 (87)**

Note: Treatment groups are defined in Table 6.
[a] Adverse events that occurred in at least 5% of the subjects in any treatment group.
[b] Numbers of female subjects by treatment group: 186 (TPM 50), 94 (TPM 100), 92 (TPM 200), 113 (TPM 400), 60 (TPM 500), and 545 (Total).

The most frequently reported adverse events were neuropsychiatric events (including paresthesia, headache, fatigue, somnolence, dizziness, and anorexia) as well as upper respiratory infection, weight decrease, and nausea. Most of the frequently reported adverse events showed no consistent relationship with topiramate dose. However, the incidence of paresthesia—the most common adverse event and a characteristic effect associated with carbonic anhydrase inhibitors—as well as somnolence and weight decrease tended to increase with increasing topiramate dose and were reported at an incidence that was at least 5% higher in the TPM 500 vs. the TPM 50 group. Other apparent differences in adverse event incidence observed between various dose groups included the following:

- Hypoesthesia occurred more frequently in the TPM 500 group (11%) compared with the 4 lower dose groups (3-5%). A similar trend was observed for menstrual disorder (7% vs. 0-2%).

- Renal calculi were reported at a higher incidence in the TPM 400 and TPM 500 groups (2%) compared with the 3 lower dose groups (0-1%).

- Some neuropsychiatric events, including difficulty with concentration or attention and depression, were more frequently reported in the TPM 200 group vs. the other dose groups (11% vs. 4-8% for both events).

- Difficulty with memory was more common among subjects who received doses of TPM 100 and higher (8-9%) vs. TPM 50 (4%).

Clinical Reviewer comment: This reviewer notes that the sponsor does not discuss the issues of headache, somnolence and fatigue seen across the entire study population. Since there is no placebo group in which to compare, these significant incidences a might reduce the overall tolerability of the medication in the study population.

8.2.9 Pediatric (N=245)

For pediatric subjects in the Double-Blind Topiramate group, the most common adverse events reported by the subgroup of pediatric subjects were neuropsychiatric events. For most of the frequently reported adverse events, no noteworthy differences were observed in adverse event incidence between all subjects and pediatric subjects in this data set. Paresthesia, fatigue, dizziness, and nausea were reported with a higher incidence in the 1,131 subjects (adults and pediatric subjects) who received double-blind topiramate compared to the 245 pediatric subjects. Upper respiratory infections were more common among pediatric subjects vs. adults. Among pediatric subjects, the incidence of weight loss was higher among subjects in the TPM 400 group (17%) compared with the other treatment groups (0-7% incidence). All but 1 of the weight decreases reported by pediatric subjects in this treatment group were mild to moderate in severity and considered by the investigators to be possibly or probably related to the study therapy. Markedly severe weight decrease was reported for 1 pediatric subject (Subject 106/613002, a 15-year-old girl in the TPM 400 group), whose baseline weight and height were 61 kg and 159 cm (BMI of 24.1), and who experienced a weight decrease to 55 kg (BMI of 21.8) at a topiramate dose of 350 mg/day. After this decrease, the subject's weight did not change for the remainder of the study. Of note, the final BMI value for this subject was above the 50th percentile for her age/sex group. Most common adverse events seen in the pediatric subgroup are illustrated in Sponsor Table 42 below.

Table 32: Subject Incidence of the Most Common[a] Adverse Events in Pediatric Subjects: Double-Blind Topiramate
(Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

Body system Preferred term	TPM 50 (N=95) n (%)	TPM 100 (N=30) n (%)	TPM 200 (N=29) n (%)	TPM 400 (N=77) n (%)	TPM 500 (N=14) n (%)	Total (N=245) n (%)
Psychiatric						
Anorexia	12 (13)	4 (13)	4 (14)	10 (13)	2 (14)	32 (13)
Somnolence	13 (14)	4 (13)	1 (3)	9 (12)	0	27 (11)
Difficulty with concentration/ attention	5 (5)	2 (7)	6 (21)	8 (10)	1 (7)	22 (9)
Insomnia	4 (4)	2 (7)	2 (7)	2 (3)	2 (14)	12 (5)
Nervousness	5 (5)	1 (3)	2 (7)	4 (5)	0	12 (5)
Mood problems	2 (2)	1 (3)	2 (7)	6 (8)	0	11 (4)
Difficulty with memory	1 (1)	4 (13)	0	2 (3)	2 (14)	9 (4)
Cognitive problems	1 (1)	0	1 (3)	5 (6)	0	7 (3)
Psychomotor slowing	2 (2)	2 (7)	1 (3)	2 (3)	0	7 (3)
Aggressive reaction	1 (1)	1 (3)	2 (7)	1 (1)	1 (7)	6 (2)
Depression	0	0	3 (10)	2 (3)	0	5 (2)
Sleep disorder	2 (2)	1 (3)	2 (7)	0	0	5 (2)
Personality disorder (behavior Problems s)	2 (2)	0	0	2 (3)	0	4 (2)
Confusion	0	0	1 (3)	2 (3)	0	3 (1)
Central & peripheral nervous system						
Headache	26 (27)	8 (27)	6 (21)	12 (16)	4 (29)	56 (23)
Dizziness	10 (11)	1 (3)	2 (7)	7 (9)	0	20 (8)
Paresthesia	3 (3)	2 (7)	3 (10)	9 (12)	1 (7)	18 (7)
Hyperkinesia	1 (1)	1 (3)	0	0	3 (21)	5 (2)
Language problems	0	0	2 (7)	1 (1)	1 (7)	4 (2)
Migraine	2 (2)	0	0	1 (1)	0	3 (1)
Muscle contractions involuntary	1 (1)	0	0	2 (3)	0	3 (1)
Tremor	2 (2)	1 (3)	0	0	0	3 (1)
Vertigo	0	0	1 (3)	2 (3)	0	3 (1)
Respiratory						
Upper resp. tract infection	23 (24)	9 (30)	12 (41)	14 (18)	3 (21)	61 (25)
Pharyngitis	8 (8)	3 (10)	2 (7)	3 (4)	3 (21)	19 (8)
Rhinitis	5 (5)	1 (3)	1 (3)	5 (6)	3 (21)	15 (6)
Sinusitis	2 (2)	2 (7)	3 (10)	3 (4)	2 (14)	12 (5)
Bronchitis	2 (2)	1 (3)	0	4 (5)	0	7 (3)
Coughing	2 (2)	0	0	1 (1)	0	3 (1)
Gastrointestinal						
Diarrhea	7 (7)	4 (13)	0	7 (9)	1 (7)	19 (8)
Vomiting	6 (6)	4 (13)	2 (7)	4 (5)	2 (14)	18 (7)
Abdominal pain	7 (7)	0	1 (3)	3 (4)	2 (14)	13 (5)
Nausea	5 (5)	0	2 (7)	3 (4)	2 (14)	12 (5)
Gastroenteritis	4 (4)	3 (10)	0	0	1 (7)	8 (3)

Note: Treatment groups are defined in Table 6.
[a] Adverse events that occurred in 2 or more pediatric subjects in any treatment group.

Cross-reference: Attachment 2.3.8.1 (continued)

Clinical Reviewer comment: This reviewer notes the omission of discussion of headache in pediatric patients. The incidence of headache appears to be significant and would limit usage of topiramate at these doses in this population or require further treatment.

8.2.10 Open label extension phase (N=432)

Adverse events reported with an incidence of at least 5% in any treatment group in the open label extension phase (Studies 104 and 106 only) are summarized in Sponsor Table 33. During the open-label extension phase, the most frequently reported adverse events were similar to the double blind phase with neuropsychiatric events (including paresthesia, headache, fatigue, somnolence, and difficulty with memory) as well as upper respiratory tract infection, nausea, and injury most common.

Clinical Reviewer comment: Again, as noted by this reviewer, headache, neurologic and psychiatric symptoms appear to be the most common events.

Table 33: Subject Incidence of the Most Common[a] Adverse Events: Open-Label Extension Topiramate
(Studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106)

Body system Preferred term	TPM 50/500 (N=87) n (%)	TPM 50/400 (N=150) n (%)	TPM 400/400 (N=118) n (%)	TPM 500/500 (N=77) n (%)	Total (N=432) n (%)
Central & peripheral nervous system					
Paresthesia	13 (15)	24 (16)	6 (5)	15 (19)	58 (13)
Headache	18 (21)	13 (9)	8 (7)	15 (19)	54 (13)
Dizziness	8 (9)	10 (7)	0	9 (12)	27 (6)
Language problems	5 (6)	1 (1)	1 (1)	9 (12)	16 (4)
Hypoesthesia	5 (6)	0	1 (1)	5 (6)	11 (3)
Tremor	4 (5)	1 (1)	0	4 (5)	9 (2)
Convulsions aggravated	3 (3)	1 (1)	0	4 (5)	8 (2)
Speech disorders/related speech problems	3 (3)	0	0	4 (5)	7 (2)
Psychiatric					
Somnolence	10 (11)	12 (8)	1 (1)	9 (12)	32 (7)
Difficulty with memory	11 (13)	12 (8)	1 (1)	5 (6)	29 (7)
Depression	12 (14)	4 (3)	0	9 (12)	25 (6)
Anxiety	9 (10)	7 (5)	1 (1)	6 (8)	23 (5)
Anorexia	8 (9)	6 (4)	1 (1)	5 (6)	20 (5)
Difficulty with concentration/attention	6 (7)	7 (5)	0	7 (9)	20 (5)
Insomnia	12 (14)	1 (1)	1 (1)	3 (4)	17 (4)
Nervousness	6 (7)	3 (2)	1 (1)	4 (5)	14 (3)
Confusion	4 (5)	2 (1)	0	7 (9)	13 (3)
Psychomotor slowing	4 (5)	5 (3)	1 (1)	2 (3)	12 (3)
Cognitive problems	4 (5)	3 (2)	1 (1)	3 (4)	11 (3)
Aggressive reaction	3 (3)	1 (1)	1 (1)	5 (6)	10 (2)
Mood problems	4 (5)	1 (1)	0	3 (4)	8 (2)
Emotional lability	1 (1)	2 (1)	0	4 (5)	7 (2)
Body as a whole – general					
Fatigue	12 (14)	13 (9)	3 (3)	8 (10)	36 (8)
Injury	10 (11)	6 (4)	0	14 (18)	30 (7)
Back pain	7 (8)	1 (1)	2 (2)	5 (6)	15 (3)
Chest pain	4 (5)	3 (2)	0	4 (5)	11 (3)
Fever	5 (6)	2 (1)	0	2 (3)	9 (2)
Pain	4 (5)	1 (1)	0	3 (4)	8 (2)
Asthenia	1 (1)	0	1 (1)	4 (5)	6 (1)
Respiratory					
Upper resp. tract infect.	27 (31)	6 (4)	4 (3)	18 (23)	55 (13)
Sinusitis	7 (8)	3 (2)	0	9 (12)	19 (4)
Bronchitis	5 (6)	1 (1)	2 (2)	7 (9)	15 (3)
Pharyngitis	7 (8)	2 (1)	3 (3)	1 (1)	13 (3)
Rhinitis	2 (2)	2 (1)	1 (1)	6 (8)	11 (3)
Coughing	5 (6)	3 (2)	2 (2)	0	10 (2)

Note: Treatment groups are defined in Table 6.
[a] Adverse events that occurred in at least 5% of the subjects in any treatment group.

Table 33: Subject Incidence of the Most Common[a] Adverse Events: Open-Label Extension Topiramate (Continued)
(Studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106)

Body system Preferred term	TPM 50/500 (N=87) n (%)	TPM 50/400 (N=150) n (%)	TPM 400/400 (N=118) n (%)	TPM 500/500 (N=77) n (%)	Total (N=432) n (%)
Gastrointestinal					
Nausea	14 (16)	5 (3)	3 (3)	8 (10)	30 (7)
Diarrhea	6 (7)	9 (6)	3 (3)	4 (5)	22 (5)
Abdominal pain	6 (7)	3 (2)	1 (1)	5 (6)	15 (3)
Vomiting	5 (6)	3 (2)	3 (3)	3 (4)	14 (3)
Dyspepsia	4 (5)	3 (2)	1 (1)	5 (6)	13 (3)
Constipation	4 (5)	1 (1)	0	3 (4)	8 (2)
Tooth disorder	1 (1)	0	0	5 (6)	6 (1)
Metabolic and nutritional					
Weight decrease	11 (13)	4 (3)	1 (1)	7 (9)	23 (5)
Resistance mechanism					
Infection viral	13 (15)	3 (2)	1 (1)	9 (12)	26 (6)
Urinary					
Urinary tract infection	8 (9)	1 (1)	1 (1)	5 (6)	15 (3)
Skin and appendages					
Skin dry	4 (5)	0	0	0	4 (1)
Vision					
Vision abnormal	5 (6)	4 (3)	0	3 (4)	12 (3)
Conjunctivitis	2 (2)	2 (1)	0	6 (8)	10 (2)
Musculoskeletal					
Arthralgia	5 (6)	2 (1)	0	4 (5)	11 (3)
Reproductive, female[b]					
Dysmenorrhea	3 (7)	0	0	0	3 (1)
Cardiovascular general					
Hypertension	1 (1)	0	1 (1)	4 (5)	6 (1)
Any adverse event	**78 (90)**	**71 (47)**	**31 (26)**	**67 (87)**	**247 (57)**

Note: Treatment groups are defined in Table 6.
[a] Adverse events that occurred in at least 5% of the subjects in any treatment group.
[b] Number of females in each treatment group: TPM 50/500 (N=43); TPM 50/400 (N=82), TPM 400/400 (N=56), TPM 500/500 (N=36). Total number of females who received open-label topiramate = 217.

8.2.11 Clinically significant adverse events

Clinically significant adverse events are described by the sponsor as "deaths and nonfatal serious adverse events, treatment limiting adverse events and adverse events that resulted in a dosage reduction or a temporary interruption in therapy."

8.2.11.1 Deaths

10 deaths occurred among the 1131 topiramate treated subjects in studies 104, 105 and 106. None were considered related to topiramate treatment. No pediatric subjects died.

Narrative descriptions were reviewed and not reproduced here. Deaths are summarized in Sponsor Table 36. Per the sponsor, eight of these deaths were considered unlikely to be related or of doubtful relationship to topiramate treatment, and the other 2 deaths were considered unrelated to the study drug. All 10 deaths were related to concomitant illnesses or conditions, injuries, or seizure-related events. None of the subjects died during the open-label extension phase.

Table 36: Subjects Who Died: Double-Blind Topiramate and Open-Label Extension Topiramate Data Sets (Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

Investigator Subject No Study phase.	Age Sex	Preferred Term Investigator Term	Day of AE Onset/ Dosage at AE Onset (mg/day)	Total Days of TPM/Final Dosage (mg/day)	Relationship[a]
TPM 50 (TOPMAT-EPMN-104)					
Kern	43	Brain neoplasm malignant	61	67	Unlikely
2055	F	Glioblastoma	0	50	
DB					
TPM 50/500 (TOPMAT-EPMN-104)					
Gazda	69	Injury	831	834	Unlikely
9542[a]	M	Broken hip right	300	300	
OL		Megacolon acquired	834		Unlikely
		Acute Ogilvie Syndrome/ (postoperative megacolon)	300		
		Sepsis	844		Unlikely
		Septic shock	0		
Hoffstetter	80	Aspiration	876	876	Unlikely
9102[a]	F	Aspiration	250	250	
OL					
TPM 50/400 (TOPMAT-EPMN-106)					
Ryvlin	42	Cerebral hemorrhage	324	214	Doubtful
571002[a]	M	Fatal cerebral hemorrhage	0	100	
OL					
TPM 500/500 (TOPMAT-EPMN-104)					
Bomhof	61	Claudication intermittent	24	189	Unlikely
2006[a]	M	Peripheral vascular disease	300	500	
OL					
Chadwick	75	Death	2059	Unknown	Not related
2101[b]	M	(suspected cause of death: bowel obstruction	500	500	
OL		or CVA)			
Ayala	35	Cardiac arrest	136	146	Unlikely
9500[a]	F	Cardiac arrest	0	500	
OL		Convulsions aggravated			Unlikely
		Prolonged seizure			
		Encephalopathy			Unlikely
		Anoxic encephalopathy			
Veloso	39	Pulmonary carcinoma	953	1054	Unlikely
2081	M	Carcinoma lung	200	200	
OL					
Browne	49	Arrhythmia	1223	1222	Unlikely
9020[a]	M	Cardiac arrhythmia	0	800	
OL					
Gazda	24	Seizures (sudden death of epilepsy)	1412	1412	Not related
9544[b]	M	Sudden death of epilepsy	400	400	
OL					

Key: CVA=cerebrovascular accident, DB=double-blind phase, OL=open-label extension phase.
[a] Based on the investigator's assessment at the time of the occurrence of the adverse event.
[b] Detailed information regarding this subject's death, which is not included in the clinical database as of 15 February 2002, was obtained from the DSS (CIOMS forms).

8.2.11.2 Serious Adverse Events (SAE's)

SAEs were reported by 8% (88/1,131) of subjects in the Double-Blind Topiramate data set, 12% (50/432) of subjects in the Open-Label Extension Topiramate data set, and 11% (120/1,127) of subjects in the Total Topiramate Monotherapy Exposure data set.

Generally, SAEs were experienced by smaller percentages of pediatric subjects vs. all subjects in the data sets. In the Double-Blind Topiramate data set, serious adverse events were more commonly observed during the stabilization vs. titration period, including all cases of serious renal calculi. Most of the serious adverse events were considered unlikely to be related or unrelated to topiramate treatment, and most resolved with continued topiramate treatment. Of the smaller numbers of serious adverse events that were considered treatment related (generally neuropsychiatric or seizure-related events), most resolved, either with continued topiramate treatment or following discontinuation of study medication. The only new or unexpected serious event reported during these trials was a case of polymyalgia rheumatica, which was considered unrelated to the study medication and resolved without discontinuation of topiramate treatment.

Double Blind Topiramate Data set (N=1131)

- SAEs were less common in the pediatric groups and more likely during the stabilization period than the titration period.
- SAEs were more often seen in the TPM 500 treatment group (19/127 or 15%)
- The most common serious events were grand mal convulsions (9 subjects), aggravated convulsions (6 subjects), infection (5 subjects), chest pain (4 subjects), and renal calculus (4 subjects).
- Most of the serious adverse events were considered by the investigators to be of doubtful/unlikely or no relationship to topiramate therapy. Most serious adverse events resolved by the final study visit.
- 20 subjects discontinued the study therapy due to the serious adverse events.
- Serious adverse events considered possibly or probably/very likely related to double-blind topiramate were reported for 15 subjects; 9 of these subjects discontinued treatment because of these adverse events. The most common serious events considered related to topiramate treatment were grand mal convulsions (5 subjects) and renal calculus (4 subjects). The remaining treatment-related serious events included various gastrointestinal system (3 subjects) or psychiatric disorders (3 subjects). The serious psychiatric disorders considered related to double-blind topiramate treatment included worsening psychosis, suicide attempt, and a combination of confusion, aggravated depression, and emotional lability.
- Pediatric Subjects in the Double-Blind Phase: Nine (4%) of the 245 pediatric subjects who received double-blind topiramate experienced 1 or more serious adverse events. The only serious adverse event reported for more than 1 pediatric subject was grand mal convulsions (2 subjects; 1%). Serious cases of aggressive reaction, personality disorder (behavior problems), suicide attempt, testis disorder, infection, asthma, and rash were each reported for 1 pediatric subject.
- With 1 exception, all adverse events reported as serious during double-blind treatment had been observed in previous clinical trials of topiramate. The 1 case of polymyalgia rheumatica, observed in Subject 104/2197 in the TPM 50 group, was the first reported case of this type. The subject's initial symptoms (pain in the joints and difficulty walking) were moderate in severity; the event was judged by the

investigator as unlikely to be related to topiramate and resolved without discontinuing topiramate therapy.

Open label extension topiramate (N=432)

- 50/432 (12%) subjects experienced 1 or more serious adverse events
- Serious adverse events reported for more than 1 subject included aggravated convulsions (n=6), grand mal convulsions (n=5), adverse event not specified (n=4); these events included hospitalization for arthroscopy, a psychotic episode, pelvic surgery, and intercranial electrode placement), psychosis (n=3), injury (n=3), headache (n=2), fever (n=2), deep thrombophlebitis (n=2), myocardial infarction (n=2), pulmonary embolism (n=2), and urinary tract infection (n=2).
- As with all adverse events, the incidence of serious adverse events was higher among subjects who were in the study with the longer duration (Study 104), which included subjects receiving an extension phase target dose of 500 mg/day (TPM 50/500 and TPM 500/500).
- Serious adverse events were among the reasons cited for discontinuation of topiramate treatment by 10 subjects.
- Thirteen subjects experienced serious adverse events considered possibly, probably, or certainly related to topiramate. All of these treatment-related serious adverse events resolved by the final study visit except weight decrease, which persisted in a subject who also experienced serious persistent gastric dilatation (Subject 104/2078).
- Pediatric Subjects: Five (4%) of the 128 pediatric subjects who received topiramate in the open-label extension phase reported 1 or more serious adverse events. All serious adverse events reported for pediatric subjects resolved, except convulsions reported for Subject 104/9403 in TPM 500/500 group, judged as having an unlikely relationship to topiramate; all but 1 event (status epilepticus in Subject 104/9371 in the TPM 500/500 group, possibly related) were considered unrelated or unlikely to be related to the study medication.

Total Topiramate Monotherapy Group N=1127

- Treatment-emergent serious adverse events were reported by 120 (11%) of 1,127 subjects who received topiramate monotherapy during Studies 104, 105, and 106.
- Serious adverse events reported by 2 or more subjects during treatment with topiramate monotherapy are summarized by maximum topiramate dose in Sponsor Table 39. The most common serious adverse events reported during topiramate monotherapy were grand mal convulsions, aggravated convulsions, infection, injury, chest pain, unspecified adverse events (generally hospitalizations for various procedures or treatment of various conditions), and renal calculus. Overall, serious adverse events were most common among subjects whose maximum topiramate dose was >500 mg/day; however, the incidence of individual serious events did not indicate any relationship with the maximum topiramate dose.

Table 39: Subject Incidence of the Most Common[a] Serious Adverse Events: Total Topiramate Monotherapy Exposure
(Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

	Maximum topiramate dose (mg/day)					
Body system Preferred term	1-<100 (N=164) n (%)	100-<200 (N=311) n (%)	200-<300 (N=225) n (%)	300-<500 (N=279) n (%)	≥500 (N=148) n (%)	Total (N=1,127) n (%)
Central & peripheral nervous system						
Convulsions grand mal	1 (1)	3 (1)	2 (1)	2 (1)	3 (2)	11 (1)
Convulsions aggravated	2 (1)	2 (1)	0	1 (<1)	4 (3)	9 (1)
Convulsions	1 (1)	0	0	1 (<1)	1 (1)	3 (<1)
Headache	0	0	1 (<1)	1 (<1)	1 (1)	3 (<1)
Body as a whole – general						
Injury	0	0	1 (<1)	2 (1)	2 (1)	5 (<1)
Adverse event	1 (1)	0	1 (<1)	1 (<1)	1 (1)	4 (<1)
Chest pain	1 (1)	0	1 (<1)	1 (<1)	1 (1)	4 (<1)
Back pain	0	0	1 (<1)	0	1 (1)	2 (<1)
Fever	0	0	1 (<1)	0	1 (1)	2 (<1)
Psychiatric						
Confusion	0	0	2 (1)	1 (<1)	0	3 (<1)
Depression aggravated	0	1 (<1)	1 (<1)	0	1 (1)	3 (<1)
Psychosis	0	0	1 (<1)	0	2 (1)	3 (<1)
Suicide attempt	0	1 (<1)	0	1 (<1)	1 (1)	3 (<1)
Aggressive reaction	0	1 (<1)	0	1 (<1)	0	2 (<1)
Emotional lability	0	0	1 (<1)	1 (<1)	0	2 (<1)
Personality disorder (behaviour problems)	0	0	0	1 (<1)	1 (1)	2 (<1)
Gastrointestinal						
Nausea	0	0	1 (<1)	1 (<1)	1 (1)	3 (<1)
Abdominal pain	0	0	0	2 (1)	0	2 (<1)
Vomiting	0	0	0	1 (<1)	1 (1)	2 (<1)
Respiratory						
Pneumonia	0	0	1 (<1)	0	2 (1)	3 (<1)
Vascular (extracardiac)						
Cerebrovascular disorder	1 (1)	0	1 (<1)	1 (<1)	0	3 (<1)
Thrombophlebitis deep	1 (1)	1 (<1)	0	0	1 (1)	3 (<1)
Claudication intermittent	0	0	0	0	2 (1)	2 (<1)
Neoplasms						
Brain neoplasm malignant	2 (1)	0	0	0	0	2 (<1)
Urinary						
Renal calculus	0	1 (<1)	1 (<1)	1 (<1)	1 (1)	4 (<1)
Urinary tract infection	1 (1)	0	0	1 (<1)	1 (1)	3 (<1)
Resistance mechanism						
Infection	0	0	0	4 (1)	1 (1)	5 (<1)
Myo-endo, pericardial, & valvular						
Myocardial infarction	1 (1)	0	0	0	2 (1)	3 (<1)
Angina pectoris	0	0	1 (<1)	1 (<1)	0	2 (<1)
Platelet, bleeding, & clotting						
Embolism pulmonary	0	1 (<1)	0	1 (<1)	1 (1)	3 (<1)
Any serious adverse event	**17 (10)**	**18 (6)**	**20 (9)**	**20 (7)**	**45 (30)**	**120 (11)**

[a] Serious adverse events reported by 2 or more subjects in the total group.
NOTE: An individual subject might have experienced more than serious 1 adverse event.
Cross-reference: Table 37 and Table 38; Attachment 4.2

8.2.12 Abnormal labs, vital signs, body weight, BMI

- Per the sponsor, the results of clinical laboratory evaluations, vital sign measurements, body weight measurements, and BMI determinations (Study 106 only) in the Double-Blind Topiramate and Open-Label Extension Topiramate data sets were consistent with the established safety profile of topiramate and did not reveal any unexpected findings. To summarize:

- No clinically important treatment-emergent mean changes from baseline to the final visit were observed in the 2 data sets in hepatic, renal, or hematology laboratory evaluations or in pulse or blood pressure measurements.
- These findings are consistent with the low incidence of treatment-emergent markedly abnormal laboratory or vital sign results and the low incidence of adverse events related to abnormal laboratory findings or vital sign measurements.
- Topiramate is known to inhibit carbonic anhydrase; thus, serum CO2 levels showed mean decreases and chloride levels showed mean increases during topiramate treatment. The incidence of treatment-emergent markedly low CO2 levels tended to increase with increasing topiramate doses at or above 100 mg/day.
- Mean body weight and BMI (Study 106 only) decreased from baseline values in topiramate-treated subjects. Mean increases in body weight and small decreases in BMI were observed in topiramate-treated pediatric subjects. As observed in previous topiramate studies, most of the observed weight decreases occurred during the first 6 to 12 months of topiramate treatment, and the weight loss was rarely serious or treatment-limiting.
- A review of the BMI data for individual subjects indicated that topiramate treatment rarely resulted in a posttreatment 'underweight' BMI value in a pediatric subject with a 'normal' BMI at baseline.

Labs - Double-Blind Topiramate

There were no noteworthy changes from the baseline to the final visit of the double-blind phase in liver function, renal function, or hematology tests. Serum CO2 showed a mean decrease (-2.6 mmol/L) and serum chloride showed a mean increase (+3.3 mmol/L). The magnitudes of the mean increase in serum chloride and mean decrease in serum CO2 were higher among subjects who received topiramate doses of TPM 100 or higher vs. those in the TPM 50 group. The decrease in serum CO2 levels is consistent with the activity of topiramate as a carbonic anhydrase inhibitor.

Labs - Open-Label Extension Topiramate:

Among subjects who received topiramate during the open-label extension phase of Studies 104 and 106, there were no noteworthy changes from the baseline to the final visit in liver function, renal function, or hematology tests. Serum CO2 showed a mean decrease (-3.5 mmol/L), and serum chloride showed a mean increase (+3.9 mmol/L) in the Open-Label Extension Topiramate data set.

8.2.12.1 Treatment emergent Markedly Abnormal Laboratory findings

The markedly abnormal values reported at an incidence of at least 2% included low CO2 levels (15%), high inorganic phosphorus (6%), high GGT levels (4%), low neutrophils

(3%), high eosinophils (3%), and high (3%) and low (2%) lymphocytes. Among these more common markedly abnormal findings, a higher percentage of decreased CO2 values was reported during the stabilization vs. titration periods, and a higher percentage of elevated GGT values occurred during the titration vs. stabilization periods; for the other analytes, the incidence of markedly abnormal analytes showed no noteworthy differences between the titration and stabilization periods.

8.2.12.1.1 **DOUBLE BLIND PHASE**:

The most common markedly abnormal laboratory finding, low CO2 levels (i.e., values below 18 mmol/L), per the sponsor, were attributed to the carbonic anhydrase activity of topiramate. The incidence of markedly low CO2 levels increased with topiramate dose at doses of TPM 200 and higher. For individual subjects, most of the markedly abnormal values were not lower than 16 mmol/L and were reported on single or occasional test dates. The lowest treatment-emergent markedly abnormal CO2 values among the topiramate-treated subjects generally occurred in subjects receiving higher topiramate doses.

Two of the markedly abnormal laboratory findings (high GGT and high inorganic phosphorus) occurred among subjects in Study 106, the only study in which these analytes were measured. Most of the markedly abnormal increases in inorganic phosphorus (26 of 29 subjects) were reported for pediatric subjects. The high incidence of markedly abnormal phosphorus levels was due, at least in part, to the fact that the markedly abnormal criteria for this analyte were not stratified by age. The high levels of phosphorus in the 26 pediatric subjects were likely attributable to developmental effects that per the Sponsor, did not represent clinically notable abnormalities. The incidence of elevated GGT values was higher in subjects in the TPM 400 group compared to those who received the lower (TPM 50) dose. The occurrence of markedly high inorganic phosphorus, low neutrophil counts, and high and low lymphocyte counts showed no consistent relationship with topiramate dose. High eosinophil counts were observed in a higher percentage of subjects in the TPM 500 group compared with the other treatment groups (Refer to Sponsor Table 48).

Table 48: Subject Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Double-Blind Topiramate (Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

		TPM 50 (N=359)		TPM 100 (N=210)		TPM 200 (N=199)		TPM 400 (N=236)		TPM 500 (N=127)		Total (N=1131)	
Laboratory analyte		prop[a]	(%)	prop[a]	(%)	prop[a]	(%)	prop[a]	(%)	prop[a]	(%)	prop[a]	(%)
Blood Chemistry													
Alkaline phosphatase	(High)	3 / 358	(1)	0 / 201		0 / 198		6 / 235	(3)	0 / 127		9 / 1119	(1)
ALT	(High)	3 / 358	(1)	4 / 200	(2)	0 / 198		2 / 235	(1)	2 / 127	(2)	11 / 1118	(1)
AST	(High)	3 / 358	(1)	3 / 200	(2)	2 / 198	(1)	2 / 235	(1)	1 / 127	(1)	11 / 1118	(1)
Bilirubin, total	(High)	2 / 358	(1)	0 / 200		1 / 198	(1)	1 / 235	(<1)	0 / 127		4 / 1118	(<1)
Carbon dioxide	(Low)	35 / 358	(10)	20 / 195	(10)	27 / 190	(14)	50 / 235	(21)	39 / 127	(31)	171 / 1105	(15)
Chloride	(High)	3 / 358	(1)	2 / 201	(1)	3 / 198	(2)	3 / 235	(1)	4 / 127	(3)	15 / 1119	(1)
	(Low)	0 / 358		1 / 201	(<1)	0 / 198		0 / 235		0 / 127		1 / 1119	(<1)
Creatinine	(High)	0 / 358		0 / 201		0 / 198		0 / 235		2 / 127	(2)	2 / 1119	(<1)
GGT	(High)	4 / 222	(2)	0 / 0		0 / 0		14 / 229	(6)	0 / 0		18 / 451	(4)
Glucose	(High)	6 / 358	(2)	4 / 200	(2)	1 / 198	(1)	0 / 235		0 / 127		11 / 1118	(1)
	(Low)	5 / 358	(1)	4 / 200	(2)	1 / 198	(1)	2 / 235	(1)	3 / 127	(2)	15 / 1118	(1)
Lactate dehydrogenase	(High)	1 / 346	(<1)	0 / 0		0 / 0		1 / 229	(<1)	1 / 127	(1)	3 / 702	(<1)
Phosphorus	(High)	13 / 222	(6)	0 / 0		0 / 0		16 / 229	(7)	0 / 0		29 / 451	(6)
	(Low)	1 / 222	(<1)	0 / 0		0 / 0		3 / 229	(1)	0 / 0		4 / 451	(1)
Potassium	(High)	2 / 358	(1)	0 / 201		1 / 198	(1)	3 / 235	(1)	1 / 127	(1)	7 / 1119	(1)
	(Low)	0 / 358		0 / 201		0 / 198		0 / 235		1 / 127	(1)	1 / 1119	(<1)
BUN	(High)	1 / 358	(<1)	0 / 196		0 / 190		0 / 235		0 / 127		1 / 1106	(<1)
Uric acid	(Low)	1 / 346	(<1)	0 / 0		0 / 0		0 / 229		0 / 127		1 / 702	(<1)
Cholesterol	(Low)	1 / 124	(1)	0 / 0		0 / 0		0 / 0		0 / 127		1 / 251	(<1)
Triglycerides	(High)	0 / 124		0 / 0		0 / 0		0 / 0		3 / 127	(2)	3 / 251	(1)
Hematology													
Hemoglobin	(Low)	3 / 358	(1)	0 / 200		1 / 197	(1)	3 / 236	(1)	1 / 127	(1)	8 / 1118	(1)
Hematocrit	(Low)	1 / 358	(<1)	0 / 199		1 / 197	(1)	1 / 236	(<1)	1 / 127	(1)	4 / 1117	(<1)
RBC, total	(High)	0 / 358		0 / 200		1 / 197	(1)	0 / 236		0 / 127		1 / 1118	(<1)
	(Low)	0 / 358		0 / 200		1 / 197	(1)	1 / 236	(<1)	1 / 127	(1)	3 / 1118	(<1)
WBC, total	(High)	2 / 358	(1)	1 / 200	(1)	1 / 197	(1)	4 / 236	(2)	0 / 127		8 / 1118	(1)
	(Low)	3 / 358	(1)	5 / 200	(3)	5 / 197	(3)	0 / 236		2 / 127	(2)	15 / 1118	(1)
Neutrophils	(Low)	21 / 358	(6)	3 / 200	(2)	2 / 197	(1)	6 / 236	(3)	2 / 127	(2)	34 / 1118	(3)
Lymphocytes	(High)	18 / 358	(5)	3 / 200	(2)	3 / 197	(2)	6 / 236	(3)	2 / 127	(2)	32 / 1118	(3)
	(Low)	7 / 358	(2)	1 / 200	(1)	5 / 197	(3)	2 / 236	(1)	2 / 127	(2)	17 / 1118	(2)
Eosinophils	(High)	10 / 358	(3)	3 / 200	(2)	3 / 197	(2)	8 / 236	(3)	10 / 127	(8)	34 / 1118	(3)
Platelet count	(High)	1 / 358	(<1)	0 / 200		0 / 197		0 / 236		0 / 127		1 / 1118	(<1)
	(Low)	0 / 358		1 / 200	(1)	0 / 197		3 / 236	(1)	1 / 127	(1)	5 / 1118	(<1)
Urinalysis													
pH	(High)	1 / 124	(1)	0 / 0		0 / 0		0 / 1		2 / 126	(2)	3 / 251	(1)

[a] Proportion of subjects with at least 1 occurrence of a laboratory abnormality indicated. Denominators represent the numbers of subjects with data available.

Three subjects experienced serious adverse events related to abnormal laboratory findings including 1 subject each with hypoglycemia, hospitalization for aggravated diabetes mellitus, and hepatic function abnormal (elevated liver function tests); all of these serious adverse events resolved with continued topiramate therapy, and none were considered related to the study drug. During double-blind topiramate treatment, adverse events related to abnormal laboratory findings contributed to the discontinuation of study drug for 4 subjects, including 2 subjects each with hematuria and leucopenia.

8.2.12.1.2 OPEN LABEL EXTENSION TOPIRAMATE:

The markedly abnormal values reported at an incidence of at least 3% included low CO2 levels (30%), high eosinophils (6%), high inorganic phosphorus (4%), low glucose (4%), high chloride (3%), low hemoglobin (3%), and low WBC count (3%).

Among these cases was 1 noteworthy case of a child with markedly low CO2 levels and markedly elevated WBC counts (Subject 104/9270). Subject 104/9563 experienced hypokalemia, which was moderate in severity and did not fulfill the criteria for a markedly low potassium level, in association with increased seizure activity after receiving topiramate treatment for approximately 2 years. The hypokalemia, which the investigator judged as unlikely to be related to the study drug, resolved 8 days after onset. No subject discontinued topiramate treatment during the open-label extension due to an abnormal laboratory finding.

Vital Signs - Blood pressure and pulse rate

- Double-Blind Topiramate: The incidence of treatment-emergent markedly abnormal vital sign measurements was low, with <1% of subjects having markedly high or low pulse or diastolic or systolic blood pressure. These results are consistent with the low incidence of adverse events related to abnormal vital signs, with each of the following reported for <1% of subjects: palpitation (11 subjects), tachycardia (8 subjects), hypertension (6 subjects), hypotension (4 subjects), bradycardia (1 subject), aggravated hypertension (1 subject), and postural hypotension (1 subject). Serious events related to vital sign abnormalities included 1 case each of palpitation, tachycardia, and hypotension. All 3 of these serious vital sign abnormalities resolved, and all were considered unrelated or unlikely to be related to topiramate treatment.

- Open Extension: In the Open-Label Extension Topiramate data set, these included hypertension (6 subjects; 1%), hypotension (3 subjects, 1%), aggravated hypertension (2 subjects, <1%), palpitation (2 subjects. <1%), tachycardia (2 subjects, <1%), and bradycardia (1 subject, <1%). None of these adverse events were treatment-limiting and only 1 such event was serious (moderate bradycardia in Subject 104/9061).

Body Weight

Total population - Double Blind phase: Approximately 51% of subjects had mean weight decreases of 1-9%. 9% of the subjects had mean weight decreases of 10-19% and <1% had mean weight decreases of 20-29%. The proportions of subjects with any decreases were higher in the higher TPM dose groups. Weight decrease was reported as an adverse event for 128 (11%) of the 1,131 subjects in the Double-Blind Topiramate data set , with a higher incidence of this adverse event observed in the higher topiramate dose groups. Weight increases were reported as adverse events for 8 (1%) subject. Topiramate treatment was discontinued in 14 (1%) subjects due to weight loss and in 2 (<1%) subjects due to weight increase; none of these subjects were younger than 16 years. No cases of serious weight decrease or serious weight increase were reported.

Pediatric Double Blind Phase - In pediatric patients, body weight showed a mean increase (+0.6 kg; mean percent increase, +2.5%) from baseline to the final evaluation of the double-blind phase. Most pediatric subjects experienced an increase in body weight (51% of subjects) or no change in body weight (13% of subjects). Most of the pediatric subjects who exhibited weight loss during double-blind therapy had decreases of 1-9% (32%).

Thirteen pediatric subjects, 3 in the TPM 50 group, 2 in the TPM 200 group, and 8 in the TPM 400 group, had weight decreases of 10% or more . Twelve of these subjects (10 girls and 2 boys) were 12 to 15 years old , and 1 was in the 6 to 11 year age group. Ten of these subjects (2 in the TPM 50 group and 8 in the TPM 400 group) participated in

Study 106, the only study in which BMI determinations were made. Of these 10 subjects, BMI data were available for 9 subjects. Only 1 of the 9 pediatric subjects with BMI data had a BMI value at the final double-blind evaluation that was below the 5th percentile for his age/sex group based on the Centers for Disease Control (CDC) criteria (Subject 106/537003, see below).

Weight and BMI data for the 3 pediatric subjects in the Double-Blind Topiramate data set who experienced a weight loss of 20% or more from baseline to the final visit are presented below as reproduced from the ISS.

> Subject 106/537003, an 11-year-old boy in the TPM 400 group, experienced a weight loss of 11 kg in 41 days, including a 6-kg loss in 14 days; during this period, his weight decreased from 44.0 kg (BMI, 18.6) to 33.0 kg (BMI, 13.9).
>
> Subject 106/651005, a 12-year-old girl in the TPM 400 group, experienced a 13-kg weight loss; her body weight decreased from 61.0 kg (BMI, 25.0) at baseline to 48.0 kg (BMI, 19.5) at the final visit. Her BMI at the final visit was above the 50th percentile for her sex/age group.
>
> Subject 106/522006, a 14-year-old boy in the TPM 400 group, experienced a 19.6-kg weight loss; his body weight decreased from 96.4 kg (BMI, 32.6) at baseline to 76.8 kg (BMI, 25.8) at the final visit. His BMI at the final visit was above the 90th percentile for the sex/age group.

Among pediatric subjects, adverse events of weight decrease were reported in 21 (9%) of 245 subjects. No pediatric subjects experienced serious weight loss, and no cases of weight loss were treatment-limiting in pediatric subjects. Subject 106/613002, a 15-year-old girl in the TPM 400 group whose baseline weight and height were 61 kg and 159 cm (BMI of 24.1), experienced a weight decrease to 55 kg (BMI of 21.8). Although this girl was the only pediatric subject with an adverse event of weight decrease that was considered marked in severity, her final BMI value was above the 50th percentile for her age/sex group.

Open Label Extension Phase - During topiramate treatment through completion of the open-label extension phase, mean body weight decreased in the total population (-2.3 kg) and in the subjects in each treatment group. Body weight showed a mean percent increase (+0.9%) in the TPM 50/500 group and mean percent decreases in the TPM 50/400, TPM 400/400, and TPM 500/500 groups (-1.2, -3.5, and –4.0%, respectively). Approximately half of the subjects (48%) in the Open-Label Extension Topiramate data set had mean weight decreases of 1 to 9%; 15% and 2% of the subjects had mean weight decreases of 10 to 19% and 20 to 29%, respectively. One subject had a weight decrease of >30%.

Weight decrease was reported as an adverse event for 23 (5%) of the 432 subjects in this data set. Of these cases, Subject 104/2078, an adult woman in the TPM 500/500 group, experienced serious weight loss in conjunction with gastroparesis. Two women, both in the TPM 50/500 group, discontinued topiramate treatment due to weight loss that was marked (Subject 104/2043) or moderate (Subject 104/9393) in severity; the weight loss lasted 61 and 47 days, respectively, and resolved following discontinuation of the study drug.

Overall, the mean body weight of pediatric subjects increased from baseline to the final visit of the open-label extension phase of Studies 104 and 106. The largest mean percent increases in body weight were observed among pediatric subjects in the TPM 50/500 (+26.5%) and TPM 500/500 (+11.5%) groups of Study 104. The subjects in the TPM 50/500 and TPM 500/500 groups had a mean duration of topiramate therapy (834.1 and 718.9 days, respectively, for the double-blind and open-label phases combined) that was substantially longer than that of subjects in the TPM 50/400 and TPM 400/400 groups (385.6 and 385.5 days, respectively) of Study 106.

Weight decrease and weight increase were each reported as adverse events for 1 pediatric subject in the TPM 50/500 group of the Open-Label Extension Topiramate data set There were no cases of serious or treatment-limiting weight changes reported for pediatric subjects, and no pediatric subjects discontinued topiramate treatment due to weight changes reported as adverse events.

Body Mass Evaluation/BMI

BMI was only evaluated in Study 106. This is summarized in Sponsor table 56 below. Mean changes from baseline to the final evaluation during the double-blind and open-label extension phases are presented for all subjects and for pediatric subjects. During the double-blind phase, mean decreases in BMI were observed for all subjects in the data set and for pediatric subjects, with the larger decreases observed in subjects who received target topiramate doses of 400 mg/day vs. 50 mg/day. Among the smaller numbers of subjects who participated in the open-label phase, mean **decreases** in BMI were observed for all subjects in both treatment groups and for pediatric subjects in the TPM 50/400 group. Separate height measurements were not reported individually by subject and no information regarding growth curves or failure to progress on a baseline growth curve was provided.

Clinical Reviewer comment: This reviewer has some concerns regarding a negative BMI especially in pediatric patients as this implies combined general weight and/or height loss in the affected patients. The Division has further concerns regarding this issue and an endocrine consultation was requested separately regarding the possibility of growth retardation and/or bone demineralization in children related to the drug induced metabolic acidosis.

Table 56: Means and Mean Changes From Baseline in BMI to Final Evaluations: Double-Blind Phase and Open-Label Extension Phase of Study TOPMAT-EPMN-106

Study phase (subjects)		Baseline	Change from baseline				
Treatment group	N	mean	Mean	SD	Median	Minimum	Maximum
Double-blind (all subjects)							
TPM 50	203	24.8	-0.5	1.53	-0.5	-7.2	4.7
TPM 400	207	24.2	-1.3	1.92	-0.8	-8.4	7.2
Double-blind (pediatric subjects)							
TPM 50	63	20.1	-0.7	1.48	-0.4	-5.2	2.5
TPM 400	70	20.7	-1.1	2.01	-0.8	-6.9	7.2
Open-label extension (all subjects)							
TPM 50/400	44	27.2	-1.6	1.99	-1.4	-7.5	2.5
TPM 400/400	25	24.5	-1.2	1.70	-1.1	-5.0	2.8
Open-label extension (pediatric subjects)							
TPM 50/400	11	21.9	-1.2	1.91	-2.1	-3.5	2.5
TPM 400/400	4	18.1	0.4	1.94	0.1	-1.2	2.8

Note: Treatment groups are defined in Table 6.

87 of the 134 pediatric subjects (65%) with baseline and postbaseline BMI data had a decrease in BMI during the study. Of these 87 subjects, the final BMI values of only 4 subjects (see descriptions below) fell below the 5th percentile for their age/sex group, i.e., were 'underweight' based on the CDC criteria. Of note, 3 of these 4 subjects had a weight loss of 2 kg or less:

Treatment group	Baseline Values		Final Visit Value	
Subject No. (age and sex)	Weight (kg)	BMI	Weight (kg)	BMI
TPM 50				
106/649003 (13-year-old girl)	35	15.4	36	15.0
TPM 400				
106/537003 (11-year-old boy)	44	18.6	33	13.9
106/634005 (11-year-old boy)	34	15.3	33	14.1
106/646005 (12-year-old boy)	31	16.0	29	14.0

8.2.13 Pregnancy

Among the double blind and extension phases, 14 topiramate treated subjects became pregnant. Three had therapeutic abortions, the other 11 chose to continue. Of the 11, 1 had a missed abortion, 1 had an ectopic pregnancy, 3 had miscarriages and 6 patients had normal deliveries.

8.3 Safety Topics of Special Interest (ISS Review)

8.3.1 Hepatic events

16 of 1131 double blind topiramate and 2 of the 432 subjects in the open label extension group had hepatic events. The investigators considered most of the hepatic-related adverse events to be mild or moderate in severity and either not related or of doubtful relationship to topiramate treatment .

- 1 serious episode was reported, a 36 year old woman in the TPM 100 group with a history of elevated liver enzymes due to isotretinoin experienced increased ALT and AST levels and was diagnosed with fatty liver.

- During the double-blind phase (including open-treatment phase), hepatic-related adverse events reported for more than 1 subject were increased GGT (6 subjects); abnormal hepatic function (3 subjects); and cholelithiasis, increased hepatic enzymes, increased alkaline phosphatase, increased AST, and increased ALT, each of which was reported for 2 subjects. No individual hepatic-related adverse event was reported by more than 1 subject during topiramate treatment in the open-label extension phase.

- With the exception of 1 hepatic-related adverse event (increased GGT) reported by a pediatric subject (Subject 106/645013, a 15-year-old girl), all of the hepatic-related adverse events were experienced by adults. The elevated GGT level (84 U/L) for Subject 106/645013 was observed in the open-treatment period (Day –1) while she was receiving carbamazepine as well as topiramate 25 mg/day; her GGT returned to the normal range (22 U/L) by Day 27 of double-blind treatment while she was receiving a topiramate dose of 200 mg/day.

- There was no evidence of hepatic failure or direct hepatotoxicity among topiramate treated subjects.

- Markedly severe hepatic related events included 2 cases of elevated liver function tests in to adults and 1 case of cholecystitis and cholelithiasis.

- Hepatic related events considered possibly or probably related to topiramate included 3 cases of elevated GGT (TPM 400 group), 2 cases of increased alkaline phosphatase, 2 cases of abnormal hepatic function, one case of increased bilirubin and increased AST. All events resolved spontaneously during continued topiramate treatment.

- Multiple hepatic events were experienced by six subjects. These are summarized as follows from the ISS

- Subject 104/2074 in the TPM 50 group (hepatomegaly, increased AST and ALT).
- Subject 106/552003 in the TPM 50 group (increased AST, ALT, and GGT).
- Subject 106/566009 in the TPM 50 group (hepatic enzymes increased, >20-fold elevations in ALT, AST, and lactate dehydrogenase). Relationship of these events to topiramate was described by the investigator as doubtful. This subject, who had a history of an autoimmune connective-tissue disorder (CREST syndrome).
- Subject 105/63001 in the TPM 100 group (abnormal hepatic function and fatty liver)
- Subject 106/566001 in the TPM 400 group, a 39-year-old man with mild transient elevations in GGT and AST (relationship to topiramate, possible) early in titration.
- Subject 106/547005 in the TPM 400 group (increased GGT and hepatic function abnormal)

Liver Function tests

Generally, there were no noteworthy mean changes from baseline to the final visit in any liver function test in the Double-Blind Topiramate or Open-Label Extension Topiramate data sets in all subjects or across age groups or treatment groups.

The majority of the subjects entering the studies had liver function test values at baseline that were within the laboratory normal range. During double-blind and open-label treatment with topiramate, subjects with normal baseline values showed small mean decreases from baseline to the final visit in alkaline phosphatase levels and only slight mean changes from baseline to the final visit in total bilirubin, AST, and ALT levels. There were no apparent age-related or dose-related trends in mean liver function test results.

8.3.2 Metabolic Acidosis

- Per the sponsor, metabolic acidosis and acidosis related adverse events were uncommon among subjects who received topiramate.

- In the Double-Blind Topiramate data set, 2 (<1%) of 1,131 topiramate-treated subjects had an adverse event of metabolic acidosis; neither case was serious. In both cases the subject's topiramate dosage was reduced to control the event. In the Open-Label Extension Topiramate data set, 1 (<1%) of 432 topiramate-treated subjects had an adverse event of metabolic acidosis that was not considered serious. The subject's topiramate dosage was reduced to control the event.

- The incidence of adverse events possibly related to metabolic acidosis was 1% in the Double-Blind Topiramate and 2% in the Open Label Extension Topiramate data sets, respectively. Of the 8 subjects who reported adverse events of the musculoskeletal system, none also reported metabolic acidosis. None of the osseous events were associated with recurrent markedly abnormal CO2 (i.e., carbon dioxide or bicarbonate) values. No changes were seen for either calcium or phosphorus.

- The investigators considered most of the metabolic acidosis-related adverse events to be mild or moderate in severity and either not related or of doubtful relationship to topiramate treatment.

- Most metabolic acidosis, acidosis-related, or musculoskeletal adverse events were experienced by adults.

- In the Double-Blind Topiramate data set, there was a mean decrease in serum CO2 (–2.6 mmol/L) and a mean increase in serum chloride (+3.3 mmol/L). Mean decreases in CO2 were comparable for pediatric (-1.9 mmol/L) and adult (-2.8 mmol/L) subjects. Results from the Open-Label Extension Topiramate data set were essentially comparable to those of the Double-Blind Topiramate data set.

- 2 out of 1131 patients in the double blind group experienced mild hyperchloremic acidosis. Neither case was serious and topiramate dosages were lowered.

    - Subject 104/009503, a 12-year-old girl in the TPM 500 group had mild hyperchloremic acidosis on Day 66. The subject's topiramate dosage was reduced to control this event. Acidosis, considered to be possibly related to the study medication, resolved in 128 days. The subject had CO2 values of 17.00 mmol/L on Days 22 and 66, with corresponding chloride values of 109 mmol/L and 112 mmol/L.

    - Subject 104/009504, a 28-year-old man in the TPM 500 group had mild hyperchloremic acidosis on Day 71 associated with moderately severe diarrhea. The subject had a CO2 value of 18.00 mmol/L on Day 71. Acidosis and diarrhea were considered possibly related to topiramate and the subject's topiramate dosage was reduced to control these events. Acidosis and diarrhea resolved in 29 days.

- Other adverse events suggestive of possible acidosis included one episode of hyperventilation and 9 reports of renal calculi. The incidence of osseous adverse events was low consisting of 2 reports of bone disorder, 3 reports of skeletal pain and 1 report of hypophosphatemia.

- During Open Label Extension, 1 of 432 subjects experienced acidosis. 2 of 432 patients experienced hypothyroidism and 8 reported renal calculi.

    - Subject 106/591001, a 28 year-old white man in the TPM 400 group developed mild acidosis (Day 113; CO2=16 mmol/L) considered by the investigator to be of very likely relationship to treatment. Following dose reduction, the follow-up CO2 level was 21 mmol/L.

8.3.3 Renal Calculi

In the Double-Blind Topiramate and Open-Label Extension Topiramate data sets, four subjects had renal calculi that were considered serious by the investigator:

- Subject 104/2022, a 21-year-old man in the TPM 500 group, experienced renal calculus (investigator term: nephritic colic) of marked severity and of probable relationship to treatment. The event resolved in 2 days.

- Subject 105/057001, a 44-year-old white man in the TPM 200 group, reported renal calculus of marked severity and of very likely relationship to treatment. Topiramate was discontinued. Follow-up information was not available.

- Subject 106/571005, a 17-year-old white man in the TPM 400 group had renal calculus of marked severity and of very likely relationship to treatment. Topiramate was discontinued and the renal calculus resolved.

- Subject 105/78001, a 40-year-old white man in the TPM 100 group, reported renal calculus of marked severity and of possible relationship to treatment. The renal stone passed spontaneously.

Clinical Reviewers comments on Metabolic Acidosis and CO2 levels

The Sponsor is well aware of metabolic acidosis in association with topiramate both in the literature and in labeling. The sponsor notes that serum C02 levels showed mean decreased and chloride levels showed mean increases during topiramate therapy. The incidence of treatment emergent markedly low CO2 levels tended to increase as the topiramate dose increased over 100mg. This is summarized in Reviewer Table 3 below. The sponsor relates that these findings are consistent with topiramate's activity as a carbonic anhydrase inhibitor. The incidences of markedly low CO2 levels increased with topiramate dose at doses of TPM 200 and higher. For individual subjects, at topiramate doses of 200mg or higher, most of the markedly abnormal values were not lower than 16 mmol/L and were reported on single or occasional test dates. The lowest treatment-emergent markedly abnormal CO2 values among the topiramate-treated subjects generally occurred in subjects receiving higher topiramate doses.

Reviewer Table 3 - Percent decrease in CO2 levels from normal baseline in subjects with metabolic acidosis (Double Blind Phase)			
Adults		Pediatrics	
Dose	% decrease from nl baseline	Dose	% decrease from nl baseline
TPM 50	10 (26/250)	TPM 50	4 (4/91)
TPM 100	8 (13/162)	TPM 100	5 (1/21)
TPM 200	11 (17/158)	TPM 200	30 (7/23)
TPM 400	16 (23/145)	TPM 400	13 (9/71)
TPM 500	18 (20/110)	TPM 500	62 (8/13)
TPM total	12 (99/825)	TPM total	13 (29/219)

Of more concern is the possibility of osteomalacia. This may occur due to biochemical abnormalities of bone metabolism and is associated with hypocalcemia, hypophosphatemia, elevated serum alkaline phosphatase and reduced serum levels of vitamin D metabolites. The Sponsor does not feel that the results of the laboratory changes in calcium, alkaline phosphatase or magnesium are any more significance than

those seen with other anticonvulsants. The Sponsor has conducted a separate analysis of metabolic acidosis and metabolic acidosis-associated events and laboratory findings across several populations of topiramate-treated subjects at the request of the FDA. No evidence was seen of osseous sequelae secondary to metabolic acidosis in topiramate-treated subjects with acidosis. However, since there is no evidence that bone scans were performed, I am not certain how the sponsors came to that conclusion regarding this particular study.

8.3.4 Oligohydrosis/hyperthermia

Per the sponsor:

- A total of 3 topiramate-treated subjects in the monotherapy trials experienced an oligohydrosis-related adverse event coded to a primary preferred term (decreased sweating). Two were adult men, 1 each in the TPM 400 and TPM 500 groups, who reported decreased sweating while receiving double-blind topiramate. The remaining subject was an 11-year-old boy in the TPM 500/500 group who experienced decreased sweating in an open-label extension phase. None of these events were serious or treatment-limiting.

- Among the subjects who experienced adverse events coded to secondary terms (i.e., terms possibly related to oligohydrosis), 4 subjects (3 pediatric subjects and 1 adult) experienced a combination of fever and flushing. None of these cases were serious, and there were no clinical signs or laboratory indicators of dehydration in any of these subjects. The symptoms reported by the 3 pediatric subjects were mild or moderate in severity and resolved following discontinuation of topiramate treatment, and the fever and flushing reported for the adult subject resolved with continued topiramate treatment. Although the fever and flushing reported for the 3 pediatric subjects were considered very likely related to topiramate treatment, an infectious etiology could not be ruled out for 2 of these subjects. No clear alternate etiology was apparent for the third pediatric subject and the adult with fever and flushing.

- Fever was the most common secondary event term, and was reported by 31 subjects (16 pediatric subjects, 15 adult subjects) in the Double-Blind Topiramate data set and by 9 subjects (5 pediatric and 4 adult subjects) in the Open-Label Extension Topiramate data set. Among the 40 subjects across both data sets, the fever had a likely infectious etiology in 21, was potentially related to oligohydrosis in 4, and had no clear alternate etiology in 15.

- Two of the 1,131 subjects (<1%) in the Double-Blind Topiramate data set reported a primary oligohydrosis-related adverse event term. Neither event was serious, and neither necessitated a temporary or permanent discontinuation of study treatment.

    - Subject 106/540002, a 46-year-old man in the TPM 400 treatment group reported decreased sweating beginning on Day 15 at a dose of 150 mg/day. This event was considered to be

moderate in severity and probably related to the study drug; the decreased sweating persisted following a dose reduction.

- Subject 104/9179, a 33-year-old man in the TPM 500 treatment group reported intermittent decreased sweating beginning on Day 290 while receiving topiramate 500 mg/day. The event, which was mild in severity and considered probably related to the study drug, resolved during continued topiramate during the open-label extension phase.

- One of the 432 (<1%) subjects in the Open-Label Extension Topiramate data set reported a primary oligohydrosis-related adverse event term.

  - Subject 104/9331, an 11-year-old boy in the TPM 500 group experienced decreased sweating on Day 590 at a dose of 200 mg/day. No concomitant antiepileptic drugs were reported. This subject did not have any clinical signs or laboratory indicators of dehydration. This event was assessed as mild in severity and possibly related to study treatment. Sensory disturbance (mild heat intolerance) was reported on the same day. Neither event resulted in a change in topiramate therapy.

Secondary terms related to oligohydrosis were checked and summarized in Sponsor Table 72.

Table 72: Oligohydrosis-Related Adverse Events – Secondary Term: Double-Blind Topiramate (Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

Body System/ Preferred Term	TPM 50 (N=359)		TPM 100 (N=210)		TPM 200 (N=199)		TPM 400 (N=236)		TPM 500 (N=127)		Total TPM (N=1,131)	
	n	%	N	%	n	%	n	%	n	%	n	%
Body as a Whole												
Fever	6	2	3	1	6	3	12	5	4	3	31	3
Hot flushes	0		1	<1	1	1	0		1	1	3	<1
Metabolic & Nutritional												
Dehydration	1	<1	0		0		0		1	1	2	<1
Resistance Mechanism												
Abscess	1	<1	0		0		0		1	1	2	<1
Skin & Appendages												
Folliculitis	1	<1	0		0		0		0		1	<1
Rash follicular	0		1	<1	0		0		0		1	<1
Rash pustular	0		1	<1	1	1	0		0		2	<1
Skin disorder	0		2	1	1	1	0		1	1	4	<1
Sweating increased	2	1	3	1	1	1	0		2	2	8	1
Vascular (Extracardiac)												
Flushing	3	1	1	<1	1	1	5	2	1	1	11	1
Any Secondary Term Adverse Event	**13**	**4**	**12**	**6**	**11**	**6**	**14**	**6**	**11**	**9**	**61**	**5**

Notes: Treatment groups are defined in Table 6. This table presents the number of subjects with adverse events.

- Fever was the most common possibly oligohydrosis-related event coded to a secondary event term. Other than fever, all secondary event terms were reported by 1% or less of the 1,131 topiramate-treated subjects in the Double-Blind Topiramate data set or the 432 subjects in the Open-Label Extension Topiramate data set.

- Across all dosage groups for the Double-Blind Topiramate data set, the overall proportion of topiramate-treated subjects who reported at least 1 secondary event term was higher in the pediatric subgroup (19 of 245 subjects, 8%) than in the adult subgroup (42 of 886, or 5%). The overall proportion of topiramate-treated subjects with 1 or more secondary event terms was also higher in the pediatric subgroup (5%) than in the adult subgroup (2%) for the Open-Label Extension Topiramate data set.

- The higher incidence of possibly oligohydrosis-related adverse events in the pediatric subgroup appears to be largely due to an imbalance in the occurrence rate of fever – the most common secondary event term – among subjects aged <16 years (7% and 4% for Double-Blind Topiramate and Open-Label Extension Topiramate data sets, respectively) relative to adults (2% and 1%).

- Two of the 1,131 topiramate-treated subjects in the Double-Blind Topiramate data set, and 3 of the 432 topiramate-treated subjects in the Open-Label Extension Topiramate data set, experienced a serious secondary event term. Four of these 5 subjects were adults. All of these serious events resolved within 1 to 9 days of onset, and none were consistent with a diagnosis of oligohydrosis. These cases are described below as reproduced from the ISS

    - Increased sweating occurred on double-blind Study Day 29 in adult Subject 104/2093 (TPM 500 group) and was reported on the same day as aggravated convulsions, agitation, and tachycardia.

    - Dehydration was reported during the open-label extension on the same day as gastroenteritis in an 8-year-old girl (Subject 106/550001 in the TPM 50/400 group) and occurred while the subject was receiving topiramate 125 mg/day and lamotrigine 250 mg/day.

    - A report of fever in adult Subject 104/2103 in the TPM 500/500 group occurred during open-label extension while the subject was receiving topiramate 500 mg/day and diazepam 5 mg/day, and was associated with aggravated convulsions and headache.

    - A report of fever also occurred during the open-label extension (adult Subject 104/2096 in the TPM 50/500 group) in close temporal association with reports of an urinary tract infection, herpes simplex, pharyngitis, and headache; the subject was receiving topiramate 500 mg/day monotherapy at the time of these events.

    - A report of fever occurred during the double-blind phase at a dose of 200 mg/day in adult Subject 105/94001 (TPM 200 group) and was reported concurrently with confusion. These events were believed to be related to a transient ischemic attack or an intercurrent infection.

Overall, among subjects treated with topiramate during the double-blind or open-label phases of the monotherapy studies, the incidence of oligohydrosis and oligohydrosis-related adverse events was very low. 3 subjects (2 adults and 1 pediatric subject)

experienced decreased sweating, and 4 subjects (1 adult and 3 pediatric subjects) experienced a combination of fever and flushing, i.e., events potentially related to an oligohydrosis condition. None of these cases were serious, and there were no clinical signs or laboratory indicators of dehydration in any of these subjects.

8.3.5 Encephalopathy/hyperammonemia

- The overall incidence of adverse events coding to 1 of the primary terms associated with encephalopathy was low in all treatment groups, in both Double-Blind Topiramate and Open-Label Extension Topiramate data sets (Refer to Sponsor Tables 74 and Table 75 below). Across all topiramate treatment regiments in both data sets, there were only 2 subjects with adverse events reported as encephalopathy, 1 mild case of EEG abnormalities, and 1 case of coma (verbatim: "loss of consciousness", mild in severity). No instances of stupor were reported. Confusion was reported at the overall incidences of 4% during double-blind treatment and 3% during open-label treatment.

- 6 adverse events coded to possible encephalopathy-associated terms were serious. In the Double-Blind Topiramate and Open-Label Extension Topiramate data sets combined, these events included 4 cases coded to primary terms (3 cases of confusion and 1 case of encephalopathy), and 1 case coded to a secondary term (cognitive problems). One additional serious case of confusion was reported during the crossover extension phase of Study 105. All serious events were reported in adults. Of these 6 serious adverse events, 4 had clear alternative etiology.

- The most common adverse events leading to either discontinuation of treatment or dose reduction in both Double-Blind Topiramate and Open-Label Extension Topiramate data sets were somnolence, fatigue, difficulty with concentration/attention, and psychomotor slowing. No other adverse events in either data set resulted in discontinuation of treatment or dose reduction in more than 1% of the subjects. No relationship was observed between the topiramate dose and the incidence of discontinuations or dose reductions due to any of the adverse events for either primary or secondary terms.

- With the exception of somnolence and difficulty with memory, no dose relationship was observed for adverse event terms associated with encephalopathy. Higher incidences of confusion and language problems in the Open-Label Extension Topiramate data set were observed in TPM 50/500 and TPM 500/500 dose groups, compared with TPM 50/400 and TPM 400/400 dose groups.

- The majority of adverse events reported in both Double-Blind Topiramate and Open-Label Extension Topiramate data sets in all treatment groups fell in the mild category of complaints, defined as adverse events that were not serious, were mild or moderate in severity, and did not result in any action taken with regard to the treatment regimen. There was no relationship between the target topiramate dose

and the proportion of adverse events in more severe categories during either double-blind or open-label treatment.

- Among the treatment-emergent adverse events coding to 1 of the secondary terms, i.e., terms potentially associated with encephalopathy, the most common adverse events in both Double-Blind Topiramate and Open-Label Extension Topiramate data sets were fatigue (16% and 8%), somnolence (13% and 7%), difficulty with concentration/attention (8% and 5%), and difficulty with memory (7% in both data sets). No other secondary adverse events were reported at the incidences of 5% or higher in either data set. There were no cases of hyperammonemia.

- In the Double-Blind Topiramate data set, increases in the incidences of somnolence (from 11% in TPM 50 group to 17% in TPM 500 group) and difficulty with memory (from 4% in TPM 50 group to 8-9% in TPM 200 and higher dose groups) were observed with the increases in topiramate dose. For the remaining primary and secondary adverse events, there was no apparent dose relationship.

Table 74: Incidence of Adverse Events Associated With Encephalopathy: Double-Blind Topiramate (Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

Body System	TPM 50 (N=359)		TPM 100 (N=210)		TPM 200 (N=199)		TPM 400 (N=236)		TPM 500 (N=127)		Total (N=1,131)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Primary Terms												
Psychiatric Disorders												
Confusion	11	(3)	6	(3)	11	(6)	8	(3)	8	(6)	44	(4)
Centr & Periph Nervous System												
Coma	0		1	(<1)	0		0		0		1	(<1)
Any Primary Event	**11**	**(3)**	**7**	**(3)**	**11**	**(6)**	**8**	**(3)**	**8**	**(6)**	**45**	**(4)**
Secondary Terms												
Psychiatric Disorders												
Somnolence	41	(11)	26	(12)	25	(13)	33	(14)	21	(17)	146	(13)
Difficulty With Concentration/ Attention	24	(7)	9	(4)	22	(11)	20	(8)	10	(8)	85	(8)
Difficulty With Memory	14	(4)	17	(8)	17	(9)	18	(8)	12	(9)	78	(7)
Psychomotor Slowing	7	(2)	8	(4)	11	(6)	10	(4)	9	(7)	45	(4)
Cognitive Problems	3	(1)	6	(3)	4	(2)	12	(5)	3	(2)	28	(2)
Delirium	1	(<1)	0		0		0		0		1	(<1)
Body As A Whole												
Fatigue	46	(13)	43	(20)	45	(23)	26	(11)	23	(18)	183	(16)
Centr & Periph Nervous System												
Language Problems	11	(3)	6	(3)	13	(7)	8	(3)	8	(6)	46	(4)
Ataxia	6	(2)	7	(3)	9	(5)	6	(3)	5	(4)	33	(3)
Speech Disorders/Related Speech Problems	7	(2)	4	(2)	7	(4)	5	(2)	3	(2)	26	(2)
Coordination Abnormal	4	(1)	2	(1)	2	(1)	0		3	(2)	11	(1)
Gait Abnormal	3	(1)	1	(<1)	1	(1)	0		3	(2)	8	(1)
Any Secondary Event	**113**	**(31)**	**84**	**(40)**	**99**	**(50)**	**84**	**(36)**	**58**	**(46)**	**438**	**(39)**

- In the Open-Label Extension Topiramate data set, higher incidences of confusion and language problems were observed in TPM 50/500 and TPM 500/500 dose groups, compared with TPM 50/400 and TPM 400/400 dose groups.

- Comparison of the incidences of some secondary adverse events leading to temporary discontinuation of treatment or dose reduction in TPM 400 and TPM 500 groups to TPM 50 group shows higher overall incidences for CNS-related and psychiatric disorders, as well as some individual secondary events (difficulty with memory, difficulty with concentration/attention). No dose-response relationship was observed for either individual events or categories of secondary adverse events leading to temporary discontinuation of treatment or dose reduction in the Open-Label Extension Topiramate data set.

Table 75: Incidence of Adverse Events Associated With Encephalopathy: Open-Label Extension Topiramate (Studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106)

	TPM 50/500 (N=87)		TPM 50/400 (N=150)		TPM 400/400 (N=118)		TPM 500/500 (N=77)		Total (N=432)	
Body System Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Primary Terms										
Psychiatric Disorders										
Confusion	4	(5)	2	(1)	0		7	(9)	13	(3)
Central & Peripheral Nervous System										
Encephalopathy	0		0		0		2	(3)	2	(<1)
EEG Abnormal	1	(1)	0		0		0		1	(<1)
Any Primary Term Adverse Event	**5**	**(6)**	**2**	**(1)**	**0**		**9**	**(12)**	**16**	**(4)**
Secondary Terms										
Psychiatric Disorders										
Somnolence	10	(11)	12	(8)	1	(1)	9	(12)	32	(7)
Difficulty With Memory	11	(13)	12	(8)	1	(1)	5	(6)	29	(7)
Difficulty With Concentration/Attention	6	(7)	7	(5)	0		7	(9)	20	(5)
Psychomotor Slowing	4	(5)	5	(3)	1	(1)	2	(3)	12	(3)
Cognitive Problems	4	(5)	3	(2)	1	(1)	3	(4)	11	(3)
Body As A Whole										
Fatigue	12	(14)	13	(9)	3	(3)	8	(10)	36	(8)
Central & Peripheral Nervous System										
Language Problems	5	(6)	1	(1)	1	(1)	9	(12)	16	(4)
Speech Disorders/Related Speech Problems	3	(3)	0		0		4	(5)	7	(2)
Gait Abnormal	3	(3)	2	(1)	0		1	(1)	6	(1)
Ataxia	2	(2)	1	(1)	1	(1)	1	(1)	5	(1)
Dementia	1	(1)	0		0		1	(1)	2	(<1)
Coordination Abnormal	1	(1)	0		0		0		1	(<1)
Any Secondary Term Adverse Event	**36**	**(41)**	**33**	**(22)**	**5**	**(4)**	**28**	**(36)**	**102**	**(24)**

Clinical Reviewer's comments regarding encephalopathy:

The sponsors collected cases regarding encephalopathy and separated them into primary and secondary terms. The incidence of the coded terms, "confusion" and "coma" were low. The incidences of secondary terms such as somnolence, difficulty with concentration and difficulty with memory were higher across all groups but especially noticeable in higher (400mg and greater) dose groups. This is clearly noted in Sponsor tables 74 and 75. Despite the fact that most events were felt to be mild by the investigators, the incidence of these events as a whole are significant to this reviewer. This "splitting out " of primary and secondary terms is artificial. Any of these terms in

each list even if mild, would be considered a significant form of encephalopathy. Of deepest concern is the incidence of alterations in mental status in those who received the target dose of 400mg in both the double blind phase and in the extension phase.

Combining primary and secondary terms regarding encephalopathy for the Double-Blind phase, reveals the following. (compare to Sponsor Table 74 above)

Event	TPM 50 (N=359)	TPM 100 (N=210)	TPM 200 (N=199)	TPM 400 (N=236)	TPM 500 (N=127)	Total (N=1,131)
Any Primary	11(3 %)	7(3%)	11(6%)	8(3%)	8(6%)	45(4%)
Any Secondary	113(31%)	84(40%)	99(50%)	84(36%)	58(46%)	438(39%)
Any event	123 (34%)	91 (43%)	110 (56%)	92 (39%)	66 (52%)	483 (43%)

The incidence of primary events may be low across all treatment groups, but the incidence of secondary terms (many psychiatric and neurologic) are quite high in all treatment groups and high overall.

Combining primary and secondary terms regarding encephalopathy for the extension phase reveals the following (compare to Sponsor Table 75 above)

Event	TPM 50/500 (N=87)	TPM 50/400 (N=150)	TPM 400/400 (N=118)	TPM 500/500 (N=77)	Total (N=432)
Any Primary	5(6 %)	2(1%)	0	9(12%)	16(4%)
Any Secondary	36(41%)	33(22%)	5(4%)	28(36%)	102(24%)
Any Event	41 (47%)	35 (23%)	5 (4%)	37 (48%)	118 (28%)

Most notably is the difference seen between the goal doses of 400 and the uppermost dose of 500mg. There is a significant increase in events in the 500mg groups compared to the 400mg groups. It is interesting to see that there are fewer events in those patients who remained on TPM 400mg for both the double blind phase and the extension phase.

8.3.6 Visual adverse events

- Visual adverse events, specifically abnormal vision (blurred vision, various visual disturbances, decreased vision, or worsening eyesight), were reported more frequently by adults vs. pediatric subjects.

- No cases of acute myopia, a single report of glaucoma in a subject with a prior history . No evidence of single angle glaucoma.

- No pattern or indication of drug toxicity was detected based on visual field examinations performed for a subset of subjects in Study 106.

- During double blind treatment, 47 (4%) of 1131 subjects had visual adverse events. Of these the most common were abnormal vision (3%) and conjunctivitis (1%)

- Overall incidence is reproduced in Sponsor table 76.

Table 76: Subject Incidence of Visual Adverse Events: Double-Blind Topiramate (Studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106)

Body system Preferred term	TPM 50 (N=359) n (%)	TPM 100 (N=210) n (%)	TPM 200 (N=199) n (%)	TPM 400 (N=236) n (%)	TPM 500 (N=127) n (%)	Total (N=1131) n (%)
Vision disorders						
Vision abnormal	11 (3)	3 (1)	6 (3)	7 (3)	4 (3)	31 (3)
Conjunctivitis	4 (1)	1 (<1)	2 (1)	3 (1)	1 (1)	11 (1)
Eye pain	2 (1)	0	0	0	1 (1)	3 (<1)
Eye abnormality	0	0	1 (1)	0	1 (1)	2 (<1)
Myopia	1 (<1)	0	1 (1)	0	0	2 (<1)
Glaucoma	1 (<1)	0	0	0	0	1 (<1)
Mydriasis	0	0	1 (1)	0	0	1 (<1)
Central & peripheral nervous system						
Visual field defect	1 (<1)	0	0	0	0	1 (<1)
Any adverse event	**19 (5)**	**4 (2)**	**9 (5)**	**9 (4)**	**6 (5)**	**47 (4)**

Note: Treatment groups are defined in Table 6.

Among subjects who received topiramate, isolated cases of adverse visual events were reported. Visual field measurements made for a subset of subjects in Study 106 and reviewed by an independent expert ophthalmologist did not reveal a pattern of drug toxicity. Sponsor's review of all clinical and postmarketing data found that a syndrome consisting of acute myopia associated with increased intraocular pressure or secondary angle-closure glaucoma has been reported for a number of topiramate-treated subjects. Based on these cases, a Warning about this syndrome was already added to the product labeling for topiramate. Of note, there were no reports of acute myopia with increased intraocular pressure or secondary angle-closure glaucoma in any of the study groups.

8.3.7 Thromboembolic events related to topiramate

This reviewer was concerned regarding the reports of deep venous thrombosis and pulmonary emboli in the safety database. The possibility of topiramate as a causative factor concerned me, but I was uncertain how to resolve my concerns, given the low overall incidence and the possibility that some if not all of these events were alternatively explained. This concern was validated by my Team Leader, Dr. John Feeney who apprised me of similar cases in an ALS study that was stopped due to the higher incidence of these events in the treated group. (A randomized, placebo controlled trial of topiramate in amyotrophic lateral sclerosis Neurology 2003; 61: 456-464.)

The cases of DVT and or PE reported in the submission are summarized in the following table.

Identification	Age/sex	Dose of topiramate	Duration of treatment	Diagnosis	Other comments
9392	54F	300mg Study 104 extension	2.5 years	DVT and PE	*Oral contraceptive use* continued topiramate
653002	35F	Study 106 double blind phase	5 months	DVT	Continued topiramate
95001	43F	100mg Study 105 double blind phase	1 month	DVT	Continued topiramate
103904	41F	100mg Study 105 double blind phase	18 months	PE	*History of smoking, oral contraceptives* Continued topiramate
536008	26F	400mg Study 106 extension	4 months	DVT and PE	*Oral contraceptives* continued topiramate
531012	56F	400mg Study 106 extension	Off meds for 2 weeks prior to event	DVT	Withdrew from study 2 weeks before event.

Of these 6 cases, 3 could be explained by increased risk from use of oral contraceptives. One additional case was related from a patient who stopped the study drug due to lack of efficacy and two weeks later developed a DVT. These 4 cases have reasonable alternative explanations. The remaining 2 cases of DVT may possibly be related to topiramate use, but these patients continued their therapy.

The following is a comparison in the controlled trial population and the extension phase

population.

Double Blind Phase	# Events	# Low dose Patients	#high dose patients
YI		25	25
104		125	127
105	2 (low dose)	210	199
106	1 (low dose)	234	236
Extension	#Events	Total number of patients	Total exposure (person years)
104 Extension	1	164	347.14
105 Extension		37	Not given
106 Extension	2	268	79.32

I checked the Post Marketed Comprehensive Safety Summary and did not find any more cases of DVT, but there were 17 cases of pulmonary embolism in the sponsor's database. Per the sponsor, thrombocytopenia, epistaxis, purpura and pulmonary embolism are currently described in the adverse events section of the topiramate label. Further information regarding DVT would be useful if there is a causal relationship between topiramate use and this adverse event.

8.4 4 Month Safety Update Results

The sponsor submitted a 4 month safety update in February 2003. The original ISS cutoff date for safety information was February 15, 2002. The 4MSU comprised mainly updated information from the Open Label Extension Topiramate data set. The cutoff date for the 4MSU included all serious adverse events through August 31, 2002.

Notable inclusions to the 4MSU are noted below.

Number of subjects – As of August 31, 2002, 500 patients had enrolled in the extension phases of Study 104 and Study 106 (compared to the previously reported 432 patients.) The additional 62 patients were enrollees from Study 106 as these subjects did not have time to enroll in the extension phase. 107 patients received concomitant AEDs most commonly carbamazepine, valproate and phenytoin.

Adverse events – Per the sponsor, no noteworthy differences were observed in the adverse event rates reported in the ISS and the 4MSU for subjects in either data set. As of the cutoff dates for the 4MSU vs. the ISS, 330 (66%) of 500 subjects vs. 247 (57%) of 432 subjects in the Open-Label Extension Topiramate data set reported adverse events; thus, between the cutoff dates for the ISS (February 15, 2002) and the 4MSU (August 31, 2002), adverse events were reported for an additional 83 subjects. Adverse events (preferred terms) reported with an incidence of at least 5% in any treatment group included: neuropsychiatric events (including, headache, paresthesia, fatigue, somnolence, difficulty with memory, dizziness) as well as upper respiratory tract

infection, injury, nausea, weight decrease, and viral infection. These were similar to those reported in the ISS.

- The sponsor makes note that the highest incidences of adverse events occurred in the TPM 50/500 and TPM 500/500 groups from Study 104. Lower incidences were noted in the 50/400 and TPM 400/400 groups from Study 106. The sponsors felt that the dose ranges were similar between groups and that the observed incidences of adverse events were likely related to differences in the duration of the open label extension phase in the two studies with the Study 104 groups having a longer duration of exposure (Median durations - Study 104 TPM50/500 – 588 days; TPM 500/500 – 743 days vs Study 106 - TPM 50/400 – 73 days; TPM 50/400 51 days)

- Pediatric subjects - As of the 4MSU cutoff date vs. the ISS cutoff date, 75 (49%) of 153 pediatric subjects vs. 49 (38%) of 128 pediatric subjects experienced 1 or more adverse events. The most common adverse events reported by pediatric subjects were headache, respiratory system disorders (upper respiratory infection, pharyngitis), somnolence, injury, diarrhea, and viral infection. Compared with all subjects in the Open-Label Extension Topiramate group, the subset of pediatric subjects had a lower incidence of paresthesia, difficulty with memory, fatigue, depression, and nausea. No individual adverse event was reported in pediatric subjects with an incidence that was at least 5% greater than that observed in the entire Open-Label Extension Topiramate data set.

- Between the ISS cutoff and the 4MSU report, no new **deaths** or unexpected serious adverse events were reported.

- **Serious adverse events** – 9 more serious adverse events were reported in the open label extension phases of Studies 104 and 105. These events are included in the following table provided by the sponsor.

Table 13b: Subjects With Nonfatal Serious Adverse Events Reported in the ISS and Added to the Clinical Database Since the ISS Cutoff Date Through 31 August 2002: Open-Label Extension Topiramate (Studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106)

Investigator Subject No.	Age Sex	Serious adverse event Preferred term Investigator term	Day of AE Onset/Dosage at AE onset (mg/day)	Total days of therapy/[a] Final dosage (mg/day)[b]	Severity/ Relationship[c]	Outcome/ Duration (Days)
TPM 50/400 (TOPMAT-EPMN-106)						
Sittenfeld 543002[d]	20 M	Retinal hemorrhage Left retinal hemorrhage	692 300	865 25	Marked Possible	Resolved 147
Grinspan 638039[d,e]	19 M	Aggravated convulsions Hospitalization (epileptic seizures)	250 300	296 300	Marked Probable	Resolved 4
TPM 400/400 (TOPMAT-EPMN-106)						
Imbus 522006	14 M	Infection Acute appendicitis	490 0	542 350	Marked Not related	Resolved 1
Hong 524002	73 F	Infection bacterial Cellulitis of right arm	733 400	752 400	Moderate Not related	Resolved 4
Lehkuniec 644002[e]	23 M	Grand mal convulsions Status epilepticus Grand mal convulsions Status epilepticus	618 400 635 not reported	670 500	Marked Doubtul Marked Doubtul	Resolved 1 Resolved 15
Lehkuniec 644003	27 F	Cholelithiasis Biliary lithiasis (cholecystectomy)	454 400	507 400	Moderate Not related	Resolved 14
Rabinowics 647010[e]	37 M	Nervousness Nervousness perseveration and repetitive	291 400	346 400	Marked Possible	Resolved 32
Raggio 648001	19 F	Infection Acute appendicitis	615 400	791 100	Marked Nor related	Resolved 4
TPM 500/500 (TOPMAT-EPMN-104): High-Dose Group)						
Starreveld 2062	35 M	Agitation Panic attack	2047 400	2122 400	Moderate Doubtful	Resolved 2

Note: CIOMS forms for all of the serious events presented in this table were provided in Attachment 3.4.5 of the ISS.
[a] From the start of treatment to the end of treatment, including tapering, if applicable.
[b] Last dose or last dose prior to tapering, if applicable.
[c] Based on the investigator's assessment at the time of the occurrence of the adverse event.
[d] A narrative description of this case was included in Attachment 3.5.4 of the ISS
[e] A CIOMS form for this subject is provided in Attachment 3.4.3.

- 6 of the 153 pediatric subjects in the open label extension data set experienced 1 or more serious adverse events through the 4MSU cutoff date. One 14 year old boy experienced acute appendicitis. This report is included in table 13 above and was felt by the sponsor to be unrelated to topiramate use.

- Information for serious adverse events for 6 subjects was added to the clinical database since the ISS preparation. The most common serious adverse events reported during topiramate monotherapy were grand mal convulsions, aggravated convulsions, infection, injury, unspecified adverse events (generally hospitalizations for various procedures or treatment of various conditions), chest pain, convulsions, cerebrovascular disorder, and renal calculus.

- An additional 12 subjects (all from Study 106) in the open label extension group (N=500) experienced treatment limiting adverse events since the ISS. Most were neuropsychiatric events and felt to be mild to moderate in severity to the sponsor. An additional 22 patients in this group experienced adverse events that resulted in a

dose reduction or temporary cessation of study treatment. Of these, an additional 7 pediatric subjects were reported . These events were similar to those reported in the ISS and consisted mostly of neuropsychiatric events.

- Incidence of adverse events in the open label Extension Topiramate data set was examined by sex, age group, race, baseline weight group, geographic region, baseline AED use and time since diagnosis of epilepsy. With inclusion of all data through August 31, 2002, the sponsor noted the following associations.

  - Overall adverse event incidence was similar in male and female subjects (headache and fatigue more common in females vs. males).

  - Overall incidence of adverse tended to increase with increasing subject age and increasing baseline body weight.

  - The numbers of black subjects and subjects in other non-white racial groups were too small for a meaningful assessment of associations between race and adverse event incidence.

  - The overall incidence of adverse events and the incidence of many frequently reported adverse events were highest among subjects at North American sites and lowest among subjects at South American sites.

  - The overall incidence of adverse events and the incidence of most of the frequently reported adverse events showed no noteworthy differences between subjects who received baseline AEDs and those who did not receive these medications.

  - Although the overall incidence of adverse events was higher among subjects for whom a diagnosis of epilepsy was made <24 months before study start, the incidence of most individual events differed by less than 5% between these 2 subject subgroups.

- Laboratory data –Although there were continued cases of patients with low CO2, high inorganic phosphorus and high eosinophils noted in the 4MSU, no serious adverse events were related to changes in laboratory findings. Also, per the sponsor, a comparison of the data available between the ISS and 4MSU did not reveal any noteworthy increases in percentages of subjects reporting adverse events related to laboratory abnormalities. No subjects either discontinued open label topiramate, lowered the dose or temporarily discontinued use due to an abnormal laboratory finding.

- Blood pressure and pulse rate – consistent with the ISS, results in the 4MSU did not indicate any notable adverse effect of topiramate on pulse rate or blood pressure.

- Pregnancy. Since the ISS cutoff date, there were no additional pregnancies reported.

- Body weight. – For the open label group, mean body weight decreased in the total population (-2.1kg) with a mean percent increase (+3.8%) in the TPM 50/500 group and mean percent decreases in the TPM 50/400, TPM 400/400, and TPM 500/500 groups (-1.5, -3.4, and –1.2%, respectively). Compared with the results at the ISS cutoff date, a larger mean weight gain was observed in the TPM 50/500 group and a smaller mean weight decrease was observed in the TPM 500/500 group with continued treatment through the 4MSU cutoff date. Weight decrease was reported as an adverse event for 33 (7%) of the 500 subjects in the Open-Label Extension Topiramate data set through the 4MSU cutoff date. Ten of these subjects reported weight decrease since the ISS cutoff. No serious or treatment limiting cases of weight loss were reported since the ISS.

    - Pediatric body weight - Consistent with the results presented in the ISS, the mean body weight of pediatric subjects increased from baseline to the final visit of the open-label extension phases of Studies 104 and 106. Through the 4MSU cutoff date, the largest mean percent increases in body weight were observed among pediatric subjects in the TPM 50/500 (+34.0%) and TPM 500/500 (+29.5%) groups of Study 104. Weight changes from baseline were observed during the open-label extension phase for 93% of pediatric subjects; 59% of the subjects had weight increases and 32% had weight decreases. Among the pediatric subjects with weight decreases, 24% and 7% had decreases of 1-9% and 10-19%, respectively; 2 pediatric subjects (1%) had body weight decreases of 20-29%. Similar results were observed through the ISS cutoff date. All 12 pediatric subjects who had weight decreases of 10% or more through the 4MSU cutoff date were in the 12-15 year age group.

- BMI (Study 106 only) – Because most of the subjects in the TPM 400/400 group did not enter the extension phase until early 2002, many of these subjects did not have a height measurement taken before August 31, 2002, so BMI could not be calculated. However, more subjects in the TPM 50/400 group entered the extension phase so BMI data was more available for this group. Consistent with the findings in the ISS, mean BMI decreases were observed for all subjects in both treatment groups and for pediatric subjects in the TPM 50/400 group.

- Hepatic events – one case of cholelithiasis was reported since the ISS, overall no cases of hepatic failure, direct hepatic toxicity or treatment emergent effects on liver function

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- Metabolic acidosis. During the 4MSU, there were no new cases of adverse events related to metabolic acidosis. 4 cases of renal calculi and 2 cases of bone disorder were reported (bone spur removal and bilateral turbinate bone hypertrophy). None were felt to be serious. Cumulative results obtained for the open label extension data set were in agreement with the ISS data. Topiramate was associated with mean decreases in CO2 levels and mean increases in serum chloride concentrations. The incidence of markedly low CO2 levels decreased from 30% reported in the ISS to

25%; the incidences of marked abnormalities in other relevant laboratory analytes remained essentially unchanged from the ISS cutoff date to the 4MSU cutoff date (increased chloride, 3% vs. 2%; increased alkaline phosphatase, 1% vs. <1%; increased phosphorus, 4% vs. 5%).

- Oligohydrosis/hyperthermia. There were no new cases reported in the 4MSU.

- Encephalopathy/hyperammonemia. After the cutoff date for the ISS, there were no new cases coded as encephalopathy, stupor, coma or EEG abnormalities, however, an additional 5 cases of confusion were reported in 4 subjects. No new adverse events were coded to encephalopathy primary or secondary terms. Although there were 20 additional reports of adverse events, the overall percentages of events coding to primary and secondary events did not change significantly. Most of the events of encephalopathy were neurobehavioral events.

- Visual adverse events. 11 new visual adverse events were reported after the ISS cutoff, the overall distribution was similar to that in the ISS.

8.5 Post Marketing Safety Analysis (From ISS through 4MSU)

Per the sponsor, through October 1, 2002 cutoff, 5877 individual spontaneous postmarketing case reports have been received by DSS for topiramate for all indications for therapy from all post marketing sources worldwide. The section of the submission was reviewed at length but not reproduced here. The most pertinent information related to the overall use of topiramate and issues related to reports of its use in monotherapy are discussed briefly.

A total of 11651 adverse events were reported within the postmarketing case reports. The most frequent adverse events are summarized in Sponsor Table 34.

Table 34: Most Frequently Reported Adverse Events From Spontaneous Postmarketing Case Reports for Topiramate for All Indications

Body System Preferred Term	Original Reporting Period (18 July 1995- 31 May 2002)		Cumulative Reporting Period (18 July 1995- 01 October 2002)	
	No. of Adverse Events[a]	Percentage of All Reported Adverse Events	No. of Adverse Events[b]	Percentage of All Reported Adverse Events
		(Total=10,260)		(Total=11,651)
Metabolic and Nutritional Disorders				
Weight Decreased	416	4.1%	477	4.1%
Central & Peripheral Nervous System Disorders				
Paraesthesia	355	3.5%	414	3.6%
Speech Disorder	189	1.8%	203	1.7%
Dizziness	162	1.6%	185	1.6%
Convulsions Aggravated	154	1.5%	165	1.4%
Headache	118	1.2%	129	1.1%
Vision Disorders				
Vision Abnormal	292	2.8%	347	3.0%
Glaucoma	122	1.2%	150	1.3%
Psychiatric Disorders				
Somnolence	210	2.0%	238	2.0%
Anorexia	170	1.7%	199	1.7%
Amnesia	162	1.6%	188	1.6%
Thinking Abnormal	161	1.6%	181	1.6%
Confusion	158	1.5%	172	1.5%
Psychosis	133	1.3%	161	1.4%
Depression	146	1.4%	159	1.4%
Insomnia	118	1.2%	130	1.1%
Aggressive Reaction	117	1.1%	130	1.1%
Hallucination	109	1.1%	122	1.0%
Skin and Appendages Disorders				
Alopecia	174	1.7%	214	1.8%
Gastrointestinal Disorders				
Nausea	140	1.4%	157	1.3%
Diarrhea	114	1.1%	130	1.1%
Body as a Whole – General Disorders				
Fatigue	127	1.2%	145	1.2%
Urinary System Disorders				
Renal Calculus	128	1.2%	141	1.2%

[a]Based on 5,152 case reports
[b]Based on 5,877 case reports

2987 Serious adverse events were reported in 1222 of the 5877 cases account for 21% of the postmarketing case reports. These are reproduced in the following Sponsor Table 2

Table 2: Most Frequently Reported (>1% Cumulative Total) Serious Adverse Events From Spontaneous Postmarketing Case Reports for Topiramate - All Indications

	Original Reporting Period (18 July 1995- 31 May 2002)		Cumulative Reporting Period (18 July 1995- 01 October 2002)	
Body System Preferred Term	No. of Adverse Events[a]	Percentage of All Reported Adverse Events (Total=2,065)	No. of Adverse Events[b]	Percentage of All Reported Adverse Events (Total=2,987)
Vision Disorders				
Glaucoma	55	2.7%	63	2.1%
Vision Abnormal	46	2.2%	56	1.9%
Psychiatric Disorders				
Psychosis	51	2.5%	95	3.2%
Confusion	39	1.9%	55	1.8%
Somnolence	28	1.4%	51	1.7%
Depression	30	1.5%	44	1.5%
Thinking Abnormal	25	1.2%	44	1.5%
Anorexia	26	1.3%	43	1.4%
Suicide Attempt	26	1.3%	41	1.4%
Hallucination	16	<1.0%	37	1.2%
Agitation	20	<1.0%	35	1.2%
Aggressive Reaction	21	1.0%	35	1.2%
Amnesia	24	1.2%	33	1.1%
Urinary System Disorders				
Renal Calculus	48	2.3%	62	2.1%
Metabolic and Nutritional Disorders				
Weight Decreased	47	2.3%	69	2.3%
Central & Peripheral Nervous System Disorders				
Convulsions Aggravated	36	1.7%	65	2.2%
Convulsions	23	1.1%	44	1.5%
Speech Disorder	23	1.1%	38	1.3%
Convulsions Grand Mal	22	1.1%	35	1.2%
Paraesthesia	26	1.3%	32	1.1%
Encepalopathy	23	1.1%	30	1.0%
Body as a Whole – General Disorders				
Drug Exposure During Pregnancy	29	1.4%	37	1.2%
Fever	23	1.1%	31	1.0%
Gastrointestinal Disorders				
Vomiting	26	1.3%	35	1.2%
Nausea	24	1.2%	30	1.0%

[a]Based on 862 case reports
[b]Based on 1,222 case reports

Central and peripheral nervous system disorders

A total of 1529 case reports have been received accounting for approximately 26% of the 5877 cumulative postmarketing case reports. These are summarized in Table 3.

Table 3: Most Frequently Reported (>1% of Cumulative Total) Cases of Central and Peripheral Nervous System Disorders From Spontaneous Postmarketing Case Reports for Topiramate – All Indications

	Original Reporting Period (18 July 1995- 31 May 2002)		Cumulative Reporting Period (18 July 1995- 01 October 2002)	
Preferred Term	No. of Adverse Events	Percentage of All Case Reports (N=5,152)	No. of Adverse Events	Percentage of All Case Reports (N=5,877)
Paraesthesia	355	6.9%	414	7.0%
Speech Disorder	189	3.7%	203	3.5%
Dizziness	162	3.1%	185	3.1%
Convulsions Aggravated	154	3.0%	165	2.8%
Headache	118	2.3%	129	2.2%
Convulsions	98	1.9%	103	1.8%
Hypoaesthesia	83	1.6%	87	1.5%
Tremor	66	1.3%	82	1.4%
Ataxia	65	1.3%	69	1.2%

Postmarketing Safety Surveillance – Special Topics –All indications

31 Spontaneous postmarketing case reports of overdose were received.
14 spontaneous postmarketing case reports of drug abuse, dependence or withdrawal were received.
255 reports of drug exposure during pregnancy were reported.

Epilepsy as monotherapy postmarketing reports (4MSU only)

55 adverse events were reported for 33 cases identified as monotherapy. These most common reported were decreased sweating, alopecia, and weight decrease. 117 adverse events were reported in 59 case reports of potential monotherapy. The most common reported were decreased weight and anorexia. There was a higher reported frequency of neuropsychiatric disorders in potential monotherapy vs. explicit monotherapy.

Deaths in monotherapy – 1 report of suicide as reproduced from sponsor.

- Case APCDSS2002000768, received from China, described a 19-year-old man with no history of psychiatric problems, except sleep problems. He was diagnosed with epilepsy 2 years before the report date and was treated with topiramate 100mg for over a year. The patient developed a fever associated with a common cold, and his epilepsy relapsed. This was followed the next day by "symptoms of illusion and phonism" (visual and auditory hallucinations); the patient was reported to have jumped to his death from a high building. The relationship of the event to topiramate treatment was assessed as possible. No autopsy was performed.

Per the sponsor, the current topiramate product labeling describes suicide attempt as a potential adverse event reported infrequently based on controlled clinical trials of topiramate as adjunctive therapy for epilepsy.

Serious adverse events in monotherapy – 7 reports in pediatric patients involving decreased sweating.

Overall, per the sponsor, the post marketing safety profile is reflected in current Topiramate labeling.

9. Sponsor's conclusions regarding safety

The results of 3 well-controlled clinical studies (TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106) demonstrate that topiramate monotherapy has an acceptable safety profile and is reasonably well tolerated by subjects aged 6 years and older with newly diagnosed epilepsy. Neuropsychiatric adverse events, known side effects of topiramate, were the most common treatment-related adverse events. The adverse events profile established for topiramate monotherapy based on the findings of these 3 studies is generally consistent with the previous clinical experience when topiramate was administered as adjunctive therapy for epilepsy. However, despite the longer duration of the monotherapy studies, topiramate monotherapy was associated with a lower incidence of many frequently reported neuropsychiatric adverse events than topiramate adjunctive therapy. A higher incidence of paresthesia reported during topiramate monotherapy may be related to the generally higher plasma topiramate concentrations achieved at similar topiramate doses in the monotherapy vs. adjunctive therapy studies.

The incidence and severity of the adverse events and abnormal laboratory findings related to hepatic events, metabolic acidosis, oligohydrosis/hyperthermia, encephalopathy, or visual adverse events observed in the monotherapy trials are consistent with the known safety profile of topiramate and with the results of previous analyses of these special safety topics across several populations of topiramate-treated subjects. The results do not suggest an increase in the risk of any of these abnormal findings among subjects with epilepsy treated with topiramate monotherapy vs. adjunctive therapy. The incidence of some neuropsychiatric adverse events (in particular, paresthesia, the most common adverse event) and weight loss, the incidence of treatment-emergent markedly low CO2 levels, and the frequency of decreases in body weight appeared to increase with the dose of topiramate monotherapy.

Sponsors Dose Recommendations

Based on these dose relationships and efficacy results from the pivotal study (TOPMAT-EPMN-106) and the supportive studies (TOPMAT-EPMN-104 and TOPMAT-EPMN-105), the initial topiramate monotherapy target dose recommended for the treatment of newly diagnosed epilepsy patients aged 6 years and older is 100 mg/day and the maximum recommended monotherapy dose is 400 mg/day.

10. Reviewer's Evaluation of Safety

The sponsor's safety conclusions are noted above. I am in agreement with most of the safety conclusions as stated. Dose related increases in neuropsychiatric events, paresthesias, weight loss and low CO2 related to metabolic acidosis were noted and discussed within this report. Some of the following safety concerns have already been discussed in this report and are briefly referred again in this section.

10.1 Titration Schedule.

The titration schedule used in the pivotal trial may place patients at risk for seizure events during the 6-week titration to the effective dose. This would preclude the use of topiramate as initial monotherapy and place it more likely to be used as conversion to monotherapy. This is illustrated in Sponsor Table 4.

Table 4: Dose Titration Schedule
(Study TOPMAT-EPMN-106)

	Open-Treatment	Titration Period (Days)						Stabilization
Dose Group	Days -7 to -1	1 to 7	8 to 14	15 to 21	22 to 28	29 to 35	36 to 42	Period
50 mg/day	25	25	25	50	50	50	50	50
400 mg/day	25	50	100	150	200	300	400	400

NOTE: Topiramate dosages are provided in mg/day.

The dose titration schedule for monotherapy is confusing overall as a lower dose may be just as efficacious in some patients as the goal dose of 400mg. Also, there is no pediatric dose titration schedule based on a mg/kg/day recommendation. The sponsors relate a dose recommendation above, but it is difficult to ascertain if the 100mg dosage was efficacious or not. I do agree that the 400mg dosage should be a maximum dose rather than a goal dose. The sponsor proposes a starting dose of (b) (4) mg with a maximum dose for monotherapy of 400mg. The dose of 100mg is chosen based on the separation of Kaplan Meier curves seen in Study 106 at the 100mg two weeks after double blind treatment. The Division does not recognize the significance of the separation of the curves at that dosage. The actual dosages reached in Study 106 are reproduced below in Sponsor Table 11.

Table 11: Daily Dosage of Topiramate
(Intent-to-Treat Population; Study TOPMAT-EPMN-106)

	TPM 50 (N=234)	TPM 400 (N=236)
Average Daily Dose (mg/day)		
Mean	42.5	275.3
SD	8.95	120.97
Median	47.5	335.3
Range	17.0 - 61.7	27.4 - 399.1
Maximum Daily Dose (mg/day)		
Mean	48.5	339.7
SD	9.43	121.42
Median	50.0	400.0
Range	25.0 - 100.0	50.0 - 800.0
Final Daily Dose (mg/day)		
Mean	42.8	309.4
SD	14.07	128.90
Median	50.0	400.0
Range	0.0 - 50.0	0.0 - 450.0

Cross-reference: Attachment 4.1.1

The current dose titration schedule for adjunctive therapy in epilepsy is reproduced below for comparison.

The recommended total daily dose of TOPAMAX ® as adjunctive therapy is 400 mg/day in two divided doses. In studies of adults with partial onset seizures, a daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. It is recommended that therapy be initiated at 25-50 mg/day followed by titration to an effective dose in increments of 25-50 mg/week. Titrating in increments of 25 mg/week may delay the time to reach an effective dose. Daily doses above 1,600 mg have not been studied.

In the study of primary generalized tonic-clonic seizures the initial titration rate was slower than in previous studies; the assigned dose was reached at the end of 8 weeks (see CLINICAL STUDIES, Controlled Trials in Patients With Primary Generalized Tonic-Clonic Seizures).

Pediatric Patients (Ages 2-16 Years)--Partial Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome
The recommended total daily dose of TOPAMAX ® (topiramate) as adjunctive therapy for patients with partial seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut Syndrome is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome.

In the study of primary generalized tonic-clonic seizures the initial titration rate was slower than in previous studies; the assigned dose of 6 mg/kg/day was reached at the end of 8 weeks (see CLINICAL STUDIES, Controlled Trials in Patients With Primary Generalized Tonic-Clonic Seizures).

The final dosages to be approved should reflect the maximal doses reached. Separate data regarding exposures in pediatric patients was sent by email from the sponsor and reproduced below.

The maximum daily dose achieved during the double-blind phase of Studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106 are summarized for pediatric subjects in Tables 1 and 2, respectively. The maximum daily dose represents the maintenance dose achieved for the majority of subjects. For those who required a dose reduction, the maintenance dose was usually within 50 mg/day of the maximum daily dose.

Table 1: Maximum Daily Dose During the Double-Blind Phase (Study TOPMAT-EPMN-104: Pediatric Subjects in High Dose Group)

Age (years)	N	Mean	Range
Maximum Daily Dose (mg/day)			
6	2	200.0	200.0- 200.0
7	2	137.5	75.0- 200.0
8	1	200.0	200.0-200.0
9	2	137.5	75.0-200.0
10-15	7	310.7	75.0-500.0
Maximum Daily Dose (mg/kg/day)			
6	2	7.4	7.2 - 7.5
7	2	4.2	2.9 - 5.4
8	1	7.6	7.6 - 7.6
9	2	3.3	2.2 - 4.5
10-15	7	5.9	1.8 - 9.7

Table 2: Maximum Daily Dose During the Double-Blind Phase (Study TOPMAT-EPMN-106: Pediatric Subjects in High Dose Group)

Age (years)	N	Mean	Range
Maximum Daily Dose (mg/day)			
6	2	400.0	400.0 - 400.0
7	4	400.0	400.0 - 400.0
8	9	361.1	50.0 - 400.0
9	5	350.0	150.0 - 400.0
10-15	57	383.3	100.0 - 450.0
Maximum Daily Dose (mg/kg/day)			
6	2	14.0	12.7 - 15.4
7	4	13.9	10.8 - 16.0
8	9	11.6	1.4 - 15.4
9	5	10.8	1.9 - 16.0
10-15	57	8.4	1.8 - 14.8

10.2 Goal Dosage- overall safety concerns.

The 400mg dosage is not well tolerated as suggested by the sponsor. Again a lower dose might be efficacious and have a better safety profile. Evidence attesting to this opinion is presented as follows:

Pivotal Study TOPMAT-EPMN-106

- The number of withdrawals due to adverse events is 3 times higher in the TPM 400 group (17%) compared to the TPM 50 group (6%). According to the sponsor, these numbers are actually higher as 44 subjects (19%) in the topiramate 400 mg/day group and 16 subjects (7%) in topiramate 50 mg/day group experienced adverse events that resulted in permanent discontinuation of therapy. Per the sponsor, the discrepancy between this number and the number of subjects who withdrew from the study due to adverse events (40 subjects in topiramate 400 mg/day group and 13 in topiramate 50 mg/day group, is due to the fact that 7 subjects (4 in topiramate 400 mg/day group and 3 in topiramate 50 mg/day group) completed the double-blind phase by having a first seizure, but also experienced treatment-limiting adverse events. Due to these events, after the report of the first seizure, the decision was made to stop treatment in those patients.

- 24% of the TPM 400 versus 9% in the TPM 50 group experienced adverse events that resulted in reduction of topiramate dosage or temporary interruption of treatment (See Sponsor Table 19). Most of those subjects who experienced dose reductions or temporary interruptions of study treatment (11 out of 20 [55%] in the TPM 50 group and 42 out of 56 [75%] in the TPM 400 group) completed the study per protocol. This implies that 45% of those who experienced dose reductions in the TPM 50 group and 25% of those in the TPM 400 group did not complete the study per protocol.

- Considering the incidence of the most common adverse events leading to a dose reduction or interruption in study medication the incidence of psychiatric side effects was significantly higher in the TPM 400 group compared to the TPM 50 group, whereas the incidence of neurologic side effects, also more prevalent in the higher dose group. Of note, paresthesia was 7 times more prevalent in the TPM 400 group compared to the TPM 50 group, again raising concerns regarding the ability of those patients to continue to maintain a 400mg dosage regimen for control of seizures without needing a dose reduction or interruption due to side effects.

- Regarding common adverse events, those events with at least **twice** the incidence in the TPM 400 group, compared to the TPM 50 group were paresthesia (31% vs. 15%), as well as anorexia (14% vs. 7%), weight decrease (16% vs. 6%), difficulty

with memory (8% vs. 4%), mood problems (6% vs. 2%), and cognitive problems (5% vs 1%).

- The decreases in BMI seen in this study are concerning for retardation of growth. Further information regarding height assessment and failure to continue on a current growth curve would be useful to assess possible long-term side effects of topiramate in children.

ISS Data

- This reviewer notes the larger number of dropouts during the double blind phase due to adverse events seen in the higher dose groups in all studies. There were also a large number of discontinuation in the extension phase of Study 104 at the 500 mg dose (65% overall) and in the extension phase of Study 106 at the 400mg dose (14% overall). This is concerning as adverse events leading to dropouts seems to be more significant in the higher dose groups, although this is difficult to compare across the different studies.

- This reviewer notes that the sponsor does not discuss the issues of headache, somnolence and fatigue seen across the entire study population. Since there is no placebo group, these incidence are significant and might reduce the tolerability of the medication in the study population at recommended doses. This was especially noted in the pediatric population. The incidence of headache appears to be significant (20-25% overall) and would limit usage of topiramate at these doses in this population or require further treatment it headache is drug induced.

- Pediatric weight loss was higher in TPM 400 group. Among pediatric subjects, the incidence of weight loss was higher among subjects in the TPM 400 group (17%) compared with the other treatment groups (0-7% incidence). This reviewer has some concerns regarding a negative BMI especially in pediatric patients as this implies combined general weight and/or height loss in the affected patients. The Division has ongoing concerns regarding this issue and separately regarding the possibility of growth retardation and/or bone demineralization in children related to the drug induced metabolic acidosis.

- The overall incidences of encephalopathy and neuropsychiatric events are misleading in that the primary and secondary terms for encephalopathy are split out so that it appears that these individual incidences are smaller than they are reported as a whole. The sponsor should reevaluate the encephalopathy data as a whole (rather than splitting them into primary and secondary terms) to obtain better information regarding the incidence of neuropsychiatric side effects of the drug as used in monotherapy

11. Evaluation of Financial Disclosure/Ethical Standards

In accordance with 21 CFR §54.2 - 54.4 and 314.50 as well as JRF/RWJPRI GCP SOP 650, and as agreed at the March 12, 2002 pre-NDA meeting, financial disclosure information was only provided for investigators/subinvestigators involved in the following studies discussed in the monotherapy sNDA:

- (b) (4)
-

Per the sponsor, these studies were ongoing as of February 2, 1999, the effective date of the regulation requiring an applicant whose submission relied in part on clinical data to disclose certain financial arrangements between sponsor(s) of the covered studies and the clinical investigators and certain interests of the clinical investigators in the product under study or in the sponsor of the covered studies, as defined in 21 CFR §54.2. Therefore, investigators for these studies were contacted by the sponsor and asked to provide information as to whether or not they had any reportable financial information.

Due diligence is defined in JRF/RWJPRI GCP SOP 650 as "at least two written attempts" to contact the investigator. J&JPRD made two written attempts to obtain this information from each principal investigator and subinvestigator as listed on the Form 1572 or Statement of Investigator. However, since TOPMAT-EPMN-105 was initiated prior to the effective date of the regulation, 02 February 1999, financial disclosure was not required at the time of study initiation. In addition, financial disclosure was not able to be obtained from some subinvestigators due to loss of follow up and are noted as such in the submission.

The information was provided in table format, per study, with all investigators and subinvestigators listed alphabetically by country. The Financial Disclosure Classification Table identified:

- Investigators who provided certification or disclosure
- Investigators for whom JJPRD acted with due diligence
- Investigators who participated in the pivotal studies and were employees of the sponsor.

(b) (6) - Per the sponsor, Study (b) (6) was a large multi-center study, and therefore, the potential bias of the clinical study results by these investigators and subinvestigator was minimized. This reviewer agrees with the sponsor's conclusions.

The (b) (6) MD indicated that he had reportable equity interests, reported as Johnson & Johnson stocks exceeding USD 50,000 as well as receiving payments for (b) (6) exceeding USD 25,000. Dr. (b) (6) enrolled 0 patients in Study (b) (6) but (b) (6) enrolled (b) (6) subjects.

The [redacted], MD indicated that she had reportable equity interests, reported as Johnson & Johnson stocks exceeding USD 50,000 as well as her husband receiving payments for [redacted] exceeding USD 25,000. Dr. [redacted] was [redacted] site. Dr. [redacted] enrolled [redacted] subjects in Study [redacted].

The [redacted] indicated that he had reportable payments in the form of a grant to fund ongoing research exceeding USD 25,000. Dr. [redacted] enrolled [redacted] subjects in Study [redacted] in the [redacted].

[redacted] **– Per the sponsor Study** [redacted] which was a large multi-center study, and therefore, the potential bias of the clinical study results by the investigators and two subinvestigators was minimized. Again this reviewer agrees with the sponsor's conclusions.

The [redacted], MD indicated that he had reportable equity interests, reported as Johnson & Johnson stocks exceeding USD 50,000 as well as receiving payments for [redacted] exceeding USD 25,000. Dr. [redacted] did not enroll subjects in the study, but [redacted] enrolled [redacted] patients.

The [redacted] MD indicated that she had reportable equity interests, reported as Johnson & Johnson stocks exceeding USD 50,000 as well as her husband receiving payments for [redacted] exceeding USD 25,000. Dr. [redacted] was [redacted] site. Dr. [redacted] was [redacted] site for this study. She enrolled 0 patients in Study [redacted].

The [redacted], MD indicated that he had reportable equity interests, reported as Johnson & Johnson stocks exceeding USD 50,000. Dr. [redacted] was [redacted] site. However, no patients were enrolled at this site for the Study [redacted].

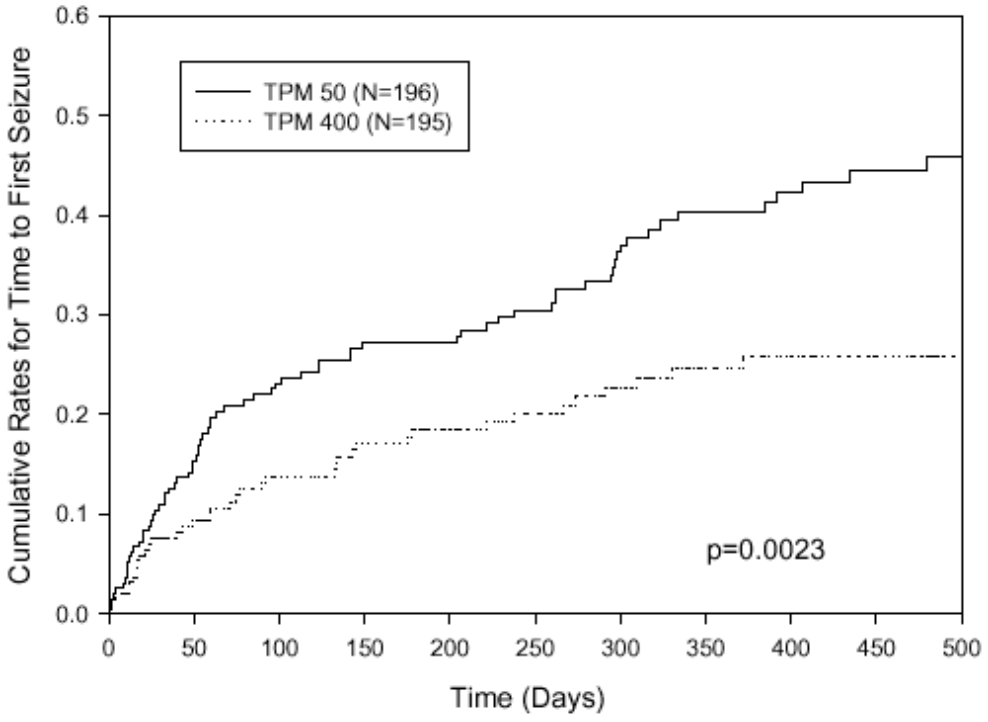
Clinical Reviewer Conclusions: The sponsors provided "Certification of Financial Disclosure" in table format for the majority of their investigators/subinvestigators. Per the sponsor, only those investigators listed above had disclosable financial interests. These financial disclosure tables were reviewed. Almost all investigators and subinvestigators had a certification on file. In some cases where financial information could not be obtained from the investigator/subinvestigator, the "Due Diligence" column had been checked in the Financial Disclosure Classification Table. [redacted] from Study [redacted] and [redacted] from Study [redacted] reported having disclosable information. Overall, the sponsor acted with due diligence to obtain financial disclosure information as required by 21 CFR §54.4.

Given the small numbers of patients enrolled by each of these investigators, it is unlikely that the final results contain any bias related to financial holdings.

12. Appendix 1 - Kaplan Meier Curves of Subgroups in Study 106

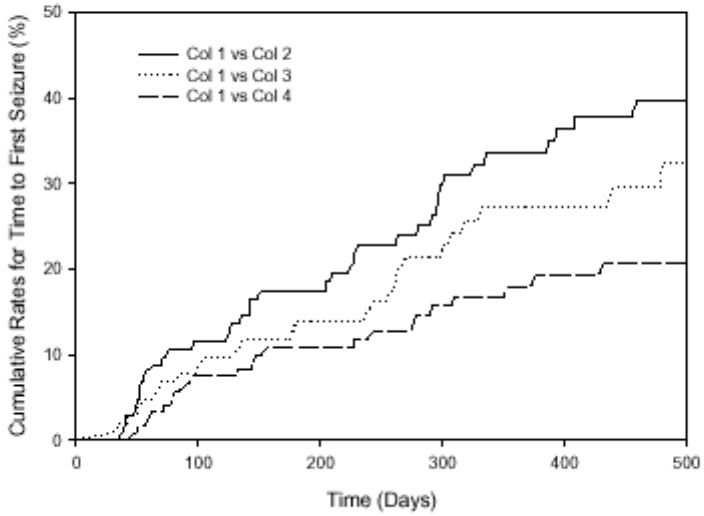
Attachment 5.7.2.1

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Time Since Diagnosis: Subjects Diagnosed No More than 2 Years Before Enrollment



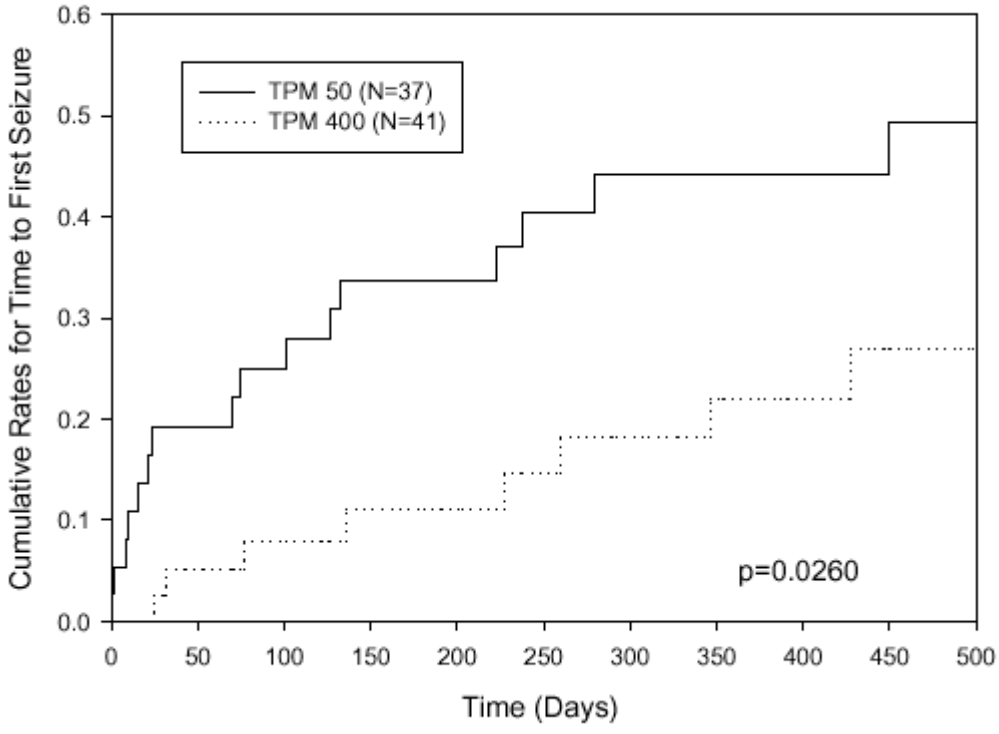
Attachment 6.2

Plot of Kaplan-Meier Estimates for Cumulative Rates for the Time to First Seizure in the 3 Topiramate Plasma Concentration Strata (Study TOPMAT-EPMN-106)



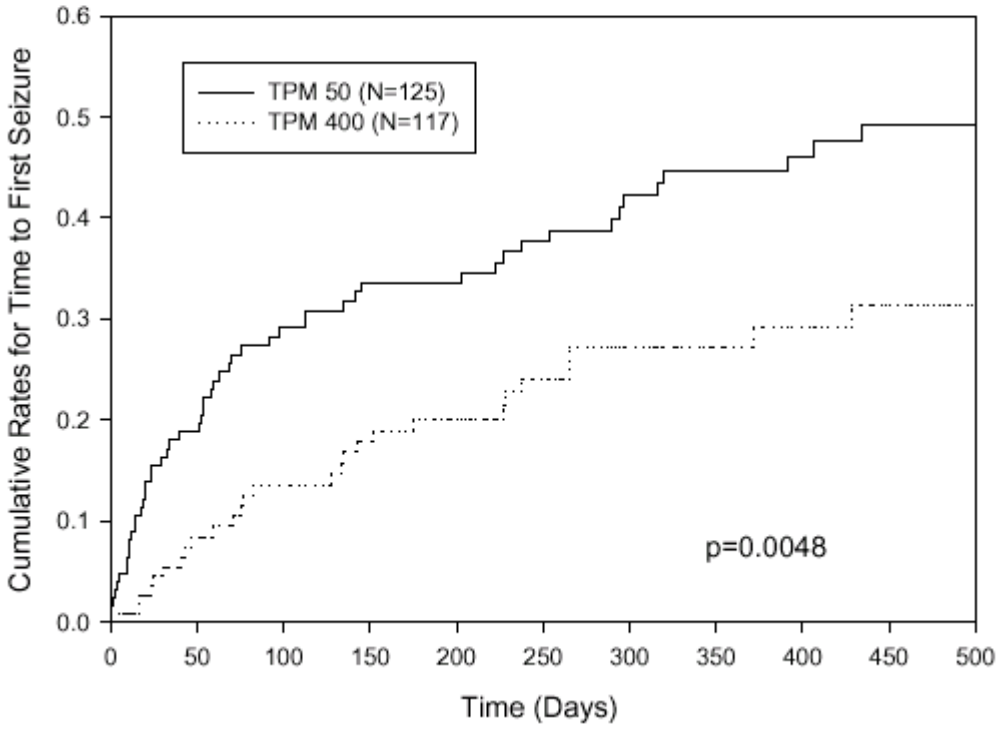
Attachment 5.7.2.2

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Time Since Diagnosis: Subjects Diagnosed More than 2 Years Before Enrollment



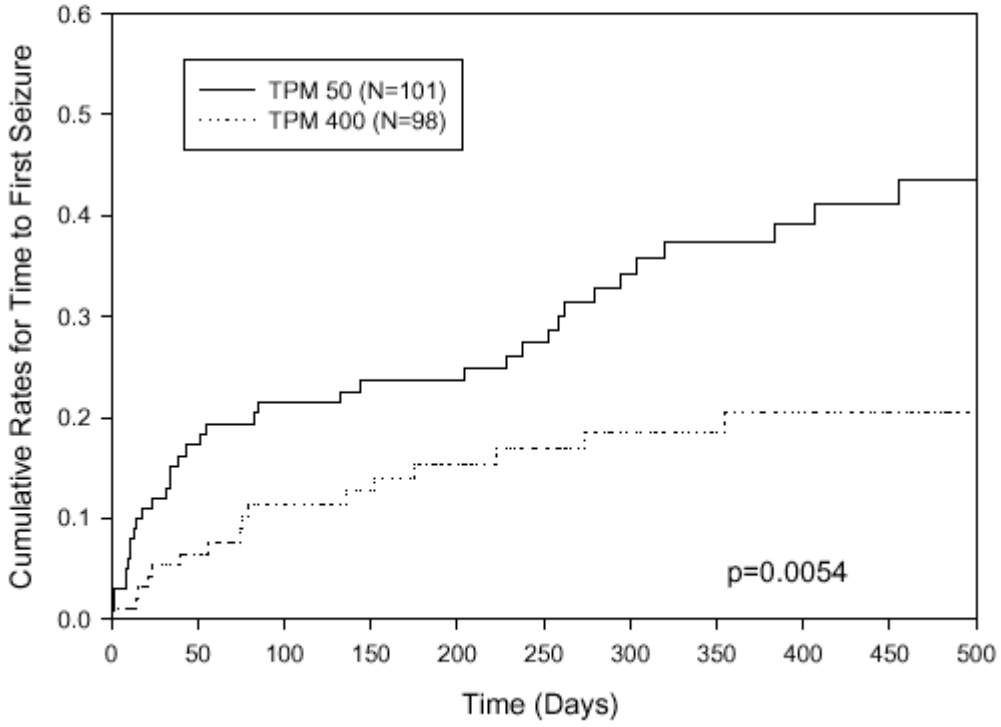
Attachment 5.6.2.2

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by AED Use Prior to Randomization: Subjects Who Used AEDs



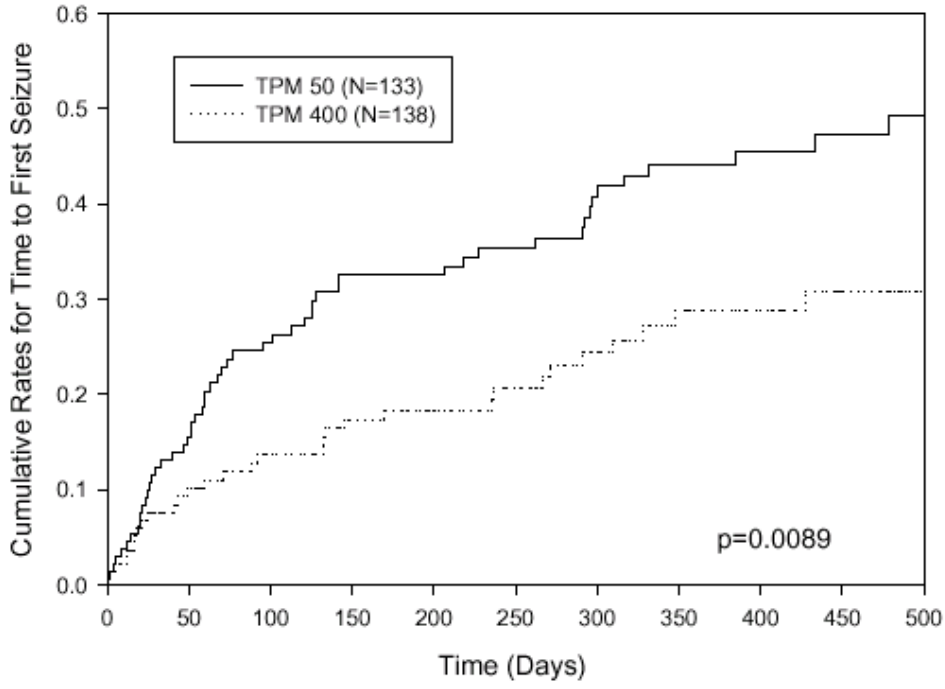
Attachment 5.5.2.2

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Baseline Seizure Type: Subjects with no Partial Onset Seizures at Baseline



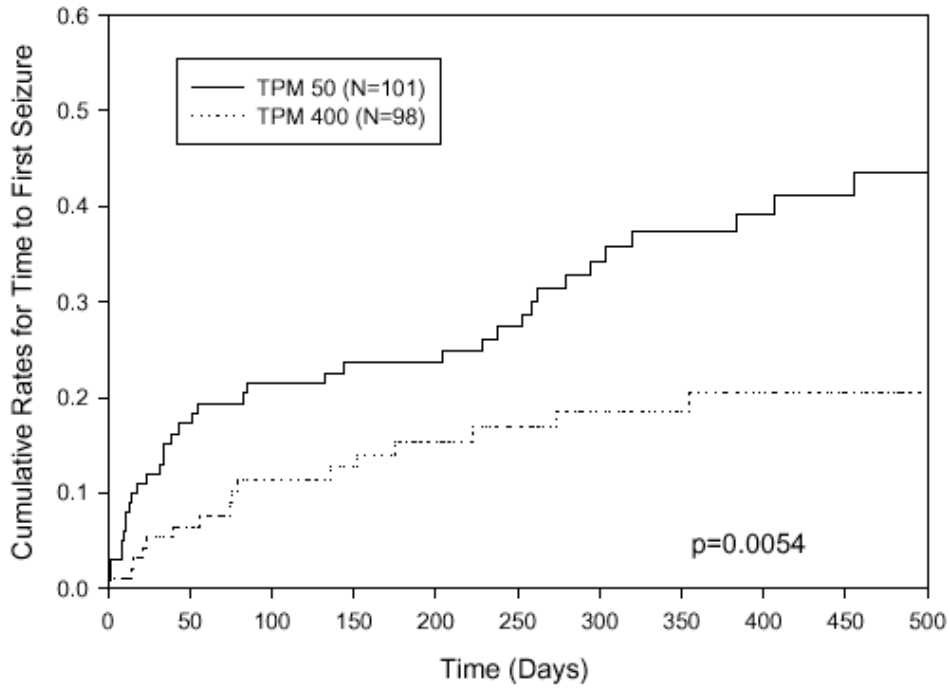
Attachment 5.5.2.1

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Baseline Seizure Type: Subjects with at Least 1 Partial Onset Seizure at Baseline



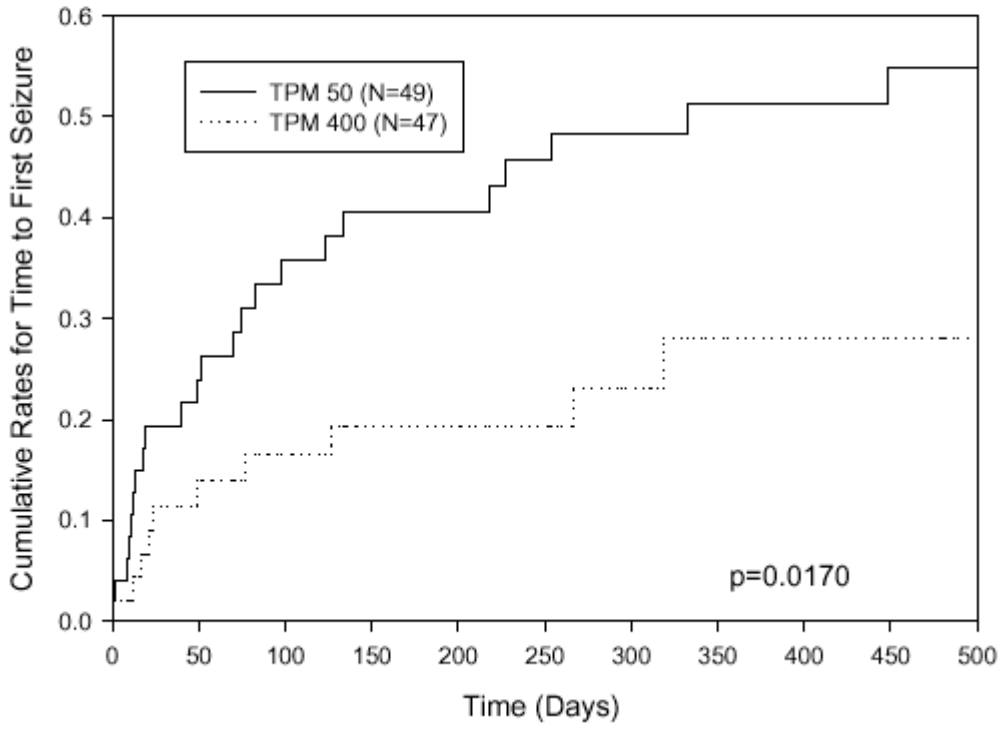
Attachment 5.5.2.2

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Baseline Seizure Type: Subjects with no Partial Onset Seizures at Baseline



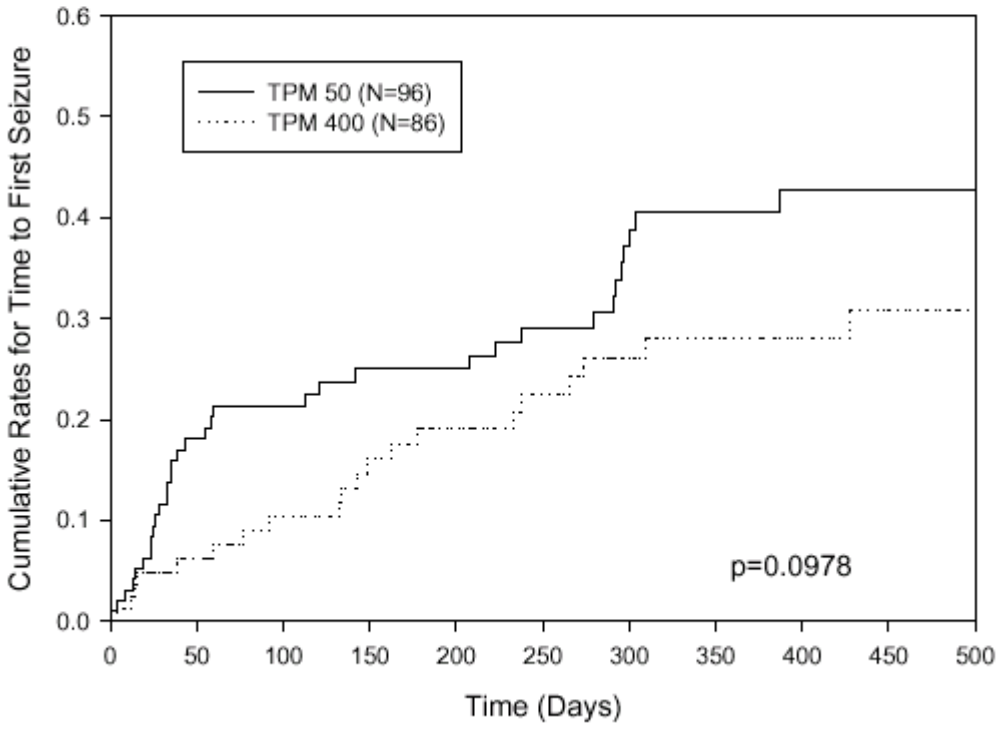
Attachment 5.4.2.3

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Baseline Body Weight: Subjects Weighing More than 85 kg



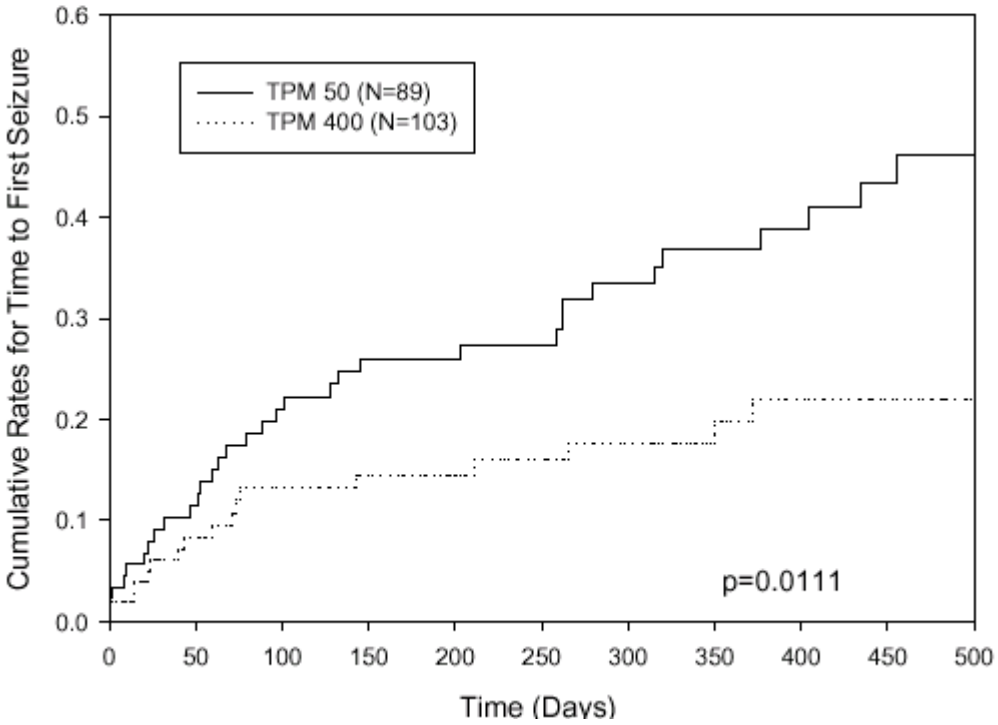
Attachment 5.4.2.2

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Baseline Body Weight: Subjects Weighing Between 60 and 85 kg



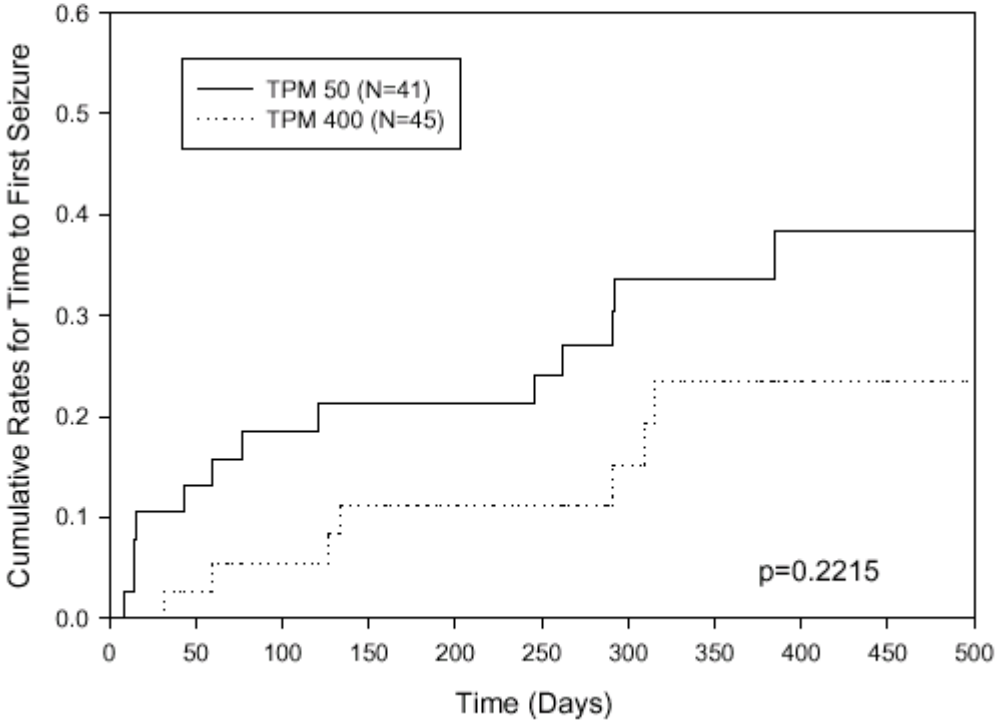
Attachment 5.4.2.1

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Baseline Body Weight: Subjects Weighing Less than 60 kg



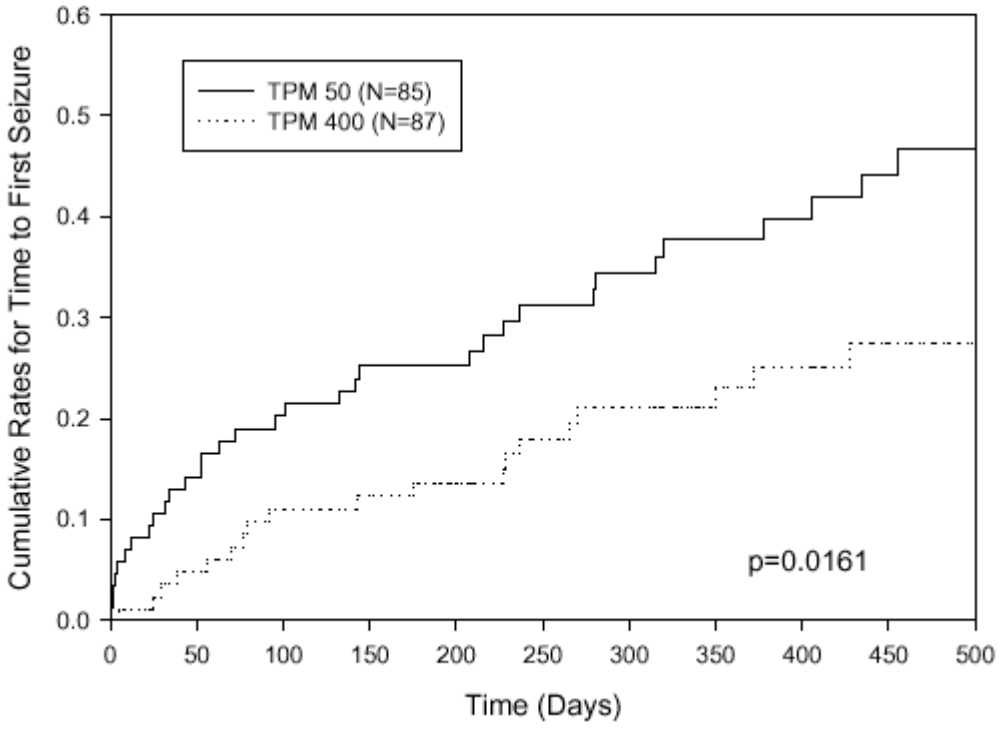
Attachment 5.3.2.3

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Geographic Region: Other Regions



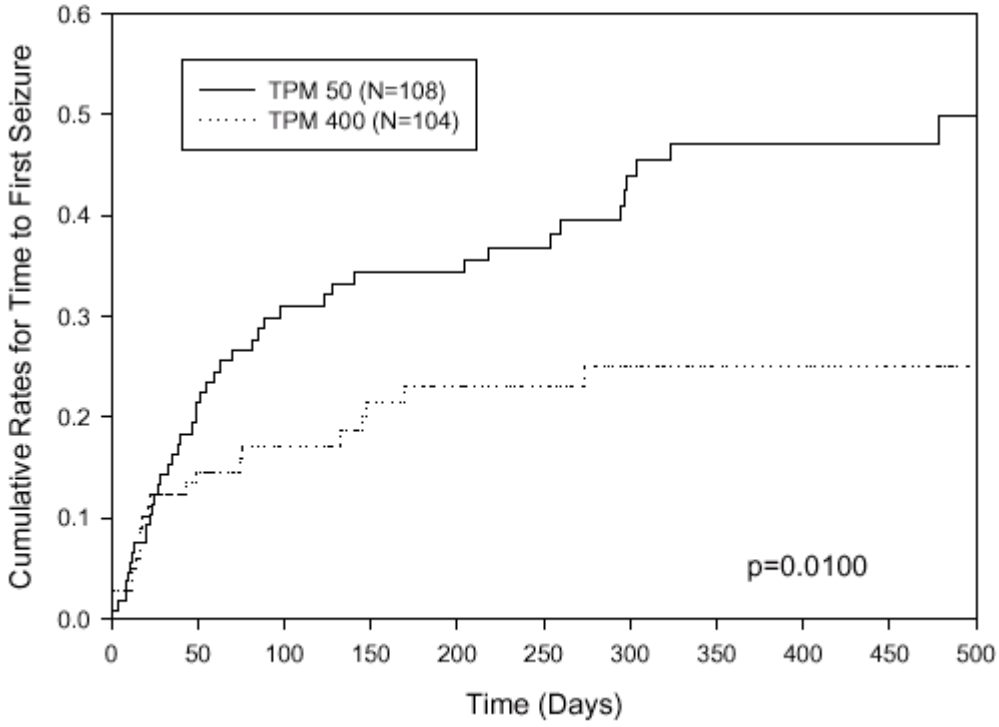
Attachment 5.3.2.2

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Geographic Region: South America



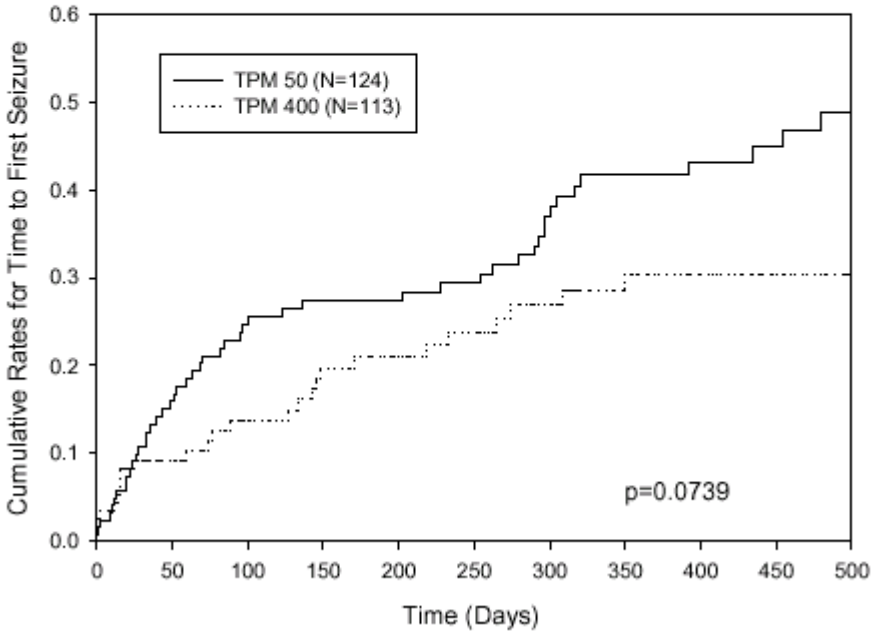
Attachment 5.3.2.1

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Geographic Region: North America



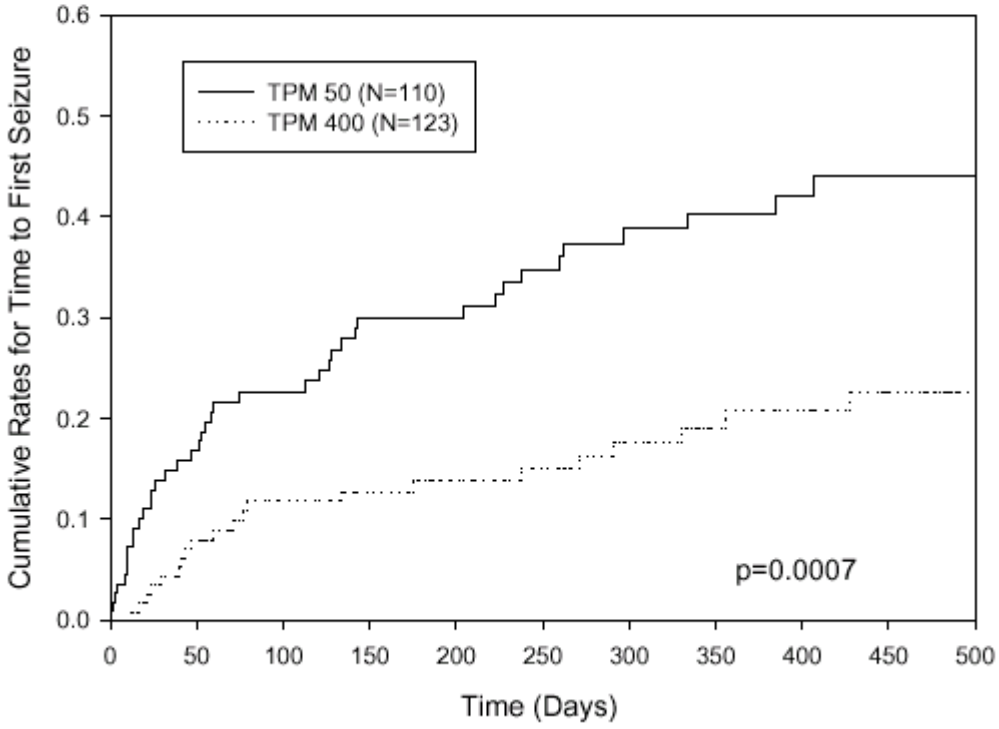
Attachment 5.2.2.2

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizureby Sex: Female Subjects



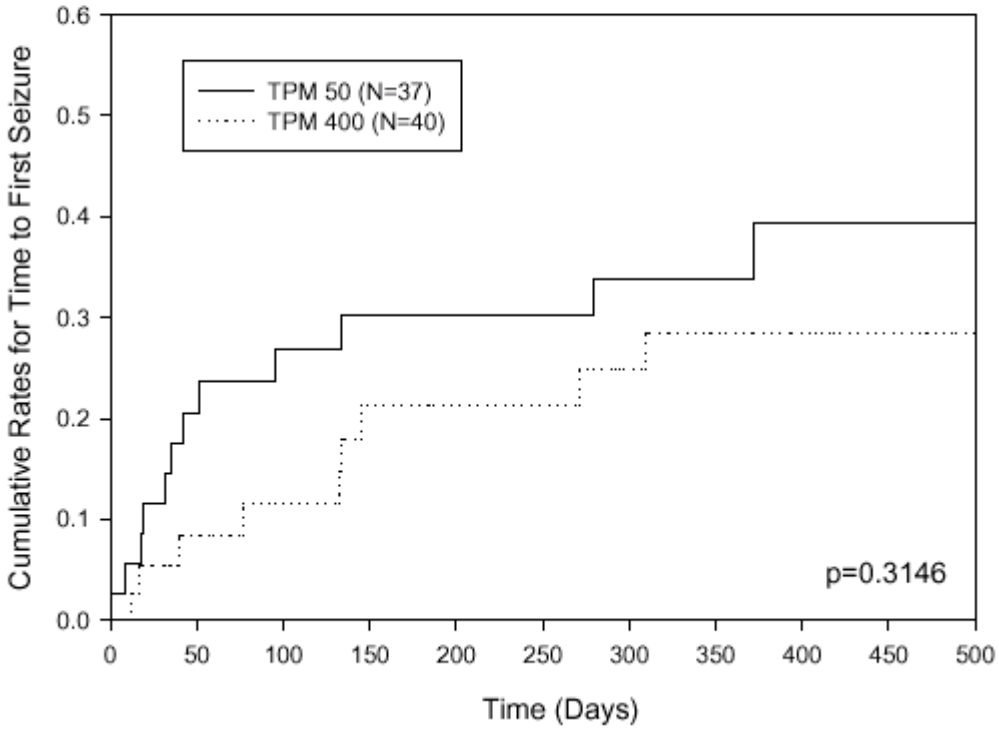
Attachment 5.2.2.1

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Sex: Male Subjects



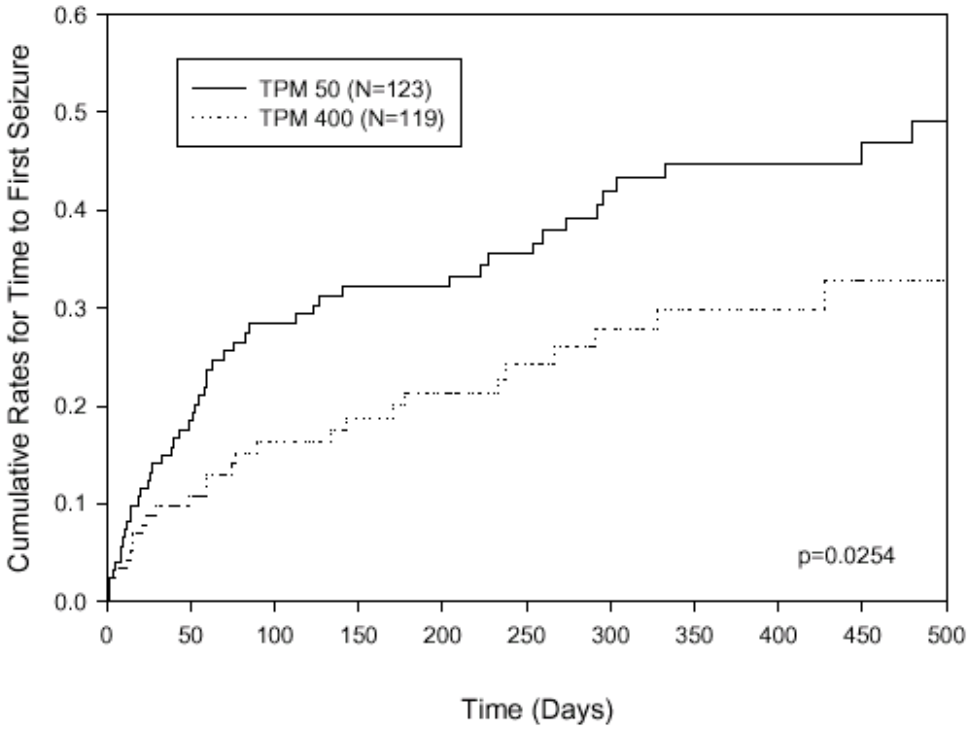
Attachment 5.1.2.3

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Age: Subjects Older than 44 Years of Age



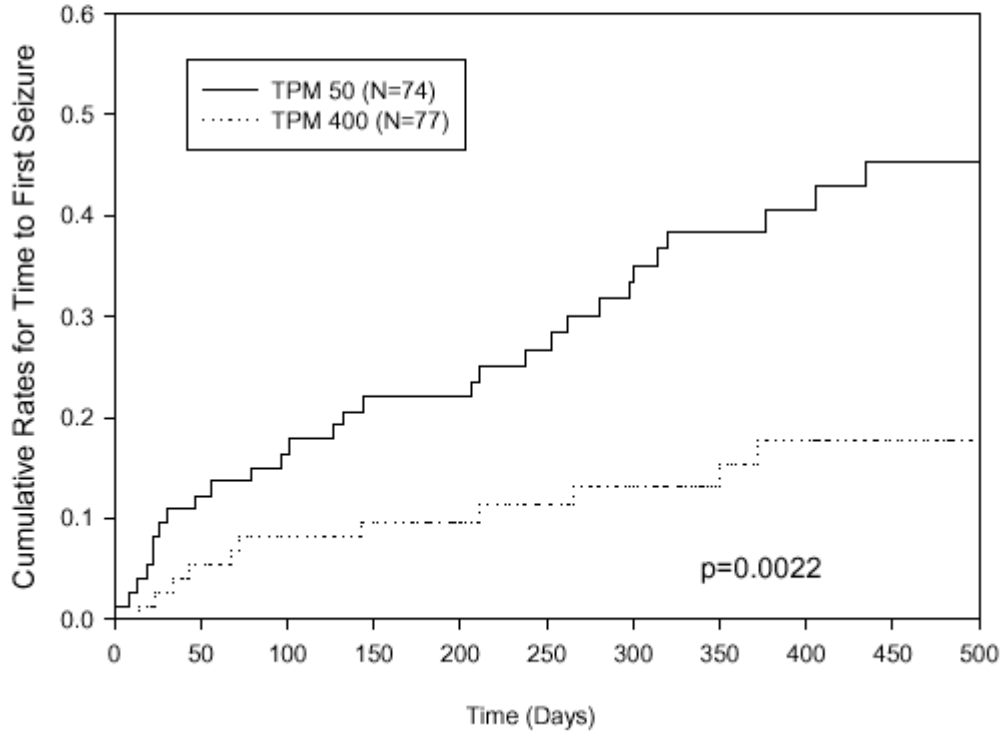
Attachment 5.1.2.2

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Age: Subjects Between 15 and 44 Years Old



Attachment 5.1.2.1

Plot of Kaplan-Meier Estimates of Cumulative Rates of Time to First Seizure by Age: Subjects 15 Years Old or Younger



Howard Chazin, M.D.
Medical Reviewer

John Feeney, M.D. _____
Neurology Team Leader

hdc
HFD-120
NDA 20-505 (S018) topiramate monotherapy supplement
NDA 20-844 (S015) topiramate sprinkles, monotherapy supplement

APPEARS THIS WAY IN ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Howard Chazin
11/26/03 02:22:07 PM
MEDICAL OFFICER

John Feeney
11/26/03 04:52:03 PM
MEDICAL OFFICER
see my cover memo

MEMORANDUM

DATE: November 26, 2003

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-505/S-018 & NDA 20-844/S-015

SUBJECT: Action Memo for NDA 20-505/S-018 & NDA 20-844/S-015, for the use of Topamax (topiramate) Tablets and Sprinkle Capsules as Monotherapy in the treatment of Partial Seizures

NDA 20-505/S-018 & NDA 20-844/S-015, for the use of Topamax (topiramate) Tablets and Sprinkle Capsules, respectively, as Monotherapy in the treatment of Partial and Primary Generalized Seizures, was submitted by R.W. Johnson Pharmaceutical Research Institute on 10/29/02. The application contained the results of four controlled trials, although the sponsor proposed that only one of the studies, Study 106, be considered as primary in establishing substantial evidence of effectiveness. Because of questions about the conduct and analysis of this trial, the division requested additional work be done to address these questions and concerns. The sponsor responded in a submission dated 7/31/03.

The submission has been reviewed by Dr. Howard Chazin, medical reviewer (review dated 11/26/03), Dr. Kun He, statistician (review dated XXXX), Dr. Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics (review dated 3/19/03), Dr. Lyudmila Soldatova, chemist (review dated 8/26/03), and Dr. John Feeney, Neurology Drugs Team Leader (memo dated 11/26/03). The clinical review team recommends that the application be considered Not Approvable. I will briefly review the clinical data, and present the rationale for the division's decision.

As noted above, the sponsor has submitted results of four controlled trials that they believe establish that topiramate is effective as monotherapy in the treatment of partial seizures, although, also as noted, they propose that Study 106 be considered the primary study on which this conclusion rests. I will briefly describe the results of the three other trials included in the application.

Study Y1

This was a randomized double blind parallel group trial in which patients with partial seizures were treated either with topiramate 1000 mg/day or topiramate 100 mg/day. Patients had been refractory to their current treatment, and were withdrawn to monotherapy. The primary outcome measure was time to reach various exit criteria. A total of 48 patients were randomized in this trial, and the p-value for the primary contrast was p=0.002.

This trial was submitted in the original NDA for topiramate (submitted 12//29/94), and was proposed by the sponsor as support for a monotherapy claim. At the time of the Agency's decision to approve topiramate as adjunctive therapy, the decision was made that Study Y1 did not support the granting of a monotherapy claim because very few patients actually achieved monotherapy (54% in the high dose group), the maximum duration of monotherapy was brief (74 days), and, due to the nature of the study, a large number of patients in the high dose group had detectable plasma levels of their previous AEDs during the period in which they were ostensibly being treated with topiramate monotherapy. In addition, the Agency's Approvable letter (12/29/95) noted that there were inadequate data to support the safety of a daily dose of 1000 mg.

Study 104

This study was similar in design to Study 106.

In this trial, a total of 252 patients with the recent onset of partial seizures were randomized to receive either topiramate 500 or 200 mg/day (depending on their weight) or topiramate 50 or 25 mg/day. The primary outcome was the time to second seizure. The p-value for this contrast was p=0.78. The sponsor also analyzed a secondary outcome in this study, the time to first (on treatment) seizure. The median time to first seizure in the high dose group was 317 days, compared to 108 days in the low dose group (p=0.062) (Kaplan-Meier plots for the primary and secondary outcomes are reproduced in Dr. Feeney's memo, page 4).

The sponsor had tried to obtain a monotherapy claim based on this trial; this effort was discussed at a meeting with the sponsor on 8/31/98. At that time, the division informed the sponsor that, although we would not refuse to file an application for monotherapy based on this study, such an application would likely be the subject of a Not Approvable letter, based on the complete absence of any effect seen on the primary outcome measure. The division informed the sponsor that an independent study would need to be conducted and submitted in order for the monotherapy claim to be granted. The sponsor did not submit a supplement based on this study.

Study 105

This was an active controlled trial in which patients were randomized to receive either topiramate 100 mg/day, topiramate 200 mg/day, or "standard" therapy (either carbamazepine 600 mg/day or valproate 1250 mg/day). Over 600 patients were randomized; the primary outcome measure appears to be time to exit, variously defined. According to Dr. Chazin, there appears to have been no difference between treatments on this primary measure.

Study 106

This was a randomized, double blind, parallel group study in which patients with the new onset of partial or primary generalized seizures were randomized to receive either topiramate 400 mg/day or topiramate 50 mg/day. Patients were required to have had 1 or 2 seizures during a 3 month retrospective baseline. All patients were treated open label with topiramate 25 mg for one week, during any AED was to be withdrawn. The primary outcome measure was time to first (on treatment) seizure. The study was to proceed until the last enrolled patient had been enrolled for 2 months.

The original sample size was calculated on the basis of the occurrence of 108 seizure events. However, blinded interim analyses (on several occasions) revealed that too few events had occurred. Therefore, the protocol was amended twice, first to increase the duration of treatment for the last enrolled patient to 4, and then, finally, to 6 months. In this trial, patients randomized to the high dose group were to be treated at the beginning of the trial with the following doses each week (except, of course, for the final dose of 400 mg/day): 50 mg/day, 100 mg/day, 150 mg/day, 200 mg/day, 300 mg/day, and 400 mg/day).

Results

A total of 440 patients, ages 6 and older, were randomized. The following chart displays patient flow in this study:

	TPM 50	TPM 400
Randomized	234	236
Completed DB	105	112
Met Exit Criterion	90	49
Withdrew	39	75
ADR	13	40
Subject choice	9	13
Lost to F/U	9	10
Other	8	12

When the trial was analyzed by the protocol specified analysis (log rank test), the p-value for the between-treatment contrast for the time to first seizure was p=0.0002. Because of the (relatively) large number of patients who discontinued the study before completion or reaching the exit criterion, as well as the disparity

between treatment groups in the number of patients who discontinued secondary to adverse events, the division was concerned that a bias could have been introduced into the trial. As a result, we asked the sponsor to address these concerns.

The sponsor addressed these concerns by performing a number of simulations, in which they evaluated the effect on the results depending upon various assumptions about the seizure rate in patients who discontinued the study. In these simulations, they considered all low dose early discontinuations as having completed the trial successfully.

In the first case, they imputed (for the high dose patients who discontinued early) the time to first seizure for the low dose patients who experienced an adverse event who stayed in the study. In the second case, they imputed for the high dose early discontinuations the time to first seizure for the high dose patients who experienced adverse events, but did not discontinue early. Of 1000 simulations, all generated p-values <0.05.

The sponsor also performed additional simulations.

They assigned various rates of seizures by Day 500 of the study to all 114 subjects who discontinued the study early (in this analysis, the same rate was given to the high dose and low dose cohorts who discontinued). In this analysis, only when the assigned rate was greater than 50% for both groups did the analyses no longer generate a p-value of <0.05. Further, when a similar analysis was performed, except that the assigned seizure rates were given to only those 53 patients who discontinued due to adverse events, the analyses were significant until a seizure rate of 95% was assigned.

An additional, similar, analysis, in which various seizure rates were assigned only to those high dose patients who discontinued due to an adverse event revealed a loss of statistical significance only when the assigned rate was 80% or greater.

Further, the sponsor performed an analysis of time to first seizure in the intent to treat high dose group (N=236) compared to those high dose patients who experienced an adverse event, but did not discontinue secondary to that adverse event (N=161); the Kaplan-Meier curves for these two groups are virtually superimposable (see Dr. Chazin's Figure 1, page 47).

Finally, the sponsor points out that the characteristics of the patients who discontinued secondary to adverse events (including the type and nature of the ADRs) were not importantly different from the population that did not discontinue early.

Dr. He also performed additional analyses to address the potential bias that could have been introduced by the early discontinuations.

First, he imputed a seizure at the time of discontinuation in patients who discontinued due to adverse events; this yielded a p-value of 0.25.

The p-value for the contrast performed in which all early discontinuations are considered to have failed at the time of departure was 0.57.

If only those patients who were lost to follow-up were considered to have had a seizure at the time they left the study, the p-value for the between treatment contrast was 0.0006 (99 "failed" in the low dose group, 59 "failed" in the high dose group).

At the request of the clinical team, Dr. He performed an additional simulation.

Given that in both Studies 104 and 106, the difference between the time to first seizure rate in the low and high dose groups was about 20%, Dr. He simulated an analysis in which the rate of time to first seizure was 50% in the high dose group and 70% in the placebo group (these were the approximate rates seen in Study 104); the p-value for this contrast was 0.005.

Analyses of the results (of the intent to treat population) at Months 2, 4, and 6 yielded highly significant results in favor of high dose topiramate (see Dr. He's table 3.1.7.3, page 21).

Finally, an analysis at Weeks 2, 3, 4, 5, and 6 in which all censored patients were considered as having had a seizure at the time of discontinuation yielded no significant differences in favor of high dose topiramate at any of the time points (see Dr. He's Table 3.1.7.2.2, page 21).

COMMENTS

The sponsor has submitted four clinical trials in support of a claim for the use of topiramate as monotherapy in patients with partial and primary generalized seizures. As has been noted earlier, two of the studies had been either previously submitted or discussed with the division: Study Y1 has already been considered and found to be inadequate, and Study 104 has been discussed and found to be inadequate because the results of the analysis of the primary outcome (time to second on-study seizure) were clearly not significant. Study 105 was an active controlled trial that failed to distinguish between two doses of topiramate and carbamazepine and valproate. As such, this trial is uninterpretable.

Finally, the sponsor has submitted the results of Study 106, an adequately designed trial that, by protocol, yields a clearly significant between-treatment difference in the time to the first on-treatment seizure (p=0.0002). However, as pointed out by the clinical team as well as the statistical reviewer, a high number

of early discontinuations, and a differential number of discontinuations due to adverse events (17% in the high dose group, 6% in the low dose group) raises questions about the interpretation of the primary result.

Specifically, these discontinuations raise two related questions.

First, early discontinuations, especially in a setting in which there is a differential discontinuation rate due to a specific cause (as is the case in Study 106), have the potential to introduce a bias, because of the possibility that the patients who left the trial early would have had a differential response to treatment than those who remained in the trial (that is, the data are missing in a non-random way; in this case, the censoring is said to be "informative"). In these cases, attempts are often made to salvage such a study by assigning various event rates to the group that discontinued. In addition, data are examined in an attempt to "determine" if there are any characteristics of the patients who left early that would suggest that they would respond similarly, or differently, than the patients who remained in the trial.

Second, it is difficult to know how to decide what seizure rate should be appropriately assigned to the various discontinuation cohorts in various simulations, and how to interpret these results. These questions seem to be independent of whether or not the data are missing at random.

The differential rate of discontinuation in patients in the high and low dose groups due to adverse events has raised the most questions about the study. However, it should be noted that even if there were similar numbers of patients who discontinued from a trial in both treatment groups, and even if the number of patients who discontinued for any given reason was the same, it would still be possible for the data to be missing in a non-random way.

In any event, the sponsor, and Dr. He, have performed numerous analyses in an attempt to evaluate the robustness of the data.

Dr. He has performed a number of analyses in which he has assigned seizures at the time of study departure to various of the cohorts who discontinued early. In my view, analyses that assign a seizure at the time of study discontinuation to all patients, or to those who discontinued due to an adverse event, are inappropriate, because we know in these cases that patients did not have a seizure at the time of discontinuation. As far as we know, the only patients for whom we do not have seizure information at the time they discontinued treatment were those who were lost to follow-up; the analysis Dr. He performed in which these patients were considered to have had a seizure at study discontinuation yielded a p-value of 0.0006 in favor of high dose topiramate.

The sponsor also performed numerous analyses in which they utilized data from the study itself, and in which they used assigned seizure data. The former

analyses all yielded significant p-values. The latter yielded significant p-values when the assigned rates were below 50-95%, depending upon the specific analysis. When a differential rate was assigned (50% for high dose, 70% for low dose) the p-value for the contrast was 0.005.

Dr. Feeney makes two observations that to him suggest that the analysis of the intent-to-treat population is unreliable.

First, he notes that the ratio of dropouts to first seizure in the treatment arms for Studies 104 and 106 suggest that the outcome in the high dose group in Study 106 is anomalous. Specifically, he notes that these ratios are as follows:

Study 104		Study 106	
LD	HD	LD	HD
0.34	0.58	0.43	1.5

These ratios obviously are directly related to the number of dropouts and inversely related to the treatment response. It is obvious that the high ratio seen in the high dose group of Study 106 is a direct consequence of the fact that there was a higher dropout rate in this group than in any of the other three groups (32%), but also to the lower time to first seizure rate in this group than in any other group (21%). Indeed, the discontinuation rate in the high dose group in Study 106 is very similar to that in the high dose group in Study 104 (32% and 27%, respectively; however, the seizure rate in the former is less than half that in the latter-21% and 46%, respectively). In sum, then, this ratio is simply another way of presenting the trial data and does not, in my view, offer a fundamentally new insight into the interpretation of the trial.

Dr. Feeney also notes that the background rate of seizures in Study 104 is 71% by Day 500. Using this rate, he points out that the p-value that corresponds to a rate of 70% for the dropout cohort in the sponsor's simulation (in which all discontinuations are given a fixed seizure rate) is 0.09, and that this suggests a non-significant comparison.

While it is always treacherous to utilize data from other studies to help interpret the analyses of a separate study, I understand that the use of these sort of data may seem reasonable in this case, given that we are trying to adjust for missing data in Study 106, and it is natural to examine the data from a similarly designed study to do so (although an inspection of the data suggests that the estimates of various measures are quite different between the two studies). However, as Dr. Feeney notes, it is the background (low dose) rate that is 71% in Study 104. Utilizing this rate for the high dose group in Study 106 surely represents a worst-case analysis of some sort. If we utilized the high dose rate from Study 104 (under the assumption that the response to the high dose in Study 106 is more

likely to be similar to the response to the high dose in Study 104-46%), the between-treatment comparison in Study 106 becomes significant.

Regarding the issue of whether or not the censoring of the data in this study was informative, it appears to me (and to Dr. Feeney), that the sponsor has undertaken reasonable efforts to evaluate whether or not the patients who discontinued the trial early (and especially those who left early secondary to an adverse event, although, as I noted earlier, consideration should not be limited to these patients) can be considered to not be fundamentally different (vis-à-vis their intrinsic seizure propensity) than those who did not discontinue early within each treatment group. However, I have discussed this issue with Drs. Jin and He; they believe that there are additional statistical methods that should be attempted to more definitively address this question.

As noted, we are still left with the question what seizure rates it would be reasonable to assign to the missing patients. As calculated by the sponsor, when identical seizure rates of greater than 50% are assigned to each of the discontinuation cohorts (high and low dose), the p-values for the between-treatment contrasts are non significant.

Is it reasonable to assign such rates?

In my view, the question can be considered in two parts. First, is it reasonable to assign similar rates to both treatment groups? Second, is it reasonable to assume the rates would be greater than 50%?

Of course, the assignment of any seizure rates to these early discontinuation cohorts is problematic. We cannot know what the rate would have been in these patients, and it seems, on the surface, that assignment of a lower rate to the high dose group presupposes that the drug is effective, which, of course, is what the study is designed to prove. On the other hand, the previously generated data (from this study as well as in Study 104, a study of similar design) suggest that it is not unreasonable to assign a differential rate to the treatment groups. Exactly what these differential rates should be is difficult to say; the one simulation performed by Dr. He using a differential rate yielded a p-value strongly in favor of high dose (p=0.005). In my view, given the previously generated data, it seems reasonable to at least consider the assignment of differential rates, although exactly what rates should be explored is not clear. That is, not only are the magnitude of the difference in rates to be assigned not clear, but the absolute rates to be explored are also unclear. That is, I believe it is reasonable to assign differential rates to the treatment groups (although I am not sure what these differences should be), but what range of absolute rates should be explored is also unknown. Would we expect rates (either for the high or low dose groups) of up to 70% or greater by Day 500? This may certainly be reasonable, as this was the realized probability of having a first seizure in the low dose group in Study 104, and the high dose probability was 50%. Further, as Dr. Chazin notes, these

patients could have had up to three seizures prior to randomization in a relatively short period of time, and previous data suggest that such patients have a 40-80% risk of experiencing another seizure within one year. We have seen that assigning equal rates for high and low dose groups greater than 50% (well within the rates reported in the literature for similar cohorts) yield non-significant between-group contrasts.

Beside the question of which rates are appropriate to assign to the discontinuation cohorts, there is another critical issue to consider.

Specifically, the finding that is most disturbing, in my view, is the observation that, in Study 104, the time to second seizure (which was the primary outcome in that study) was almost identical in the high and low dose groups, while there seemed to be a clear separation in the time to first seizure in this study. This observation, of course, raises the possibility that, had time to second seizure been assessed in Study 106 (it was not), it too would have yielded a non-significant comparison. This is important because, as Dr. Feeney notes, delaying the time to first seizure (the primary outcome in Study 106), may not be particularly clinically relevant if there is no effect on the time to the second (and presumably, further) seizures. It is further disturbing because it is entirely unexpected, and demonstrates that unexpected findings can, and sometimes do, occur. This has potential ramifications related to the previously discussed issue, because it suggests that either the rates for time to first seizure in the early discontinuations might be considerably different from what we might predict, and/or that similar seizure rates in the discontinuation cohorts for both groups actually might have obtained.

As I discussed earlier, the sponsor has previously presented the results of Study 104 to the Agency (although they did not submit it in a supplement). This study was discussed in a sponsor submission dated 7/20/98, and discussed in a meeting with the Division on 8/31/98. I have examined that document and the draft minutes of that meeting. While the sponsor argued in their briefing document that the protocol specified analysis for that study (log rank test of time to second seizure) was not appropriate (an argument that we did not find persuasive), they seem not to have provided any explanation for this extremely unexpected finding. I can think of no readily apparent reason why the treatment might delay the time to the next (first on-study) seizure (assuming this finding is "real"), but then show no difference between treatments in the time to the second seizure (this latter finding implies that the high dose patients actually "worsened" compared to the low dose patients after the first on-study seizure). However, the absence of an obvious explanation in no way dismisses the finding, in my view (indeed, the most obvious explanation for this array of findings is that the drug is ineffective [as judged by the result on the primary outcome], and the finding on the time to first seizure is entirely spurious, the [almost] nominally positive result arising entirely by chance).

However, I am not yet ready to conclude that the finding on time to first seizure in Study 104 is entirely spurious, given, at the least, a very similar finding in Study 106 (of course, the interpretation of both studies is complicated by the very issue I have been discussing, that is, a significant number of early discontinuations). On the other hand, I do believe that the finding on the primary outcome in Study 104 raises significant questions about the clinical meaning of the results of Study 106 (assuming these latter results can be considered reliable).

I also believe that I cannot yet conclude that the results in Study 106 are, in fact, reliable.

As discussed, two problems plague the interpretation of Study 106: whether the censoring was informative, and thereby introduced an unknown bias, and whether the seizure rates included in the sponsor's analyses are appropriate, and further, how best to determine this. Regarding the former problem, while the sponsor's initial attempts to address this problem are encouraging, they have not made a complete attempt to address this question, and we will ask them to do so.

The sponsor has performed simulations that attempt to get at the latter problem, as discussed earlier. As we have seen, they have assigned various fixed rates of seizures (from 1%-99%, in increments of 5%) to the discontinuation cohorts of both treatment groups, and have determined at which point these contrasts become non-significant (in this case, this occurs at rates of 55% or greater). The difficulty in interpreting this finding is that it is difficult to know how reasonable these rates are, and how reasonable it is to assign similar rates to the two treatment cohorts.

It should be noted at this point that all the simulations that the sponsor has performed (or could perform) rely on numerous assumptions (whether they are based on data in the trial itself or on "assigned" data) that are untestable. As such, relying (even in part) on the result of simulations involves a decision about whether or not the assumptions underlying any given analysis can be considered "reasonable". Ultimately, of course, this will be a personal and subjective decision; there is no way to objectively decide that a particular assumption is reasonable, let alone objectively valid.

For example, the sponsor has performed the "assigned" seizure rate simulations by assigning the same seizure rates to the discontinuation cohorts of both treatment groups. This seems appropriate and fair (under the null hypothesis, there is no difference between the treatments), but it must be recalled that, as a simulation, it is still an analysis that goes beyond the data, and is, in some sense, as arbitrary a maneuver as the assignment of different seizure rates to the treatment groups (that is, there are no formal statistical rules that must be applied that justify one particular simulation more than another). Indeed, we have already seen that the assignment of a 50% seizure rate to the high dose group

and a 70% seizure rate to the low dose group results in a between-treatment p-value of 0.005.

Because we cannot know, a priori, which assigned seizure rates are most appropriate, I believe that it would be valuable for the sponsor to perform additional simulations in which differential seizure rates are assigned to the treatment groups; as noted above, we have already performed one such analysis. In these additional analyses, the sponsor should explore a wide range of differences, including differences in favor of low dose over high dose, over a wide range of absolute seizure rates. By examining this larger range of rates and differences, we can perhaps begin to obtain a wider (and hopefully clearer) picture of how dependent the results are on these measures; while acknowledging that this approach cannot be considered to represent "truth" (any more than any of the other simulations), it should help better define the range of possible (and reasonable) outcomes, and help inform our decision about the effect of discontinuations on the interpretation of this trial.

Further, as Dr. Feeney notes, the sponsor has performed only one simulation run for each seizure rate stratum in the analyses discussed above. According to the statisticians, this is inadequate, and the sponsor should be asked to perform multiple such runs. When they do this, they must also offer an acceptable method for expressing, and interpreting, the resultant range of p-values generated.

Finally, the sponsor must address the disturbing, and unexpected, finding on time to second seizure seen in Study 104. As discussed earlier, this finding raises serious questions about the clinical meaning of the results seen on time to first seizure in Study 106. The sponsor has never offered an explanation for this finding, and why it should not cast doubt on the utility of time to first seizure as a valid measure of effectiveness of topiramate as monotherapy.

Because the issues to be addressed are fundamental to a decision to grant the proposed indication, and because they have not yet been satisfactorily resolved, we cannot approve the application at this time. Despite the fact that the issues have not been resolved, the considerable work that the sponsor has conducted and presented provides encouraging results, and for this reason I believe it is appropriate to issue an Approvable letter. However, given the scope of the unresolved questions, it seems premature at this time to draft labeling; accordingly, we will not include draft labeling with the Approvable letter.

Russell Katz, M.D.

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/s/

Russell Katz
11/26/03 04:47:33 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

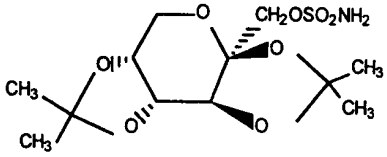
CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW OF SUPPLEMENT

ORGANIZATION:	**HFD-120**
NDA NUMBER:	**20-505 and 20-844**
SUPPLEMENT NUMBER:	**N20-505/SE1-018** **N20-844/SE1-015**
LETTER DATE	29-OCT-02
STAMP DATE	01-NOV-02
AMENDMENTS/REPORTS:	
LETTER DATE	N/A
STAMP DATE	N/A
RECEIVED BY CHEMIST:	08-JAN-03

APPLICANT NAME AND ADDRESS: Ortho-McNeil Pharmaceutical, Inc.
1000 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

NAME OF DRUG: **TOPAMAX®**
NONPROPRIETARY NAME: topiramate
CHEMICAL NAME / STRUCTURE: 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate
[97240-79-4]



DOSAGE FORM(S): Tablets (N20-505) and
Sprinkle Capsules (N20-844)

POTENCY(IES): 25, 50,100, 200, (b) (4) mg tablets;
15, 25 (b) (4) mg capsules

PHARMACOLOGICAL CATEGORY: Treatment of epilepsy
HOW DISPENSED: **XX (Rx) (OTC)**
RECORDS / REPORTS CURRENT: **XX (YES) (NO)**

RELATED IND / NDA / DMF(S): IND 49,640, NDA 20-505, (b) (4) (b) (4) IND 28,549

SUPPLEMENT PROVIDES FOR: A new indication for the use of topiramate as monotherapy in adults and children 6 years of age and older with newly diagnosed epilepsy.

COMMENTS: The submissions N20-505/SE1-018 and N20-844/SE1-015 are filed as efficacy supplements. In the supplement N20-505/SE1-018 the sponsor provides the environmental assessment and updated and annotated draft of the package insert for Topamax tablets and sprinkle capsules. The applicant is cross-referencing approved NDA 20-505 for the drug substance and drug product sections to the monotherapy supplemental NDA. The drug intended to be marketed for the use of a topiramate, as a monotherapy agent for epilepsy is identical to the approved TOPAMAX® (topiramate) tablets used for the treatment of epilepsy as adjunctive therapy. The exception is that the tablets without marking were used for blinded studies. In the supplement N20-844/SE1-015, the applicant is referencing approved NDA 20-844 for TOPAMAX® (topiramate capsules) Sprinkle Capsules, and is cross-referencing to N20-505/SE1-018 regarding clinical data, environmental assessment data and labeling. The environmental assessment was evaluated by Florian Zielinski, Quality Implementation Staff, with the conclusion "Finding of no significant impact" for both submissions, N20-505/SE1-018 and N20-844/SE1-015. The change in the Dosage and Administration section of the package insert reflects the change in the indication of the drug to the monotherapy use.

CONCLUSIONS AND RECOMMENDATIONS: From the CMC standpoint, the supplements N20-505/SE1-018 and N20-844/SE1-015 are recommended for approval.

Lyudmila N. Soldatova, Ph.D., Review Chemist

cc: Orig. NDA 20-505/20-844
HFD-120/JWare
HFD-120/LSoldatova
HFD-120/MGuzewska/Init.by: MG/, Filename: N20505-S018&N20844-S015.doc, Review Completed: 26-AUG-2003

Review Notes CMC

ENVIRONMENTAL ASSESSMENT

An Environmental Assessment has been submitted under 21 CFR 25.20(1) for N20-505/SE1-018 (V.1, item 4). The supplement N20-844/SE1-015 is cross-referencing to N20-505/SE1-018. The applicant states that the maximum expected environmental concentration (MEEC) provided in the submissions is based on the total projected fifth-year demand for the drug substance, and it is greater than 1 part per billion. The EA consult was requested, and the conclusion was made that topiramate "can be used and disposed without any expected adverse environmental effects".

EVALUATION: The conclusion "Finding of no significant impact" for both submissions, N20-505/SE1-018 and N20-844/SE1-015 is acceptable.

LABELING

The Description and How Supplied sections of the proposed draft of the package insert do not contain any changes.

Dosage and Administration Section

The proposed section contains several editorial changes to distinguish monotherapy from the previous indication, adjunctive therapy data.

The proposed section contains the following insert to reflect the change of the indication of the drug to the monotherapy use (p.30):

Monotherapy Use

The recommended (b) (4) dose for topiramate monotherapy in adults and

children 6 years of age and older is (b) (4)

400 mg/day (b) (4) in two divided doses. (b) (4)

(b) (4)

EVALUATION: Change in the package insert is acceptable from a CMC perspective.

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/s/

Lyudmila Soldatova
8/26/03 11:08:02 AM
CHEMIST

Maryla Guzewska
8/26/03 12:10:47 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

for

TOPAMAX TABLETS
(25, 50, 100, 200, (b) (4) mg topiramate)

NDA 20-505 / SE1-018
Mono-therapy for newly diagnosed epilepsy

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurological Drug Products
(HFD-120)

Date Completed: April 11, 2003

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-505 / SE1-018
TOPAMAX TABLETS
(25, 50, 100, 200, (b) (4) mg topiramate)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its supplemental new drug application for Topamax Tablets, Johnson & Johnson Pharmaceutical Research and Development, LLC, prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Topiramate is a (b) (4) drug that is currently approved for adjunctive treatment of adults and children (ages 2 to 16) with partial onset seizures or primary generalized tonic-clonic seizures. Topiramate is also indicated for treatment of patients (age 2 or older) with seizures associated with Lennox-Gaust Syndrome.

NDA 20-505 / SE1-018 requests approval of Topamax Tablets (25, 50, 100, 200, (b) (4) mg topiramate) for mono-therapy for newly diagnosed epilepsy.

Topiramate may enter the aquatic environment from patient use and disposal. Data indicate that topiramate will hydrolyze to monoacetonides and fructose. Fructose is known to be readily biodegradable. (See original EA and FONSI signed on Nov 26, 1995). The toxicity of topiramate to environmental organisms was characterized. The results indicate that topiramate is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

Empty or partially empty packages will be disposed by a community's solid waste management system that may include landfills, incineration and recycling. Minimal quantities of the unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

1. NON-CONFIDENTIAL ENVIRONMENTAL ASSESSMENT

1.1. DATE

30 July 2002

1.2. NAME OF APPLICANT

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

1.3.

(b) (6)

as adjunctive therapy for adults and pediatric patients ages 2–16 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome. Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) is filing an sNDA for the use of TOPAMAX® as monotherapy in patients with newly diagnosed epilepsy. In support of this application, an environmental assessment (EA) is required per 21 CFR, Part 25.20 (l).

The maximum expected environmental concentration (MEEC) provided in Section 1.6 of this sNDA is based on the total projected fifth-year demand for the drug substance. Since both the drug substance and the drug product formulations remain unchanged, a cross-reference is provided in lieu of the information typically found in Section 1.5 of the environmental assessment. Because the MEEC is now APPEARS THIS WAY IN ORIGINAL per billion (ppb), Section 1.6 includes a discussion of environmental fate and effects information for topiramate.

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules will be used primarily by patients in their homes and in hospitals and clinics, through physician prescription. Disposal of prescribed product will be through use, with returned product disposed through high temperature incineration at licensed disposal facilities. US hospitals, pharmacies,

or clinics will dispose of empty or partially empty packages according to their internal handling procedures. In the home, disposal will be through community solid waste management systems, which may include landfills, incineration, and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

1.5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

Please refer to NDA 20-505 for TOPAMAX® (topiramate) Tablets, submitted 29 December 1994, Volumes 2.3 and 2.4 (Pages 03 00001 through 03 00706) for detailed information on topiramate drug substance. Please also refer to amendments to NDA 20-505, dated 5 October 1995, 8 November 1995, and 20 November 1995.

1.6. ENVIRONMENTAL ISSUES

The manufacture and use of TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are not expected to result in significant environmental releases of the active ingredient or excipients, and no potential adverse environmental effects resulting from the manufacture and use of TOPAMAX® have been identified.

To meet patient demand, including that arising from this additional indication, the total fifth-year production estimate for both tablets and sprinkle capsules formulations will require APPEARS THIS WAY IN ORIGINAL kg of topiramate drug substance. This will result in a maximum expected environmental concentration (expected introduction concentration, or EIC-Aquatic, based on use) of APPEARS THIS WAY IN ORIGINAL per billion or APPEARS THIS WAY IN ORIGINAL $\times 10^{-3}$ mg/L.

The environmental assessment found in NDA 20-505 Volume 11 of 411 and Volume 12 of 411, submitted 29 December 1994, are the most recent documents addressing fate and effects information for topiramate. Three environmental effect studies have been conducted with topiramate.

A. Microbial growth inhibition (NDA 20-505, Volume 12 of 411, Appendix D, pages 03-03254 to 03-03299)

B. Daphnids (*Daphnia magna*) acute toxicity (NDA 20-505, Volume 12 of 411, Appendix E, pages 03-03301 to 03-03357)

C. Bluegill Sunfish (*Lepomis macrochirus*) acute toxicity (NDA 20-505, Volume 12 of 411, Appendix F, pages 03-03359 to 03-03424)

The results are summarized in detail in NDA 20-505, Volume 11 of 411, pages 03-03048 to 03-03054. Topiramate did not inhibit microbial activity at a concentration of 10 mg/L or less. It is reported that the 48-hour EC_{50} or median effect concentration value for Daphnids *(Daphnia magna)* is greater than 1,000 mg topiramate/L. The no observed effect concentration (NOEC) for *Daphia magna* was determined to be 1000 mg/L. Two tests were conducted for acute toxicity of topiramate to bluegill sunfish (*Lepomis macrochirus*). During the first test, mortality was observed; however, the results were not sufficient to calculate an LC_{50}. During the second test, no mortality was observed. Effects were observed in the concentration range of 84-3,000 mg/L. These effects included darkened pigmentation and loss of equilibrium. Since no concentration produced ≥50% mortality, the 96-hour LC_{50} value was empirically estimated to be greater than 2400 mg/L, the highest mean measured concentration tested. The NOEC was determined to be less than 75 mg/L, the lowest mean measured concentration tested.

These results are summarized in Table 1.

Table 1: Toxicity Testing of Topiramate with Representative Environmental Organisms

Test Organism	Conditions	Results	Report Number/ Location in Original NDA
Microbial inocula	Microbial growth inhibition	MIC ≥10 mg/L	ABC-40699 Volume 2.12, Pages 03 03254-03 03299
Daphnids *(Daphnia magna)*	Acute toxicity	NOEC = 1000 mg/L EC_{50} >1000 mg (48 h)	SLI 92-10-4484 Volume 2.12, Pages 03 03301-03 03357
Bluegill Sunfish *(Lepomis macrochirus)*	Acute toxicity	NOEC <75 mg/L[a] LC_{50} >2400 mg/L (96 h)	SLI-92-12-4543 Volume 2.12, Pages 03 03359-03 03424

MIC = the minimum inhibitory concentration for growth of the test organism.
NOEC = no observed effect concentration
EC_{50} = median effective concentration
LC_{50} = median lethal concentration

[a] Based on several of the surviving fish that exhibited darkened pigmentation, mean measured concentrations tested, corresponding cumulative percent mortalities, and observations made at the 24-, 48-, 72- and 96-hour intervals during the 96-hour static renewal exposure of bluegill sunfish (*Lepomis macrochirus*) to topiramate, NDA 20-505, Volume 12 of 411, Appendix F, Table 4b, page 03-03386

In accordance with the *Tiered approach to environmental effects testing,*{1} no further testing is required. The ecotoxicity tests performed (summarized in

Table 1) indicate that the LC_{50} or EC_{50} divided by the MEEC is greater than or equal to 1000.

As the MEEC resulting from this action will be well below the MIC and the NOEC for these organisms, the original conclusion, that no environmental impact is expected, is still valid.

The above safety margins also are increased by the fact that environmental fate data suggest topiramate will not persist in the environment. While topiramate did not undergo primary biodegradation in 28-day screening tests, it was found to have a hydrolytic half-life of approximately 80 days at pH 8.0. Hydrolysis products are monoacetonides and fructose, the latter known to be readily biodegradable.

1.7. MITIGATION MEASURES (NOT REQUIRED)

Section 1.7 is not required when there have been no adverse environmental effects identified.

1.8. ALTERNATIVES TO THE PROPOSED ACTION (NOT REQUIRED)

Section 1.8 is not required when there have been no adverse environmental effects identified.

1.9. PRODUCTION ESTIMATES

Please refer to APPENDIX 1 for information related to production estimates. Confidential information has been omitted from APPENDIX 1.

1.10. PREPARER

Edward Nowak, QEP, CHMM
Senior Environmental Engineer
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1000 U.S. Route 202 South
Raritan, NJ 08869-0602

Twenty-three years of environmental experience; 15 years with the telecommunications research and development industry, 8 years with the United States Environmental Protection Agency.

Bachelor of Science in Civil Engineering, New Jersey Institute of Technology

Master of Science in Environmental Engineering, New Jersey Institute of Technology

1.11. CERTIFICATION

I certify that the information presented is true, accurate, and complete to the best of the knowledge of the firm responsible for the preparation of the Environmental Assessment.

Edward Nowak July 30, 2002

Edward Nowak Date
Senior Environmental Engineer

1.12. REFERENCES

1. Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications. US Department of Health and Human Services, July 1998; 20-21.

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/s/

Florian Zielinski
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Nancy Sager
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Yuan-Yuan Chiu
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REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

TOPAMAX® TABLETS
(25, 50, 100, 200, (b) (4) mg topiramate)

NDA 20-505 / S-018
Mono-therapy for newly diagnosed epilepsy

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neurological Drug Products
(HFD-120)

April 11, 2003

Environmental Assessment Review， NDA 20-505 / S-018
TOPAMAX (topiramate) TABLETS
Mono-therapy for newly diagnosed epilepsy

EXECUTIVE SUMMARY

A FONSI is recommended

The environmental assessment (EA) dated July 30, 2002 supports the supplemental new drug application for a new indication, mono-therapy for newly diagnosed epilepsy. The EA was prepared in accordance with 21 CFR Part 25 by Johnson & Johnson Pharmaceutical Research and Development, LLC. The EA contains reference to previously submitted environmental fate and effects data resulting from the use and disposal of Topamax (topiramate) Tablets.

Topiramate is not volatile. It is a weak acid (pKa = 8.61 at 25°C) that is soluble in water (9.8 mg/mL at 25°C). It may enter the aquatic environment from patient use and disposal. The hydrolysis of topiramate half-life is approximately 80 days at pH 8 and 35°C; the hydrolysis products are monoacetonides and fructose. Fructose is known to be readily biodegradable. (Reference: EA and FONSI signed Nov 26, 1995) The log K_{OW} of topiramate is 0.57 at 25°C. Based on the 28-day primary biodegradation screening test, rapid degradation by aerobic and anaerobic microbes is not expected.

Assuming that no metabolism occurs, the EIC of topiramate is (b) (4) ppb.

The toxicity of topiramate to environmental organisms was characterized. The results indicate that topiramate is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

Test	Result
Microbial Growth Inhibition (activated sludge)	No inhibition at 10 mg/L or less (18% inhibition at 100 mg/L)
Bluegill Sunfish, TDA 4.11 (acute toxicity)	NOEC < 75 mg/L (96 hour) LC_{50} > 2,400 mg/L (96 hour)
Daphnia magna, TDA 4.08 (acute toxicity)	NOEC = 1000 mg/L (48 hours) EC_{50} > 1000 mg/L

REVIEW OF EA SUBMITTED IN NDA 20-505 / S-018
Mono-therapy for newly diagnosed epilepsy

I. DATE: July 30, 2002

II APPLICANT: Johnson & Johnson Pharmaceutical Research and Development, LLC

III ADDRESS: 920 US Route 202 South,
PO Box 300
Raritan, New Jersey 08869

IV DESCRIPTION OF PROPOSED ACTION:

a. Requested Approval: Johnson & Johnson Pharmaceutical Research and Development, LLC filed an NDA supplement pursuant to section 505 (b) of the FDA Act for Topamax (25, 50, 100, 200, (b) (4) mg topiramate) Tablets packaged in HDPE bottles. The EA, submitted pursuant to 21CFR part 25, refers to submissions dated 12/29/94, 10/5/95, 11/8/95 & 11/20/95.
b. Need for Action: Supplemental application (NDA 20-505 / S-018) requests approval of Topamax (topiramate) Tablets for mono-therapy for newly diagnosed epilepsy. Topamax Tablets are currently approved for adjunctive treatment of adults and children (ages 2 to 16) with partial onset seizures or primary generalized tonic-clonic seizures. Topamax Tablets also indicated for treatment of patients (age 2 or older) with seizures associated with Lennox-Gaust Syndrome.
c. Locations of Use: Hospitals, clinics and patient homes.
d. Disposal Sites: Empty or partially empty containers from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy or clinic procedures. Empty or partially empty containers from home use typically will be disposed by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed in the sewer system. Returned product will be incinerated at licensed disposal facilities.

ADEQUATE

V IDENTIFICATION OF CHEMICALS

USAN Name: topiramate Brand Name: Topamax Tablets

CAS Name: 2,3:4,5-Bis-O-(1-methylethylidene)-β-D-fructosepyranose sulfamate
CAS Number: 97240-79-4 Molecular Wt of $C_{12}H_{21}NO_8S$ is 339.36

The molecular structure of topiramate was reported in the EA dated Feb1994, page 03-02925 and appears in the FONSI dated Nov 19, 1995.

ADEQUATE

VI ENVIRONMENTAL ISSUES / Assessing Toxicity to Environmental Organisms

Information about environmental fate and effects is in the EA. Test reports were submitted in 1994. The applicant employed contractors ((b) (4)) to determine environmental fate and effects according to suitable scientific (for example, TAD 4.08 and 4.11) and GLP methodologies.

Environmental Fate:

Identification of Substances of Interest:
Topiramate may enter the aquatic environment from patient use and disposal.

Physical and Chemical Characterization of topiramate:
Topiramate is soluble in water (9.8 mg/mL).
Dissociation Constant, pK_a is 8.61 at 25°C
The log K_{OW} of topiramate is 0.57 at 25°C

Environmental Depletion Mechanisms:
Aerobic and Anaerobic Degradation: Rapid degradation of topiramate was not observed
Hydrolysis: Topiramate hydrolyzes to fructose and sulfates with an 80-day half-life at 35°C

Environmental Concentrations:
The total quantity of topiramate required for the new indication and all other products manufactured by J&J in any of the next 5 years is expected to be NMT (b) (4) (Reference: Current confidential EA dated July 30, 2002, pages 2 and 8).

Assuming that no metabolism occurs, the EIC of topiramate is (b) (4) ppb.

Summary of the Environmental Fate:
The drug substance is expected to enter the aquatic environment.

Environmental Effects:

Inhibition of Activated Sludge:
Not observed at 10 mg/L (or less); 18% inhibition at 100 mg/L

Daphnia Magna: TAD 4.08 acute testing
The 48-hour EC_{50} for daphnia magna is greater than 1000 mg/L
The 48-hour NOEC for daphnia magna is 1000 mg/L

These values are more than (b) (4) times greater than the EIC, namely (b) (4)

Bluegill Sunfish: TAD 4.11
The 96-hour LC_{50} for bluegill sunfish is greater than 2,400 mg/L
The 96-hour NOEC for bluegill sunfish is less than 75 mg/L, the lowest concentration tested.

The LC_{50} is more than (b) (4) times greater than the EIC, namely (b) (4) ppb.
The EIC, namely (b) (4) ppb, is lower than the NOEC.

Summary of Environmental Effects:

The toxicity of topiramate to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

Test	Result
Microbial Growth Inhibition (activated sludge)	No inhibition at 10 mg/L or less (18% inhibition at 100 mg/L)
Bluegill Sunfish, TDA 4.11 (acute toxicity)	NOEC < 75 mg/L (96 hour) LC_{50} > 2,400 mg/L (96 hour)
Daphnia magna, TDA 4.08 (acute toxicity)	NOEC = 1000 mg/L (48 hours) EC_{50} > 1000 mg/L

ADEQUATE

VII MITIGATION MEASURES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

VIII ALTERNATIVES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

IX PREPARER

Name, job title and qualifications were provided.

ADEQUATE

X CERTIFICATION

Certification is provided.

ADEQUATE

XI APPENDIX

Production estimate is provided in Confidential Appendix, Page 8

ADEQUATE

Review by: Florian Zielinski on April 11, 2003
Chemist, Center for Drug Evaluation and Research

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/s/

Florian Zielinski
4/11/03 04:32:52 PM
ENV ASSESSMENT

Nancy Sager
4/14/03 11:02:53 AM
ENV ASSESSMENT

Yuan-Yuan Chiu
4/18/03 03:35:39 PM
CHEMIST
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

PHARMACOLOGY REVIEW(S)

November 24, 2003

Review and Evaluation of Pharmacology and Toxicology
NDA Supplement

NDA: 20-505/S-018 & NDA 20-844/S-015

Sponsor: Johnson & Johnson Pharmaceutical
Raritan, NJ

Received: October 29, 2002

Drug: Topamax (topiramate)

Indication: Epilepsy

Evaluation and Recommendations:

These supplements provide data to support a new indication for the use of topiramate as monotherapy in adults and children 6 years of age and older with newly diagnosed epilepsy. As per agreement with the Division at the pre-NDA meeting (3/12/02), the sponsor cross-referenced all the relevant non-clinical studies contained in the tablet NDA (20-505) to the monotherapy supplement. Since the filing of the tablet NDA, several additional preclinical toxicology studies have been conducted and submitted as amendments to IND 28,549. The Division requested only that new reproduction and genetic toxicology studies be included in the monotherapy sNDA. These included an Ames test, two chromosomal aberration studies, an *in vivo* mouse micronucleus study, and a rat peri- and postnatal development study, all of which were conducted for foreign registration. These studies have been reviewed and the results found to be consistent with previous data for topiramate. They do not change the original safety assessment and provide no additional information for labeling. Therefore, the supplements are considered approvable from a pharmacology/toxicology perspective. However, in order to better label all topiramate products for use in children, more information on the potential for long-term, developmental effects in this age group is needed. To this end the sponsor should be asked to conduct a juvenile rat toxicology study during Phase 4. The following language is recommended:

We request that you agree to conduct a repeated-dose study in neonatal/juvenile rats to assess the effects of topiramate on growth and development. Since there are no standard protocols in this area, we suggest that you design a study that would address long-term effects in animals of an age range analogous to that of the pediatric patient population and submit the protocol to the Agency for review prior to study initiation.

_____
J.E. Fisher, Ph.D.

cc:
NDA (20-505/20-844)
Div File
HFD-120/LFreed/JWare/EFisher

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/s/

Edward Fisher
12/1/03 12:00:00 PM
PHARMACOLOGIST

Lois Freed
12/5/03 11:17:23 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

STATISTICAL REVIEW(S)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	20-505/S-018 and 20-844/S-015
Drug Name:	Topamax ® (topiramate)
Indication:	Seizures
Sponsor:	Johnson & Johnson
Date:	5/11/2005
Review Priority:	2 months
Biometrics Division:	Biometrics I (HFD 710)
Statistical Reviewer:	Kun He
Concurring Reviewers:	Kun Jin, , Ph.D.,Team Leader James Hung, Ph.D., Acting Deputy Director
Medical Division:	Neuropharmacological Drug Products (HFD 120)
Clinical Team:	Howard Chazin, M.D., Ph.D., Clinical Reviewer John Feeney, M.D., Team Leader Russell Katz, M.D., Director
Project Manager:	Jacqueline Ware, R. Ph.

Keywords: log-rank test, seizure, topamax

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Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

Since p-values produced without using the exponential distribution are in the range between the primary analysis (when 0% withdrawals are assumed to have seizures), and all-cause analysis (when 100% withdrawals are assumed to have seizures), the simulated results from the method without using the exponential distribution might be considered as the compromised results between the primary analysis and all-cause analysis. However, how to use the simulated results for decision making is not clear, and will depend on clinical judgment. The simulated results from method using the exponential distribution are difficult to interpret.

1.2 Brief Overview of Clinical Studies

The submission is responding to the Agency's approvable letter dated January 19, 2005. Per the Agency's requests, the applicant performed the multiple imputations without using the exponential distribution.

1.3 Statistical Issues and Findings

P-values from the method without using the exponential distribution are greater than those from the method using the exponential distribution. However, how to use the simulated results for decision making is not clear, and will depend on clinical judgment.

2. Introduction

2.1 Overview

The submission is responding to the Agency's approvable letter dated January 19, 2005. Per the Agency's requests, the applicant performed the multiple imputations without using the exponential distribution.

2.2 Data Sources

The paths to the CDER Electronic Document Room (EDR) are: \\Cdsesub1\n20505\S_018

3. Statistical Evaluation

3.1 Evaluation of Efficacy

The applicant, per the Agency's requests, performed the multiple imputations without using the exponential distribution.

3.1.1 Multiple Imputation without Using the Exponential Distribution

An approach not relying on the exponential distribution is taken here to contrast the all-cause analysis results with those of the multiple imputations method. Here it is assumed that X% of subjects had a seizure at Day 1 after withdrawal, and the remaining (100 - X)% of subjects were uninformatively censored at Day 1 after withdrawal. For each given X, 1,000 simulations were conducted. Table 3.1.1 provides the resulting p values.

Table 3.1.1 P-values without Using the Exponential Distribution

P-Values Assuming X% of Subjects had a Seizure at Day 1 After Withdrawal and the Remaining (100 - X)% of Subjects Were Uninformatively Censored at Day 1, Varying the Assumed Seizure Rates in the Low- and High-Dose Treatment Groups

		Percent of subjects with assumed seizure at Day 1 Topiramate 400 mg (high-dose group)									
		30%	40%	45%	50%	55%	60%	65%	70%	75%	80%
Percent of subjects with assumed seizure at Day 1 Topiramate 50 mg (low-dose group)	30%	0.0096	0.0514	0.0866	0.1591	0.2676	0.4127	0.5481	0.7475	0.9671	0.8185
	40%	0.0042	0.0263	0.0465	0.0922	0.1652	0.2737	0.3783	0.5516	0.7492	0.9616
	45%	0.0027	0.0184	0.0335	0.0690	0.1278	0.2190	0.3107	0.4641	0.6472	0.8546
	50%	0.0017	0.0126	0.0239	0.0504	0.0975	0.1725	0.2497	0.3863	0.5542	0.7499
	55%	0.0011	0.0086	0.0168	0.0365	0.0734	0.1336	0.1997	0.3152	0.4687	0.6506
	60%	0.0007	0.0059	0.0116	0.0263	0.0544	0.1032	0.1563	0.2566	0.3910	0.5561
	65%	0.0004	0.0039	0.0079	0.0187	0.0401	0.0782	0.1217	0.2053	0.3231	0.4725
	70%	0.0003	0.0026	0.0053	0.0131	0.0289	0.0582	0.0928	0.1624	0.2623	0.3956
	75%	0.0002	0.0017	0.0036	0.0091	0.0207	0.0431	0.0708	0.1270	0.2117	0.3278
	80%	0.0001	0.0011	0.0023	0.0062	0.0147	0.0317	0.0529	0.0983	0.1678	0.2683

Note: For each simulation, X% of subjects with a seizure was generated for N=39 in the low-dose group and N=75 in the high-dose group, comprising the N=114 withdrawn subjects. Thus, the main diagonal of the table above differs slightly from Table 2 of the 21April 2005 response which simulated results for N=114 subjects in total without specification to treatment group size.

When the seizure rate is 100%, the resultant p value (p=0.5140) is very close to the p value calculated from the all-cause analysis, p=0.5293. The small difference between the 2 p values is due to the fact that 1 day was added to the withdrawal date in the analysis in Table 3.1.1 (the p values are identical when using Day 0). In addition, the result for a seizure rate of 0% is equivalent to that of the intent-to-treat analysis result (p=0.0002).

The table demonstrates that the p values for a non-exponential method match those of the all-cause method. However, the table must be interpreted with the caveat that most seizure rates assumed at Day 1 in Table 3.1.1 are not reasonable assumptions. For example, most of these assumed seizure rates are not consistent with published data, are not consistent with follow-up data from subjects who discontinued the TOPMAT-EPMN-106 study, and are not seizure rates previously agreed to by the Agency as reasonable for imputation. Recall that partial data on post-withdrawal seizure times are available for 42 of the 114 withdrawn subjects (please refer to the data set named FOLLOWU6, located in Item 11 of the Sponsor's 27 May 2004 response to the 26 November 2003 monotherapy Approvable Letter N20505\crt\datasets\epmn-106\define.pdf). These data indicate that subjects who withdrew from the double-blind phase did not develop a seizure shortly after their withdrawal from the TOPMAT-EPMN-106 study. These findings suggest that the value of X at Day 1 should be very near zero. Moreover, the seizure rate in the sensitivity analyses, accepted as reasonable by the Agency, is in a range of 30% to 70% at Day 500 after subjects' withdrawal.

3.1.2 Multiple Imputations with Exponential Distribution

The methods used to perform multiple imputations on the data from Study 106 are described in detail in the previous submission and review. The results of this analysis are shown in Table 3.1.2 below.

Table 3.1.2 P values from 1,000 Simulated Runs
Using Combinations of Assumed Seizure Rates for Subjects who Withdrew from the Study
(Study TOPMAT-EPMN-106; Double-Blind Phase)

Seizure rate at Day 500	TPM 400						
TPM 50	30%	40%	50%	60%	70%	75%	80%
30%	.001**	.006**	.023**	.082*	.231		
40%	<.001***	.003**	.012**	.049**	.151	.238	
50%	<.001***	.001**	.006**	.025**	.094*	.165	.271
60%	<.001***	.001**	.003**	.013**	.051*	.092*	.168
70%	<.001***	<.001***	.001**	.006**	.026**	.054*	.100
75%		<.001***	.001**	.004**	.018**	.035**	.065*
80%			.	.002**	.013**	.025**	.052*

* $p < 0.1$
** $p < 0.05$
*** $p < 0.001$

The Agency asked the question in the Approvable Letter dated January 19, 2005, "However, as you know, the multiple imputations method uses a conditional exponential distribution and a chi-square test to produce p values. Given this, we note that when seizure rates approach 100%, p values from the multiple imputations method should approach those produced by the all-cause analysis, even though the patients' withdrawn times used are different in the two methods. However, we found that the p value produced by the multiple imputations method when the assumed seizure rate is approaching 100% is less than half of that calculated in the all-cause analysis. Based on this finding, we are concerned about the appropriateness of your approach and the p values it generated. Until we can understand this discrepancy and be confident that the p values you have presented are appropriate, we cannot definitively decide the question of effectiveness."

The applicant responded that the "all cause analysis" assumes all 114 subjects who withdrew from the double-blind phase of the TOPMAT-EPMN-106 Study had a seizure on the day they withdrew. The p-value of the log-rank test comparing the two Kaplan-Meier curves for this analysis is 0.5293. The applicant agrees with the Agency's statement that when seizure rates approach 100%, p-values from the multiple imputations method should approach those produced by the all-cause analysis, even though the patients' withdrawal times used are different in the two methods.

To address the Agency's observation that the p-value produced by the multiple imputations method when the assumed seizure rate is approaching 100% is less than half of that calculated in the all-cause analysis, the applicant believes that it is a computer precision issue and not a methodological issue.

The applicant ran the program using SAS version 8 allowing the assumed seizure rates at day 500 after withdrawal to approach 100%. The p-values from the multiple imputation method are listed in the following table.

Table 3.1.3 P-Values from Multiple Imputation Method When Assumed Seizure Rates are Approaching 100%, Where the Seizure Rates are at 500 Days After Withdrawal

At days after withdrawal	Assumed seizure rates	p-value from multiple imputation approach
500	99 %	0.2378
500	99.99 %	0.3486
500	99.9999 %	0.3876
500	99.999999 %	0.4107
500	99.99999999 %	0.4320
500	99.9999999999 %	0.4425

As the Agency indicated, when one uses a seizure rate, say a value between 99% and 99.99%, the p-value could be about half that of the p-value from the all cause analysis. Yet as seen in the above table, as the seizure rates approach 100%, the p-values approach that of the all cause analysis, 0.5293, leading the applicant to suspect that this is an issue in computer precision regarding the calculation.

The applicant further gave an example of how the seizure rate relates to the time to seizure using the formula and censoring rule. Assuming a subject who withdrew 100 days before study termination, an assumed 500-day seizure rate of 99% would correspond to a 60% chance of experiencing a seizure within the 100 remaining days, while an assumed 500-day seizure rate of 99.99% would correspond to a 100-day seizure rate of 84%. Now, consider a different subject who withdrew 500 days prior to the 15 February 2002 study termination date; though the chance of having a simulated seizure would be not much different between the 99% and 99.99% seizure rate assumptions at Day 500, the simulated seizure with the assumed seizure rate of 99% at Day 500 would tend to be substantially *earlier* than with the assumed seizure rate of 99.99% at Day 500. Thus, these 2 examples demonstrate that a small increase in the assumed seizure rate at Day 500 results in both more seizures and earlier seizures. This is an important finding because the survival analysis of the primary endpoint, time-to-first seizure, is influenced by both the seizure counts and the times of seizure occurrence. This explains why the p value changes more dramatically when the assumed seizure rate at Day 500 approaches 100%. However, this phenomenon is particular to the rates approaching 100%.

3.1.3 Reviewer's Comment

This reviewer validated the results in Table 3.1.1.

Without using the exponential distribution: p-values produced here are in the range between the primary analysis (when 0% withdrawals are assumed to have seizures), and all-cause analysis (when 100% withdrawals are assumed to have seizures).

In the approvable letter dated November 25, 2003, the Agency stated that "we are not confident that we can know how to reliably choose the particular seizure rate which should best inform our decision about the drug's effectiveness as monotherapy. Further, while we acknowledge and understand your choice of assigning equal seizure rates to both treatment groups, it is possible that performing simulations using a range of different absolute rates of seizures and different differences between the rates (i.e., varying the absolute rates yielding a given difference between the rates as well as varying the differences between different absolute rates) might provide additional insights into how to best make this decision. The purpose of these analyses would be to examine an increased range of outcomes possible under various assumptions about seizure rates, thereby hopefully providing better support for an informed decision about the effectiveness of the drug." The Agency meant to have information between the primary analysis and all-cause analysis because all-cause analysis is conservative. The simulated results from the method without using the exponential distribution might provide useful information, but one should be cautions using these results.

As pointed out in the previous review, p-values produced from the method using the exponential distribution are less than half from the trial data for the all-cause analysis, so it is hard to interpret. Although the applicant thought that it might be computer precision problem, the problem is not completely solved. This reviewer performed several cases for various "Day" using the exponential distribution and found that the larger a "Day" is used, the smaller p-values will be produced. Since the applicant doesn't completely solve the problem, the results using the exponential distribution might not be reliable, and might not be useful.

P-values from the method without using the exponential distribution are greater than those from the method using the exponential distribution. However, how to use the simulated results for decision making is not clear, and will depend on clinical judgment.

Since p-values produced without using the exponential distribution are in the range between the primary analysis (when 0% withdrawals are assumed to have seizures), and all-cause analysis (when 100% withdrawals are assumed to have seizures), the simulated results from the method without using the exponential distribution might be considered as the compromised results between the primary analysis and all-cause analysis. However, how to use the simulated results for decision making is not clear, and will depend on clinical judgment. The simulated results from method using the exponential distribution are difficult to interpret.

3.2 Evaluation of Safety

N/A.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

There is no analysis performed in this resubmission.

4.2 Other Special/Subgroup Populations

There is no analysis performed in this resubmission.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

P-values from the method without using the exponential distribution are greater than those from the method using the exponential distribution. However, how to use the simulated results for decision making is not clear, and will depend on clinical judgment.

5.2 Conclusions and Recommendations

Since p-values produced without using the exponential distribution are in the range between the primary analysis (when 0% withdrawals are assumed to have seizures), and all-cause analysis (when 100% withdrawals are assumed to have seizures), the simulated results from the method without using the exponential distribution might be considered as the compromised results between the primary analysis and all-cause analysis. However, how to use the simulated results for decision making is not clear, and will depend on clinical judgment. The simulated results from method using the exponential distribution are difficult to interpret.

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Kun He
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Kun Jin
6/27/05 01:39:36 PM
BIOMETRICS

James Hung
6/27/05 05:42:14 PM
BIOMETRICS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	20-505/S-018 and 20-844/S-015
Drug Name:	Topamax ® (topiramate)
Indication:	Seizures
Sponsor:	Johnson & Johnson
Date:	6/18/2004
Review Priority:	standard
Biometrics Division:	Biometrics I (HFD 710)
Statistical Reviewer:	Kun He
Concurring Reviewers:	Kun Jin, , Ph.D.,Team Leader James Hung, Ph.D., Acting Deputy Director
Medical Division:	Neuropharmacological Drug Products (HFD 120)
Clinical Team:	Howard Chazin, M.D., Ph.D., Clinical Reviewer John Feeney, M.D., Team Leader Russell Katz, M.D., Director
Project Manager:	Jacqueline Ware, R. Ph.

Keywords: log-rank test, seizure, topamax

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Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

Currently, there is no consensus on appropriate statistical method to handle informative censoring. To address the concern on disproportional censoring rates between the high and low dose groups, the applicant performed analyses by simulating events among censored patients and by modeling data with a censoring bias function. While the analyses have generated results favoring high dose group, it is difficult to interpret these results with relevance to the regulatory decisions.

1.2 Brief Overview of Clinical Studies

TOPMAT-EPMN-106 was a randomized, double-blind, and parallel group study, conducted in USA, Canada, Europe and Latin America. Its primary objective was to compare the safety and efficacy of 2 doses of topiramate (50 mg/day and 400 mg/day) as monotherapy in pediatric and adult subjects with newly diagnosed (within 3 months) epilepsy characterized by partial-onset or generalized seizures or with recurrent epilepsy while off of AEDs. A total of 487 were enrolled resulting 471 randomized with 234 in TPM 50, 236 in TPM 400, and 1 lost to follow-up. There were 4 phases in this study: baseline, open-treatment, double-blind, and long-term extension. The primary efficacy endpoint was the time to first partial onset or generalized seizure during the double-blind phase.

The primary analysis is log-rank test which gave p-value of .0002 where there were 90 out of 234 (38%) seizure events in TPM 50, and 49 out of 236 (21%) seizure events in TPM 400 groups, respectively. Unfortunately, log-rank test of all-cause analysis gave p-value of .5706 due to unbalanced withdrawals between two treatment groups, 39 out of 234 (17%) in TPM 50, and 75 out of 236 (32%) in TPM 400, respectively. One issue needs to be addressed is whether there might be potential bias caused by the unbalanced withdrawals, because more withdrawals in high dose group will be likely to have fewer observed seizure events.

In the Approvable letter dated November 26, 2003, the Agency raised a number of statistical questions that need to be addressed before the monotherapy supplements can be approved. In this resubmission, the applicant conducted sensitivity analyses, which include multiple imputations method and modeling with a censoring bias function method, to address these issues.

1.3 Statistical Issues and Findings

The multiple imputations method is simulating random events for those missing data under an exponential distribution with various seizure rates. If the assumption could be clinically justified and seizure rates could be suitably selected, the simulation results would provide some information to evaluate the significance of treatment effect. However, with missing data, the validity of this

approach is difficult to establish.

The sensitivity analyses based on the modeling with a censoring bias function aimed at assessing the impact of informative censoring on the original primary analysis. The method itself was a new development from a peer-reviewed article, and extends from one sample to two-samples problem. The sensitivity analysis was done by varying the values of two parameters α and τ. Because the data contain no independent evidence about parameters, final substantive conclusions would depend on which values of parameters are considered plausible by relevant subject matter experts. However, the relation between the values of the parameters and clinical meaning is not well established, which made it very difficult for clinicians to choose the suitable parameters. The censoring bias function method itself is difficult to validate, and the theory of the method is not established. Specifically, the asymptotic distribution of the test statistic under null hypothesis was not provided. The applicant employed an ad-hoc bootstrap method to calculate p-value of test statistic. Although the applicant's statistical consultants assert during a face to face meeting that the proposed bootstrap method is valid to calculate the p-value in this situation, this reviewer is not comfortable to accept this statement without a rigorous proof.

2. Introduction

2.1 Overview

On October 29, 2002, the applicant submitted supplemental new drug applications (NDA 20-505/S-018 and NDA 20-844/S-015) to the Agency to provide for the use of topiramate as monotherapy in adults and children 6 years of age and older with newly diagnosed epilepsy. In the Approvable letter dated November 26, 2003, the Agency raised a number of statistical questions that need to be addressed before the monotherapy supplements can be approved. On February 11, 2004, a meeting was held between the Agency and the applicant to discuss the approaches the applicant planned to use to address the statistical issues raised by the Agency in the approvable letter.

In reviewing the results of the primary efficacy analysis (survival analysis) performed in the pivotal Study TOPMAT-EPMN-106, the Agency has questioned the validity of the assumption of non-informative censoring, i.e., the assumption that the withdrawal and seizure occurrence were independent events. Specifically, the Agency was concerned with the possibility of a potential bias introduced into the primary efficacy analysis due to the differential withdrawal patterns in the 2 topiramate dose groups.

The applicant conducted sensitivity analyses to address these issues. The sensitivity analyses conducted to evaluate the robustness of the efficacy results reported in the original application were based on two methodological approaches: multiple imputations method and censoring bias function method.

2.2 Data Sources

The paths to the CDER Electronic Document Room (EDR) are:

\\Cdsesub1\n20505\S_018\2004-05-27
\\Cdsesub1\n20505\S_018\2004-06-18
\\Cdsesub1\n20505\S_018\2004-07-19

3. Statistical Evaluation

3.1 Evaluation of Efficacy

The applicant performed multiple imputations and censoring bias function analysis. Majority materials in Section 3.1.1 and 3.1.2 are adapted from the applicant's study report.

3.1.1 Multiple Imputations

The methods used to perform multiple imputations on the data from Study 106 are described in detail in Appendix 6.1. Times to first seizure data were imputed for the 114 subjects from both treatment groups (75 from the topiramate 400 mg/day group and 39 from topiramate 50 mg/day group) who withdrew from the double-blind phase due to any reason, and were therefore seizure-free at the time of withdrawal according to the study design. The imputed seizure times were generated based on an exponential distribution, conditioned upon the time of discontinuation.

In the response submitted to the Agency on June 10, 2003, the applicant performed single simulations with equal seizure rates assigned to the discontinuation cohorts of both treatment groups. In the approvable letter, the Agency requested that these simulations be repeated multiple times for each pair of seizure rates, and that differential seizure rates be assigned to the 2 treatment groups. During the meeting on February 11, 2004, the Agency agreed to review the use of the multiple imputations approach proposed by the applicant to report p-values from the 1,000 simulations performed for each pair of assumed seizure rates (Appendix 6.1).

The seizure rate for the exponential distribution can be arbitrarily chosen. In order to determine whether the result of the original log-rank test is robust, a range of seizure rates between 30% and 80% at Day 500 was used. To increase the precision of multiple imputation results, 1,000 repeat runs were performed for each combination of the seizure rates for the 2 treatment groups. Finally, to evaluate a wide range of potential scenarios, the simulations were performed for varying combinations of seizure rates in the 2 treatment groups.

The results of this analysis are shown in Table 3.1.1.1 below.

Table 3.1.1.1 P values from 1,000 Simulated Runs
Using Combinations of Assumed Seizure Rates for Subjects who Withdrew from the Study
(Study TOPMAT-EPMN-106; Double-Blind Phase)

Seizure rate at Day 500	TPM 400						
TPM 50	30%	40%	50%	60%	70%	75%	80%
30%	.001**	.006**	.023**	.082*	.231		
40%	<.001***	.003**	.012**	.049**	.151	.238	
50%	<.001***	.001**	.006**	.025**	.094*	.165	.271
60%	<.001***	.001**	.003**	.013**	.051*	.092*	.168
70%	<.001***	<.001***	.001**	.006**	.026**	.054*	.100
75%		<.001***	.001**	.004**	.018**	.035**	.065*
80%			.	.002**	.013**	.025**	.052*

* $p < 0.1$
** $p < 0.05$
*** $p < 0.001$

In order for the difference between topiramate 400 mg/day and topiramate 50 mg/day to lose nominal statistical significance at the assumed seizure rates below 75%, the seizure rate in the high-dose group would have to exceed that in the low-dose group substantially - a clinically unlikely scenario.

Based on the multiple imputation sensitivity analysis, the results of Study 106 are highly robust with respect to the entire clinically plausible range of scenarios, since statistically significant treatment differences hold for a wide range of seizure recurrence rates, including the range of plausible rates suggested by the literature and clinical trial data.

3.1.1.1 Reviewer's Comment

The procedure of multiple imputations is as follows: subjects who were seizure-free at the time of withdrawal were imputed through an exponential distribution, conditional upon the time to discontinuation. For example, if a subject withdrew on Day 50, a random failure time is generated from an exponential distribution with a given seizure rate. The failure time is then compared with the potential duration, which is the duration between Day 50 and February 15, 2002 (i.e., the date of trial completion). If the duration is longer than the random failure time, the subject is considered to have had a seizure at the failure time plus 50; otherwise, the subject's first seizure time is censored on February 15, 2002. Note that the seizure rate for the exponential distribution can be arbitrarily chosen. Therefore, with the parametric method, one can provide a range of seizure rates to determine whether the result of the original log-rank test is robust.

One implicitly assumption is that earlier withdrawn patient would have larger chance to have seizure than that later withdrawn patient.

Table 3.1.1.1.1 presents p-values for equal seizure rates from 90% to 99% for exponential distributions at Day 500 for two treatment groups.

Table 3.1.1.1.1 P values from 1,000 Simulated Runs Using Combinations of Assumed Seizure Rates for Subjects who Withdrew from the Study

Rate	90%	91%	92%	93%	94%	95%	96%	97%	98%	99%
p	.099	.114	.12	.126	.14	.152	.165	.184	.206	.241

Notice that p-value is .241 when seizure rate is 99% for multiple imputations and p-value is .5706 for all-cause analysis using the trial data. The difference might be due to assumptions and algorithms: in multiple imputations, if a patient's withdrawn time is larger, this patient might not have seizure because its withdrawn time plus random time might be larger, and in all-cause analysis, a patient's withdrawn time is assumed to be seizure time.

As the applicant stated, "Interpretation of these analyses requires a clinical context" because there is

no statistical method to verify the assumptions using the current data. Therefore, one should take into consideration of the simulation assumptions when interpreting the result.

During the meeting on February 11, 2004, the Agency accepted the use of the multiple imputations approach proposed by the applicant to report p-values from the 1,000 simulations performed for each pair of assumed seizure rates. The agreement is on the method of calculating simulation error introduced by multiple runs, since the applicant's previous simulation is performed using single run only which doesn't take care of simulation error. However, there is no agreement made that the multiple runs, which is an exploratory analysis, would provide a right answer to resolve the issue.

Overall, if assumptions for multiple imputations could be justified clinically and seizure rates could be chosen suitably, the simulation results would provide some information to evaluate the significance of treatment effect. However, with missing data, the validity of this approach itself is difficult to establish.

3.1.2 Censoring Bias Function Analysis

The Censoring Bias Function method (see Appendix 6.2 for full details) is a sensitivity analysis method specifically developed to assess the impact of potentially informative censoring. Informative censoring effects are examined by specifying scientifically reasonable values for the non-identifiable dependence between the times of first seizure and the premature censoring times through a censoring bias function. In particular, the cause-specific hazard of premature censoring is modeled as a parameterized function of the time to first seizure. The cause-specific hazard of administrative censoring is assumed to be independent of the time to first seizure. The censoring bias function has two parameters, α and τ. The parameter α is interpreted as the log hazard ratio of prematurely withdrawal at time t between subjects who are at risk at time t, but differ by one day in their ultimate times to first seizure. The parameter τ roughly represents the mean time (in days) to first seizure for subjects who would not experience a seizure prior to 500 days (the trial's primary analysis date) after enrollment. For subjects who will experience their first seizure prior to 500 days, the quantity $\exp(\alpha d/365)$ is interpreted as the hazard ratio of withdrawal at time t comparing subjects who are at risk at time t, but differ by d days in their time to first seizure. In addition, the quantity $\exp(\alpha(d-\tau)/365)$ is interpreted as the hazard ratio of withdrawal at time t comparing subjects who are at risk and will experience their first seizure at day d prior to 500 days to subjects who are at risk and will experience their first seizure after 500 days.

The Censoring Bias Function approach provides bounds for the sensitivity analysis. When $\alpha=0$, premature censoring is equivalent to non-informative censoring. When $\alpha=-\infty$ results are equivalent to an analysis where each prematurely censored subject is assumed to have their first seizure at the next observed seizure time, similar in spirit to the analysis performed by the Agency, where prematurely censored subjects are assumed to have a seizure at their censoring time. When α is negative, subjects with shorter times to next seizure are more likely to be censored at any time t than

subjects with longer times to next seizure. Therefore, sensitivity of inference to negative values of α is the principle concern.

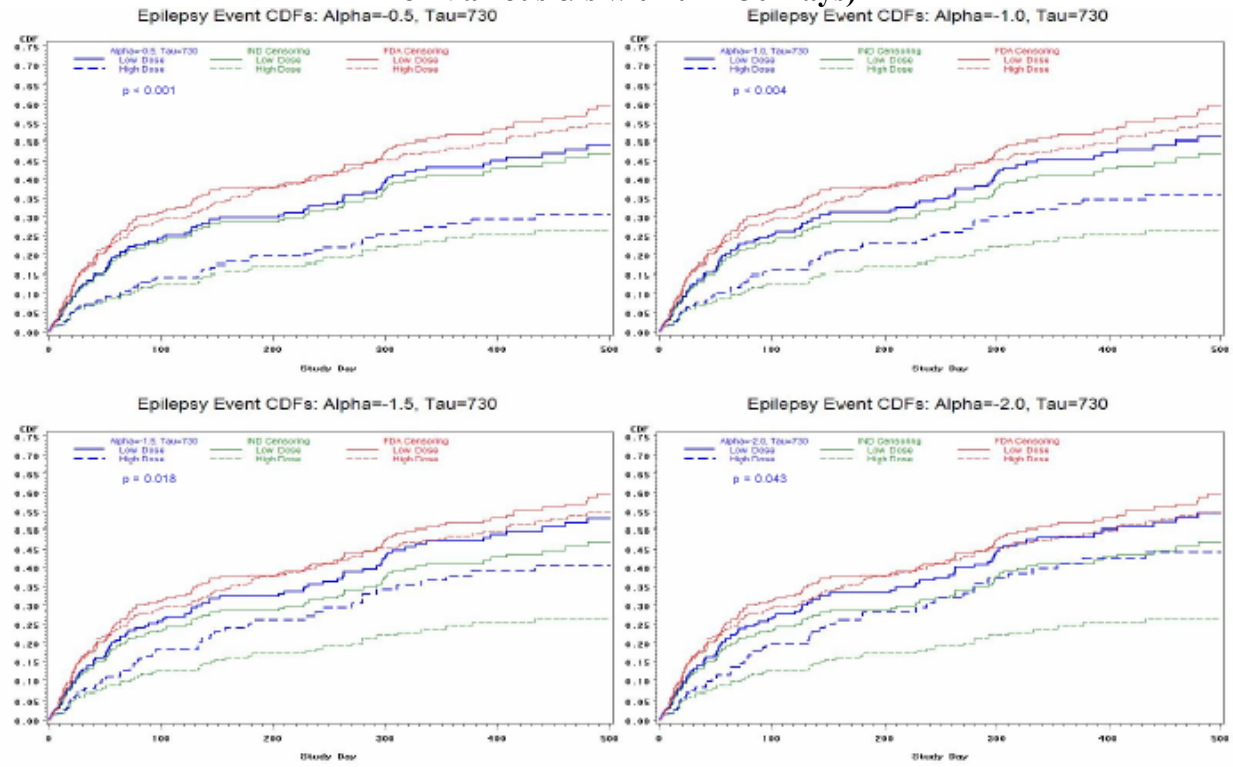
The sensitivity analysis in this section was performed over a range of the negative values of α with τ fixed at 730 days (2 years). Throughout, the applicant assumed the same α and τ for both treatment groups. Shown in Table 3.1.2.1 are p-values based on a log rank-type statistic, for the comparison between the topiramate dosage groups in Study 106 for varying values of α with τ fixed at 2 years. The high dose group consistently shows a statistically significant improvement over the low dose group for α between 0 and -2.

Table 3.1.2.1 P-values for Comparison between Treatments based on the Censoring Bias Function Method (τ = 730 days)

	α					
	0	-0.5	-1	-1.5	-2	-2.5
p-value	<0.001	<0.001	<0.004	0.018	0.043	0.079

Figure 3.1.2.1 examines the dose-specific cumulative distribution functions of time to first seizure for various α's. In each figure, the applicant displayed the distributions under non-informative censoring (green lines), under the Agency's method (red lines), and under the α-specific Censoring Bias Function method (blue lines). Solid lines refer to the low dose arm and dashed lines refer to the high dose arm. In these figures, as α is made increasingly negative, both distribution functions shift dramatically upward and the treatment-specific curves get closer to one another.

Figure 3.1.2.1 Dose-specific Cumulative Distribution Functions of Time to First Seizure for Various α's with τ = 730 Days)



There is an additional way of understanding the implications of varying α. For given α, one can derive the implied distribution of time to first seizure for subjects prematurely censored at a given time. In Figure 3.1.2.2 the applicant showed, for various α's, the probability mass function for a subject in the low dose arm who was prematurely censored at day 8 (the first premature censoring time observed in the low dose arm). The values in blue denote the probability of having a first seizure in each 50 day period for such a subject. Under non-informative premature censoring (i.e., α=0), there is a 13% chance of having a seizure by day 50 and 55% chance of not having a seizure by Day 500. In comparison, when α=-2.0, the chance of having a seizure by Day 50 more than triples to 44%, and the chance of not having a seizure by Day 500 is reduced dramatically to 3%. When α=-50 (approximately the Agency's method) there is a 100% chance of having the first seizure within 50 days (with rounding). In Figure 3.1.3, the applicant presented the similar illustration for a subject who is prematurely censored at Day 4 in the high dose arm (the first premature censoring time observed in the high dose arm). Note again that the implied distributions are substantially shifted toward shorter first seizure times for α=-2.0.

Figure 3.1.2.2 Implied First Seizure Probability Mass Functions for a Subject in the Low Dose Arm Who was Prematurely Censored at Day 8

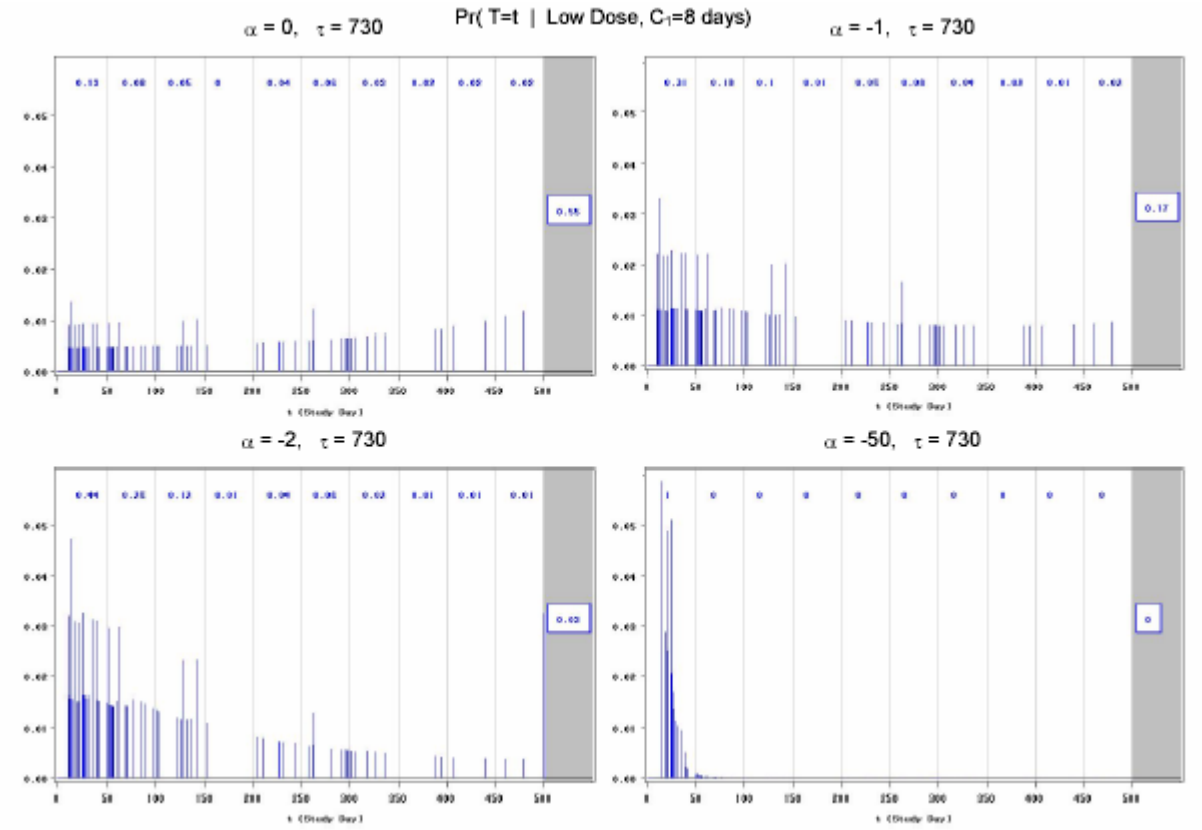
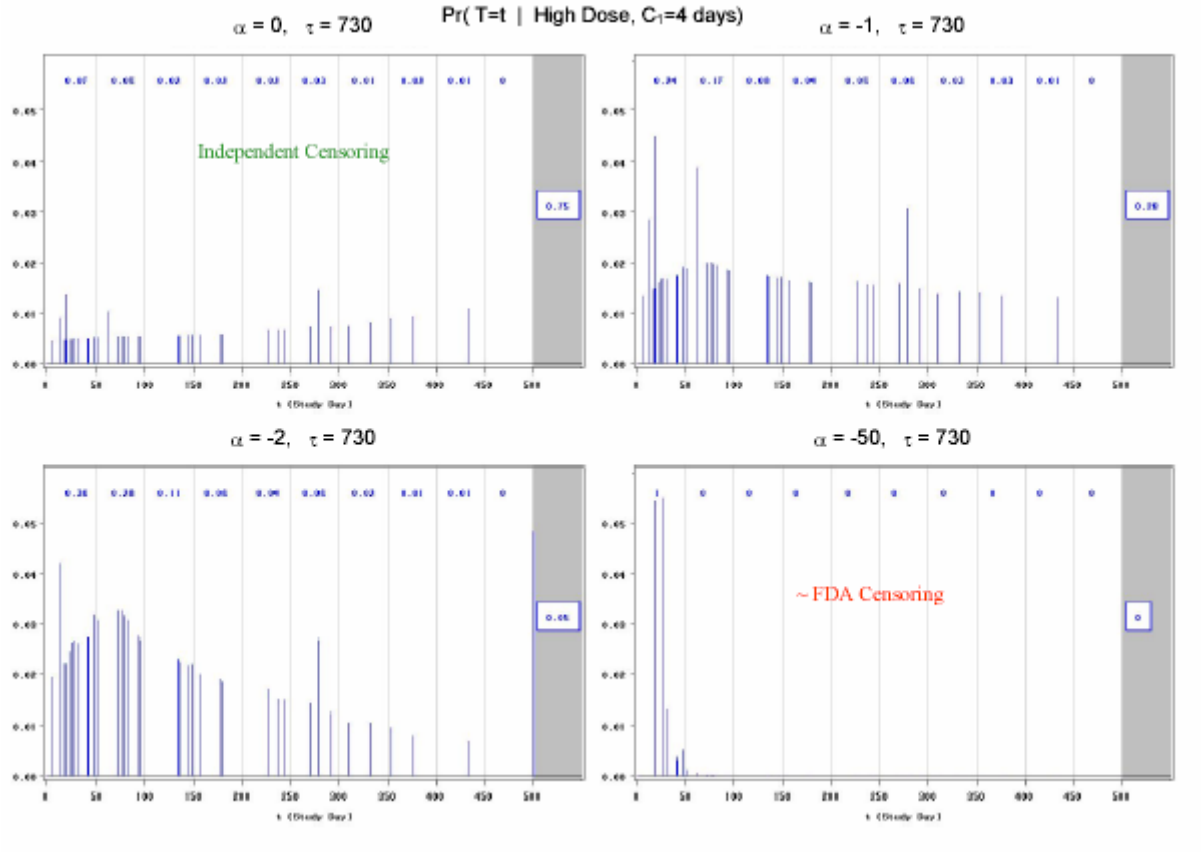


Figure 3.1.2.3 Implied First Seizure Probability Mass Functions for a Subject in the High Dose Arm Who was Prematurely Censored at Day 4



Sensitivity to Variations in τ

The sensitivity analysis presented above was conducted by the applicant with the parameter τ set to 730 days (2 years). To examine the effects of varying τ, the applicant conducted additional analyses with τ set to 630 days and 830 days.

Shown in Table 3.1.2.2 are p-values similar to those presented in Table 3.1.2.1 for the comparison between the topiramate dosage groups for varying values of α and τ. Note that, for given α, the estimated treatment-specific cumulative distribution functions shift upward and closer together as τ increases. Results are relatively insensitive to varying values of τ with the high dose group consistently showing a statistically significant improvement over the low dose group for α between 0 and -1.5 for all values of τ.

Table 3.1.2.2 P-values for Comparison between Treatments Based on the Censoring Bias Function Method

	α					
	0	-0.5	-1	-1.5	-2	-2.5
τ = 630	<0.001	<0.001	<0.003	0.009	0.028	0.053
τ = 730	<0.001	<0.001	<0.004	0.018	0.043	0.079
τ = 830	<0.001	<0.001	<0.006	0.027	0.065	0.102

Effects of varying τ in this manner appear to be non-substantial.

Comparison with the Multiple Imputations Approach

As a final method of gaining intuition on the effects of α and τ, it is useful to compare the censoring bias function approach with the multiple imputations approach. To give a sense on how particular sets of parameters in the 2 approaches are related, Figure 3.1.2.4 shows dose-specific cumulative distribution functions from both approaches, where α = –1.5 and τ = 730 for the censoring bias function method and assumed seizure rate of 75% for the multiple imputations method (the curve represents a mean of the fitted Kaplan-Meier curves from the 1,000 simulations). Note that the curves for the censoring bias function approach lie entirely above the curves for the multiple imputations approach. Therefore, the seizure rate for subjects who are prematurely censored will be greater than 75% for the censoring bias function method with α = –1.5 and τ = 730. On the other hand, in terms of the separation of the high dose curve versus the low dose curve, the censoring bias function method with α = –1.5 and τ = 730 was similar to that of the multiple imputations approach with 75% seizure rate. Results for α = -1.5, τ = 630 and α = –1.5, τ = 830 show the same pattern. In addition, as shown in Figure 3.1.2.5, the separation between the high dose and low dose in cumulative distribution curves obtained from the censoring bias function approach with α = –2 and τ = 730 is in line with that of the multiple imputations approach with 80% seizure rate.

Figure 3.1.2.4 CDF Comparisons: α = -1.5, τ = 730, Independent Censoring, FDA Censoring, and 75% Rate Imputed Exponential

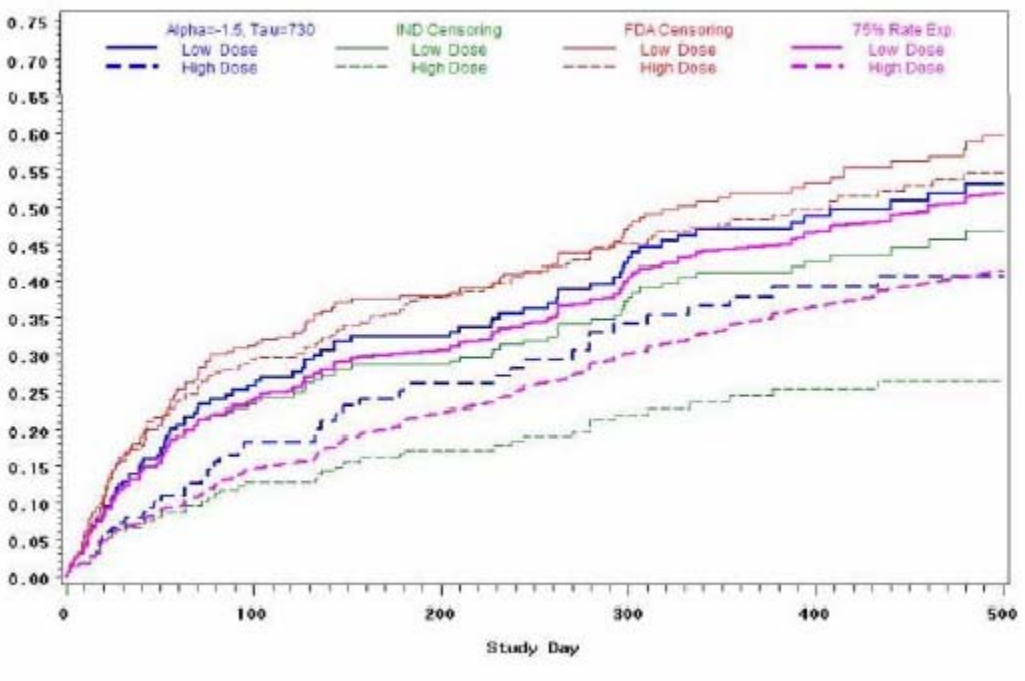
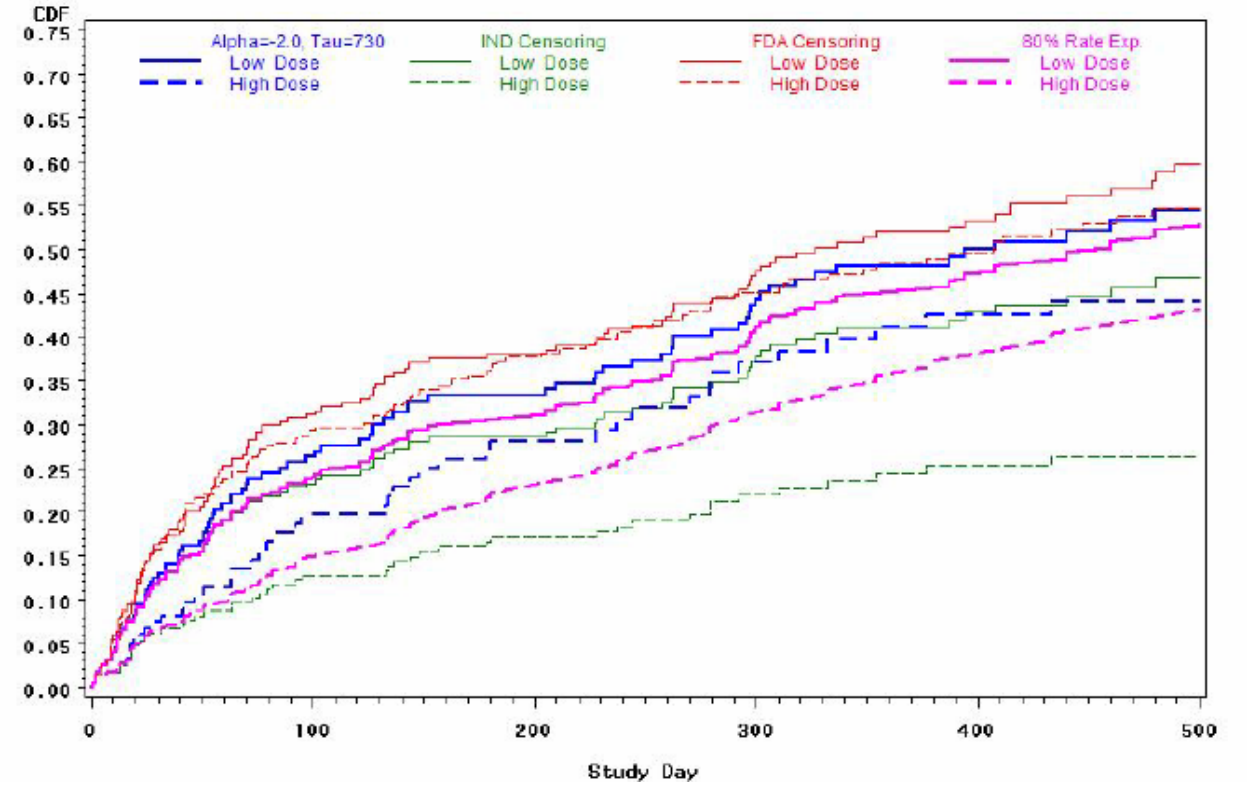


Figure 3.1.2.5 CDF Comparisons: α = -2, τ = 730, Independent Censoring, FDA Censoring, and 75% Rate Imputed Exponential



Estimation of α and τ from Study TOPMAT-EPMN-105

In the previous section, the applicant showed that the results from the censoring bias function and multiple imputation sensitivity analysis methods are consistent with one another. In this section, the applicant discussed estimation of the censoring function bias parameters based on relevant follow-up data from Study 105.

In Study 105, there were 140 subjects who were treated with topiramate and had follow-up data after stopping their double-blind medication. Almost all these subjects stopped their medication prematurely due to adverse events, lack of efficacy, or other reasons. The baseline seizure counts for the subjects enrolled in Study 105 were higher than those in Study 106. The same is also seen when comparing subjects who had follow-up data after the stop of double-blind medication in Study 105 versus the subjects who withdrew in Study 106. In addition, the median of seizure counts was 1 and, therefore, at least 50% of the subjects already had at least one seizure during the double-blind phase prior to withdrawal, while none of the Study 106 dropouts had a seizure prior to withdrawal.

This comparison demonstrates that the Study 105 subject population, including the 140 subjects who had follow-up data, is a population with more frequent seizures as compared to the subjects in Study 106. Thus, the chance of having seizures after the stop of the double-blind medication among the

140 subjects in Study 105 should be higher than that of the 114 subjects in Study 106 who withdrew prematurely. Thus, one would reasonably expect that the dependence between premature withdrawal time and time of subsequent seizure would be stronger among the 140 Study 105 subjects as compared to the 114 subjects in Study 106. This means that the α and τ estimates obtained using Study 105 follow-up data would be more conservative than the estimates based on Study 106 data, if follow-up data in study 106 were available.

To estimate α and τ in Study 105, the applicant used Day 500 as the analysis day as specified in the sensitivity analysis for Study 106 and, for subjects who prematurely withdrew prior to the minimum of time of next seizure and 500 days, the applicant assumed that their subsequent seizure time was on the day of premature withdrawal. Details of the statistical method used can be found in the attached technical report (Appendix 6.2). The estimates based on the Study 105 follow-up data are

$\alpha = -1.4$ and $\tau = 577$ days.

When the applicant applied values of α and τ in a 95% bootstrapped (1,000 re-samples) confidence region to Study 106, results are statistically significant at the 0.05 level. As mentioned previously, these estimates and associated region are conservative.

In summary, this result demonstrates that the original primary analysis of Study 106 is robust to potential informative censoring.

3.1.2.1 Reviewer's Comment

The applicant provided sensitivity analyses in solving potential informative censoring for the original primary analysis using the censoring bias function approach.

The clinical interpretation of parameters α and τ

The censoring bias function method is based on a semi-parametric model, assuming a particular parametric functional form. Its interpretation depends mainly on the choice of parameters α and τ. As stated in the technical report, the choice of parameters "can be specified by subject matter experts". During February 11, 2004 meeting between the applicant and the Agency, the Agency asked the applicant to provide an understandable clinical interpretation for clinical experts to make a right judgment in selecting the parameters.

In this submission, the applicant stated that "The parameter α is interpreted as the log hazard ratio of prematurely withdrawing at time t between subjects who are at risk at time t, but differ by one day in their ultimate times to first seizure. The parameter τ roughly represents the mean time (in days) to first seizure for subjects who would not experience a seizure prior to 500 days (the trial's primary analysis date) after enrollment. For subjects who will experience their first seizure prior to 500 days, the quantity $\exp(\alpha d /365)$ is interpreted as the hazard ratio of withdrawing at time t comparing

subjects who are at risk at time t, but differ by d days in their time to first seizure. In addition, the quantity exp(α(d-τ)/365) is interpreted as the hazard ratio of withdrawal at time t comparing subjects who are at risk and will experience their first seizure at day d prior to 500 days to subjects who are at risk and will experience their first seizure after 500 days." Although interpretation of τ has clear clinical meaning, the interpretation of α is not well linked to more understandable clinical term.

The applicant tried to give quantitative relation between α and probabilities for future seizure. From Figures 3.1.2.1 and 3.1.2.2, a low dose subject was prematurely censored at day 8 (the first premature censoring time observed in the low dose group). For τ = 730, for various α's, there are 13% (α = 0), 31% (α = -1), 44% (α = -2), and 100% (α = -50) chances of having a seizure by Day 50; and 55% (α = 0), 17% (α = -1), 3% (α = -2), and 0% (α = -50) chances of not having a seizure by Day 500, respectively. Similarly, a high dose subject was prematurely censored at day 4 (the first premature censoring time observed in the high dose group). For τ = 730, for various α's, there are 7% (α = 0), 24% (α = -1), 36% (α = -2), and 100% (α = -50) chances of having a seizure by Day 50; and 75% (α = 0), 28% (α = -1), 5% (α = -2), and 0% (α = -50) chances of not having a seizure by Day 500, respectively. The quantitative relation between α and probabilities for future seizure might be useful in understanding α, however, it is not sufficient for clinician to easily choose the parameter.

The applicant compared the multiple imputations and the censoring bias function. From comparison with multiple imputations in Figures 3.1.2.4 and 3.1.2.5, the Kaplan-Meier curves (mean of the fitted curves from 1000 simulations) for the censoring bias function method lie entirely above the curves for the multiple imputations method when α = -1.5 and τ = 730 and assumed seizure rate is 75% for multiple imputations method; and when α = -2 and τ = 730 and assumed seizure rate is 80% for multiple imputations method. In terms of the separation of the high dose curve versus the low dose curve, the censoring bias function method with α = -1.5 and τ = 730 is similar to that of the multiple imputations method with 75% seizure rate; and with α = -2 and τ = 730 is similar to that of the multiple imputations method with 80% seizure rate. These comparisons give some intuitions although the separation between high and low doses curves is observed through graphs without applying any formal procedures.

The applicant used Study 105 and estimated α = -1.4 and τ = 577 days. However, many assumptions between two studies need to be compared, despite that the applicant claimed that the estimates are more conservative.

Overall, as stated in the peer-reviewed paper for the sensitivity analysis, "clearly the biggest challenge in conducting such a sensitivity analysis is the choice of one or more sensible parameterized selection bias functions whose interpretation can be communicated to relevant subject matter experts with sufficient clarity so that they can provide plausible range for the parameters, including its magnitude and direction", and "because the data contain no independent evidence about parameters, final substantive conclusions would depend on which values of parameters are considered plausible by relevant subject matter experts." The interpretation mainly depends on the

choice of α and τ from clinical experts. Although the applicant tried to provide many ways to give clinical interpretation of the parameters, the information is not sufficient for clinical experts to choose α and τ in interpreting the simulation results.

The validity of the method

Since the censoring bias function method is proposed in a technical report, which is a major extension from one sample to two samples from a peer-reviewed article, on February 11, 2004 meeting between the applicant and the Agency, the Agency raised the question to the applicant how to validate the method. With the current data, there is no method to validate the assumptions of the method.

All analyses using censoring bias function method performed in this submission are based on bootstrap because the asymptotic distribution of test statistic is not established. As the applicant stated, "The large sample theory of the test statistics discussed during February 11, 2004 meeting between the applicant and the Agency is not provided in this response document. While the large sample theory can be developed (using similar techniques as in Scharfstein and Robins, 2002), it is mathematically complicated and computationally challenging to implement. It is the opinion of (b) (4) and Dr. Daniel Scharfstein at the Johns Hopkins University that the bootstrap technique proposed herein should possess better finite-sample properties than relying on large-sample normal theory. The theoretical work to verify the regularity conditions needed to validate the bootstrap procedure is considered beyond the scope of these sensitivity analyses, and is considered more a theoretical rather than a practical issue." The applicant employed an ad-hoc bootstrap method to calculate p-value of test statistic. However, the reviewer is not comfortable to accept the calculation without a rigorous proof of the method. The applicant also provided the Agency with a SAS computing package for the relevant calculation. It seems appropriate to have an independent validation on this package should it be used for a regulatory decision.

Overall, the sensitivity analyses based on the modeling with a censoring bias function aimed at assessing the impact of informative censoring on the original primary analysis. The method itself was a new development from a peer-reviewed article, and extends from one sample to two-samples testing problem. The sensitivity analysis was done by varying the values of two parameters α and τ. Because the data contain no independent evidence about parameters, final substantive conclusions would depend on which values of parameters are considered plausible by relevant subject matter experts. However, the relation between the values of the parameters and clinical meaning is not well established, which made it very difficult for clinicians to choose the suitable parameters. The censoring bias function method itself is difficult to validate, and the theory of the method is not established. Specifically, the asymptotic distribution of the test statistic under null hypothesis was not provided. The applicant employed an ad-hoc bootstrap method to calculate p-value of test statistic. Although the applicant's statistical consultants assert during a face to face meeting that the

proposed bootstrap method is valid to calculate the p-value in this situation, this reviewer is not comfortable to accept this statement without a rigorous proof.

3.2 Evaluation of Safety

See clinical review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

There is no analysis performed in this resubmission.

4.2 Other Special/Subgroup Populations

There is no analysis performed in this resubmission.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The multiple imputations method is simulating random events for those missing data under an exponential distribution with various seizure rates. If the assumption could be clinically justified and seizure rates could be suitably selected, the simulation results would provide some information to evaluate the significance of treatment effect. However, with missing data, the validity of this approach is difficult to establish.

The sensitivity analyses based on the modeling with a censoring bias function aimed at assessing the impact of informative censoring on the original primary analysis. The method itself was a new development from a peer-reviewed article, and extends from one sample to two-samples problem. The sensitivity analysis was done by varying the values of two parameters α and τ. Because the data contain no independent evidence about parameters, final substantive conclusions would depend on which values of parameters are considered plausible by relevant subject matter experts. However, the relation between the values of the parameters and clinical meaning is not well established, which made it very difficult for clinicians to choose the suitable parameters. The censoring bias function method itself is difficult to validate, and the theory of the method is not established. Specifically, the asymptotic distribution of the test statistic under null hypothesis was not provided. The applicant employed an ad-hoc bootstrap method to calculate p-value of test statistic. Although the applicant's statistical consultants assert during a face to face meeting that the proposed bootstrap method is valid to calculate the p-value in this situation, this reviewer is not comfortable to accept this statement without a rigorous proof.

5.2 Conclusions and Recommendations

Currently, there is no consensus on appropriate statistical method to handle informative censoring. To address the concern on disproportional censoring rates between the high and low dose groups, the applicant performed analyses by simulating events among censored patients and by modeling data with a censoring bias function. While the analyses have generated results favoring high dose group, it is difficult to interpret these results with relevance to the regulatory decisions.

6. Appendix

6.1 Multiple Imputation Approach Description

The procedure of multiple imputations is as follows: subjects who withdrew were seizure-free at the time of withdrawal were imputed through an exponential distribution, conditional upon the time to discontinuation. For example, if a subject withdrew on Day 50, a random failure time is generated from an exponential distribution with a given seizure rate. The failure time is then compared with the potential duration, which is the duration between Day 50 and 15 February 2002 (i.e., the date of trial completion). If the duration is longer than the random failure time, the subject is considered to have had a seizure at the failure time plus 50; otherwise, the subject's first seizure time is censored on 15 February 2002. Note that the seizure rate for the exponential distribution can be arbitrarily chosen. Therefore, with the parametric method, one can provide a range of seizure rates to determine whether the result of the original log-rank test is robust.

Under the above method, sensitivity analyses were performed, using all 114 subjects from both treatment groups (75 from the TPM 400 group and 39 from TPM 50 group) who withdrew from the double-phase due to any reason.

For each assumed 1st seizure rate on day 500, simulations are repeated K times. For the kth simulated data set, one calculates the numerator and denominator of the log-rank multiple imputations, one then calculates

$U = \sum_{1<=k<=K} U_k /K$
$D = \sum_{1<=k<=K} V_k /K + \sum_{1<=k<=K} (U_k - U)^2/K$,

The final test statistic is $T = U^2/ D$, which has Chi-Square distribution with 1 degree of freedom under null hypothesis. Note that there are two terms in D, the first term is the within-imputation variance and the second term is the between-imputation variance.

The p-value = $P\{\chi^2_1 > T\}$ for each of the assumed 1st seizure rates is reported.

The same is done when the two 1st seizure rates from the two treatment groups are assumed to be different.

6.2 On the Analysis of Randomized Trials Subject to Noninformative and Informative Competing Causes of Censoring

The method is developed in the Technical Report by Daniel O. Scharfstein.

On the Analysis of Randomized Trials Subject to Non-informative and Informative Competing Causes of Censoring

May 14, 2004

Abstract

In this report, we show how to analyze randomized trials with failure time endpoints which are subject to non-informative and informative competing causes of censoring. Specifically, we show how to estimate treatment-specific survival curves and to test for treatment effects using a logrank-type test statistic. Our sensitivity analysis method handles informative censoring through scientifically reasonable specifications of the non-identifiable dependence between failure and censoring. We also show how to obtain conservative estimates of this dependence from auxiliary data. Our methodology is motivated by a randomized trial designed to compare low vs. high dose topiramate for the treatment of seizures in newly diagnosed epileptic patients.

1 Introduction

TOPMAT-EPMN-106 was a double-blind, randomized trial to evaluate the effectiveness of low (50 mg/day) vs. high (400 mg/day) dose topiramate in reducing time to first seizure in pediatric and adult subjects with newly diagnosed or recurrent epilepsy. Qualified patients were randomized to a low or high dose group in a 1:1 ratio. The study design called for patients to exit the study once they experienced their first seizure after randomization. During the trial, some patients were censored due to premature withdrawal from the study for protocol-specified reasons including adverse events, subject choice, lost to follow-up, and other reasons.

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In addition, some were censored due to administrative loss when the database was locked. While the number of observed failures is greater in the low dose arm, there are more premature withdrawals (primarily due to adverse events) in the high dose arm. *If* premature withdrawal is related to the underlying time to first seizure, standard survival analysis techniques (i.e., Kaplan-Meier estimators of the treatment-specific failure time distributions and logrank test for equality of these failure distributions), which assume non-informative censoring, will be biased.

Since the failure time and censoring times are never observed jointly, the dependence between these times is non-identifiable. To analyze these data, assumptions about this dependence are required. The protocol specified primary analysis assumed all censoring was non-informative. The result of the logrank test indicated a highly statistically significant result in favor of the high dose. The concern that premature withdrawal was negatively associated with time to first seizure was raised. That is, subjects who prematurely withdrew at time t were more likely to have shorter times to failure than those who remained at risk. One way to address to address this problem is to take a highly conservative approach and assume that each subject who was prematurely withdrawn failed immediately. Assuming that administrative censoring is non-informative, the result of a logrank test would no longer be statistically significant.

Scharfstein and Robins (2002) developed a methodology for estimating treatment-specific failure time distributions in the presence of informative censoring. Specifically, they posited non-identifiable dependence relationships between the censoring and failure times, indexed by interpretable parameters, and recommended performing a sensitivity analysis over a range of parameter values considered plausible by scientific experts. In their work, Scharfstein and Robins (2002) do not distinguish between the different causes of censoring; neither, did they consider the two-sample problem. In this report, we extend their work to allow for dependencies between premature withdrawal and failure, while assuming that administrative censoring is non-informative. We also show how to test the null hypothesis of no difference between the

failure time distributions using a logrank-type statistic. We compute p-values using parametric bootstrap.

Prior to TOPMAT-EPMN-106, a randomized trial (TOPMAT-EPM-105), comparing topiramate at two different doses to standard therapy in a population of newly diagnosed epileptic patients, was conducted. In the trial design, patients were followed after their first seizure event and after they went off drug. By subsetting on patients in the topiramate arms who went off drug, we can evaluate the relationship between time off drug and time of subsequent seizure. It is scientifically reasonable to expect this relationship to be stronger than the relationship between premature withdrawal and time of first seizure in TOPMAT-EPMN-106 because the TOPMAT-EPMN-105 subset of patients have a history of more seizures than both the TOPMAT-EPMN-106 population as well as the subset of patients in this population who prematurely withdrew. We show how to estimate the sensitivity analysis parameters from TOPMAT-EPMN-105, which can be used to provide conservative bounds on the sensitivity analysis parameters in TOPMAT-EPM-106.

2 Data Structure

We focus on an individual treatment group. Let T^*, C_1^*, C_2^* be (non-negative) time to first seizure, time to premature withdrawal, and time to administrative censoring, respectively. These times are measured from time of randomization, in days. Let c^* denote the time from start of randomization until the date of analysis. Now, let $T = \min(T^*, c^*)$, $C_1 = \min(C_1^*, c^*)$, and $C_2 = \min(C_2^*, c^*)$.

Each subject is observed until time $X = \min(T, C_1, C_2)$. Let $\Delta = I(T \leq \min(C_1, C_2))$ be the categorical variable, which takes on the value 0 if T is observed, 1 if C_1 is observed, and 2 if C_2 is observed. We will assume that, on $(0, c^*)$, T, C_1, and C_2 cannot occur at the same time. The observable data for a subject is $O = (X, \Delta)$. We assume that we observe n i.i.d. copies of O, $\boldsymbol{O} = \{O_i = (X_i, \Delta_i)) : i = 1, \ldots, n\}$.

Our first goal is to use $\boldsymbol{O}$ to estimate the distribution of time to first seizure, which is characterized by the cumulative distribution, $F(t) = P[T \leq t]$, survivor function $S(t) = P[T \geq t]$, and cumulative hazard function, $\Lambda(t)$. Our second goal is to test the null hypothesis of no difference between the treatment-specific failure time distributions.

3 Models and Sensitivity Analysis

Our approach is based on assuming separate cause-specific hazards models for the two types of censoring mechanisms. For censoring due to premature withdrawal, we will assume a proportional hazards model of the form:

$$\lambda^{\dagger}_{C_1}(t|T, T > t, C_2 \geq t) = \psi_1(t) \exp\{q(t,T)\} \quad t \in [0, T) \tag{1}$$

where $\lambda^{\dagger}_{C_1}(t|T, T > t, C_2 \geq t) = \lim_{h \to 0} P[t \leq C_1 < t + h, \Delta = 1 | C_1 \geq t, T, T > t, C_2 \geq t]/h$ is conditional cause-specific hazard of censoring at time t given the true underlying failure time T, $\psi_1(t)$ is an *unknown* function of t and $q(t,T)$ is a *known* function of t and T.

Specification of the function $q(t,T)$ in (1) is equivalent to quantifying, for those who remain at risk at time t, the dependence on a hazard ratio scale between T *and* censoring due to premature withdrawal just after time t, To emphasize this important property we refer to the function $q(t,T)$ as a *censoring bias function*. The censoring bias function will be non-constant when there exists unmeasured factors which are both correlated with censoring due to premature withdrawal and failure. If the function is constant (e.g., 0), then there is no dependence relationship and censoring due to premature withdrawal is non-informative.

For administrative censoring, we will assume a proportional hazards model of the form:

$$\lambda^{\dagger}_{C_2}(t|T, T > t, C_1 > t) = \psi_2(t) \quad t \in [0, c^*] \tag{2}$$

where $\lambda^{\dagger}_{C_2}(t|T, T > t, C_1 > t) = \lim_{h \to 0} P[t \leq C_2 < t + h | C_2 \geq t, T, T > t, C_1 > t]/h$ is conditional cause-specific hazard of censoring at time t and $\psi_2(t)$ is an *unknown* function of

t. This model assumes that, for subjects who at risk for administrative censoring at time t, there is no relationship between T and censoring just after t. Thus, administrative censoring is assumed to be non-informative.

Whatever be the censoring bias function, assumptions (1) and (2) form a non-parametric model for the distribution of the observed data. Thus, there is *no* evidence in the data to empirically distinguish between censoring bias functions. As a result,the dependence relation q is non-identifiable. We recommend fixing q and performing a sensitivity analysis. In the next subsection, we describe an interpretable parameterization of the censoring bias function, which will facilitate such a sensitivity analysis.

3.1 Parameterization of Censoring Bias Function

To facilitate our sensitivity analysis approach, it is helpful to use a parameterized form $q(t, T; \boldsymbol{\beta})$ for the censoring bias function, where $\boldsymbol{\beta}$ is a parameter vector that we will vary (not estimate) and satisfies the restriction that $\boldsymbol{\beta} = 0$ implies $q(t, T; \boldsymbol{\beta}) = 0$. We impose this latter restriction so that $\boldsymbol{\beta} = 0$ corresponds to the assumption of non-informative censoring. It is also essential that $\boldsymbol{\beta}$ be chosen to be interpretable, so that a plausible range can be specified by subject matter experts. For example, a sensible parameterization could be

$$q(t, T; \boldsymbol{\beta}) = \alpha\{I(T < c^*)(T - t) + I(T = c^*)(\tau - t)\}/365 \tag{3}$$

where $\boldsymbol{\beta} = (\alpha, \tau)$ and $\tau > c^*$. The censoring bias parameter τ is meant to roughly represent the mean time to event for subjects who do not experience the event prior to c^*. The quantity $\exp(\alpha/365)$ is interpreted as the hazard ratio of withdrawing at time t between subjects who are at risk at time t, but differ by one day in their ultimate time of event (with τ as the proxy time to event for subjects whose time to event is longer than c^*). So, $\alpha > 0$ (< 0) implies that subjects with longer times to events are more (less) likely to be censored at any time t than subjects who would have shorter times to event. Note that this censoring bias function implies that a subject who would not experience the event prior to c^* has $\exp(\alpha(\tau - t)/365)$ times

the hazard of withdrawing at time t as compared to a subject who fails just after t. Together, the choice of α and τ indicate the degree to which subjects who would experience the event before and after time c^* are different than one another with respect to their risk of withdrawing prematurely.

In Figure 1, we illustrate how to interpret the parameter α, with $\tau = 730$. Figure 1a shows how the hazard ratio for being observed to be prematurely censored for subjects who would experience the event between t and 730 and whose difference between time to first seizure ranges from 0 to 500. We see that as the difference grows, the hazard ratio comparing subjects with shorter vs. longer times increases exponentially from 1. The figure shows these hazard ratio curves as α is decreased from 0.0 to -3.0. For example, if we compared two subjects who differed in time to first seizure by 90 days, then the hazard ratio would be $1.0, 1.1, 1.3, 1.5, 1.6, 1.9, 2.1$ for $\alpha = 0.0, -0.5, -1.0, -1.5, -2.0, -2.5, -3.0$, respectively. Figure 2a shows how the hazard ratio between a subject who would not fail through 500 days compares to subjects with varying times to first seizure from 0 to 500 days. We see as the time to first seizure increases, the hazard ratio decreases exponentially to 1.0. For example, if we compared a subject who would have a first seizure at 180 days to a subject who would not have failed at or before 500 days, then the hazard ratio would be $1.0, 2.1, 4.5, 9.6, 20.4, 43.3, 91.9$ for $\alpha = 0.0, -0.5, -1.0, -1.5, -2.0, -2.5, -3.0$, respectively.

4 One Sample Problem

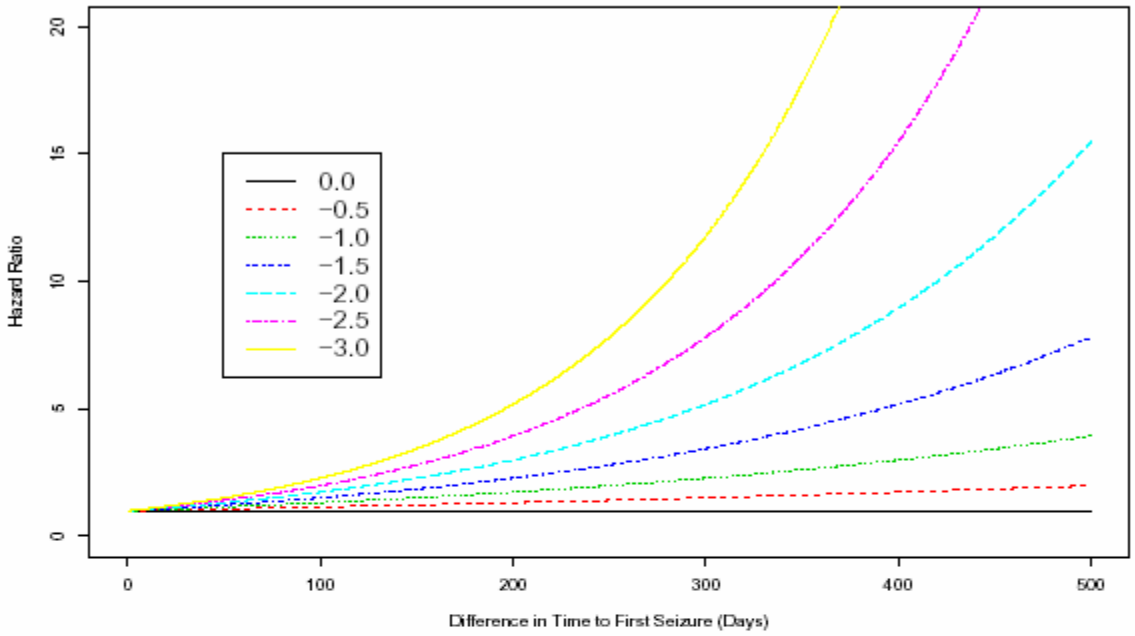
In the following subsections, we will require the following notation. Let $\Psi_1(t) = \int_0^t \psi_1(t)dt$, $\Psi_2 = \int_0^t \psi_2(t)dt$, and

$$\pi(t|T;\Psi_1,\Psi_2) = \prod_{0\leq s<t} [1 - I(T > s)\exp\{q(s,T)\}d\Psi_1(s)] \times [1 - d\Psi_2(s)]$$

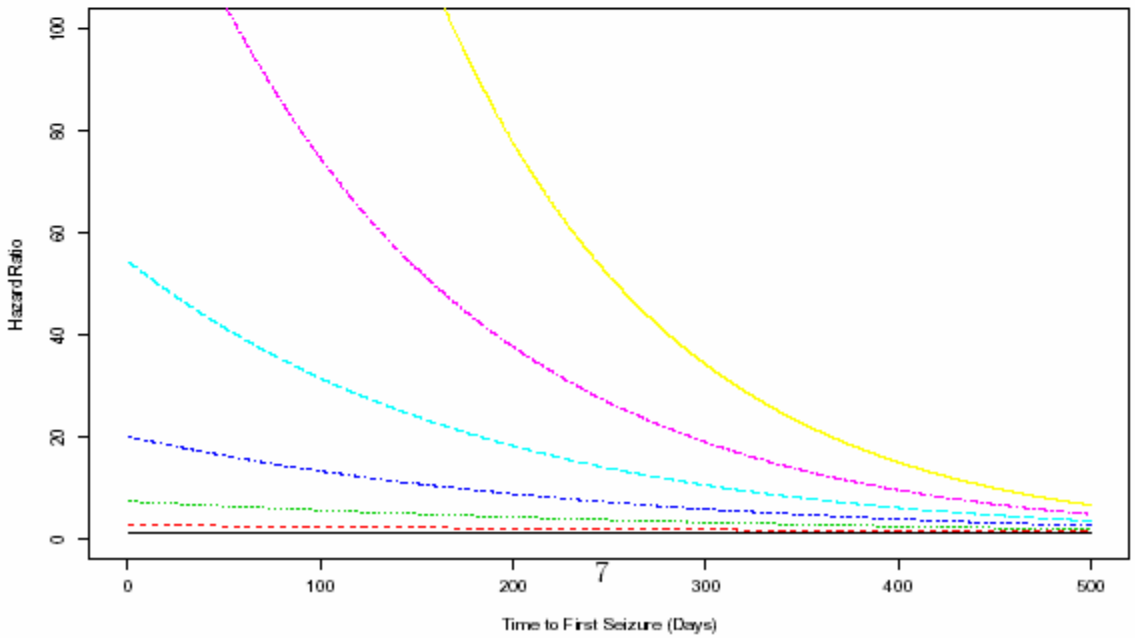
It is computationally useful to slightly perturb the dataset, so that there are no times at which failures, premature censoring, and administrative censoring are observed to occur

Figure 1: Interpretation of Censoring Bias Parameters

(a) Hazard ratio for being observed to be prematurely censored for subjects with varying differences between time to first seizure (x-axis) and α



(b) Hazard ratio for being observed to be prematurely censored for subjects who would not fail before 500 days as comparing to subjects with varying times of first seizure (x-axis) and varying $\alpha(\tau = 2.0)$



simultaneously. At the same time, we also want to properly maintain the risk sets in estimating $\Psi_1(\cdot)$, $\Psi_2(\cdot)$, and $S(\cdot)$. This is accomplished by letting (*i*) $c^* = c^* + 3\epsilon$, (*ii*) $\Delta = 0$ if $X = c^*$, (*iii*) $X = X + \epsilon$ when $\Delta = 1$, and (*iv*) $X = X + 2\epsilon$ when $\Delta = 2$, where $0 < \epsilon < 1/3$, Because of the dataset re-configuration above, the sets of unique observed failures, premature censoring, and administrative censoring times will be disjoint.

4.1 Identifiability

The distribution of the time to first seizure and the functions Ψ_1 and Ψ_2 are identified because of the following identities:

$$\Psi_1(t) = \int_0^t \frac{-dP(X \geq s, \Delta = 1)}{E\left[\frac{I(\Delta=0)I(T>s)\exp\{q(s,T)\}\pi(s|T;\Psi_1,\Psi_2)}{\pi(T|T;\Psi_1,\Psi_2)}\right]} \quad (4)$$

$$\Psi_2(t) = \int_0^t \frac{-dP(X \geq s, \Delta = 2)}{E\left[\frac{I(\Delta=0)I(T>s)\pi(s|T;\Psi_1,\Psi_2)}{\pi(T|T;\Psi_1,\Psi_2)}\right]} \quad (5)$$

$$S(t) = E\left[\frac{I(\Delta = 0)I(T \geq t)}{\pi(T|T;\Psi_1,\Psi_2)}\right] / E\left[\frac{I(\Delta = 0)}{\pi(T|T;\Psi_1,\Psi_2)}\right] \quad (6)$$

can be shown to hold for all $t \in [0, c^*]$. The functions Ψ_1 and Ψ_2 are identifiable because Equations (4) and (5) depend only on the distribution of the observed data and they can be solved uniquely via backward recursion. Then, $S(t)$ is identified because the right hand side of (6) only depends on the distribution of the observed data and the functions Ψ_1 and Ψ_2 can be replaced by the solution from (4) and (5).

4.2 Estimation of Ψ_1 and Ψ_2

Given formulas (4) and (5), it is natural to estimate the functions Ψ_1 and Ψ_2 by replacing the $P(X \geq s, \Delta = j)$ by $\widehat{P}(X \geq s, \Delta = j) = \sum_{i=1}^n I(X_i \geq s, \Delta_i = j)/n$ for $j = 1, 2$; and replacing the expectation operator by its empirical counterpart (i.e., for a random variable Z, $E[Z]$ is estimated by $\widehat{E}[Z] = \sum_{i=1}^n Z_i/n$). So, our estimators of $\Psi_1(\cdot)$ and $\Psi_2(\cdot)$, $\widehat{\Psi}_1(\cdot)$ and $\widehat{\Psi}_2(\cdot)$, satisfy

the following system of equations:

$$\widehat{\Psi}_1(t) = \int_0^t \frac{-d\widehat{P}(X \geq s, \Delta = 1)}{\widehat{E}\left[\frac{I(\Delta=0)I(T>s)\exp\{q(s,T)\}\pi(s|T;\widehat{\Psi}_1,\widehat{\Psi}_2)}{\pi(T|T;\widehat{\Psi}_1,\widehat{\Psi}_2)}\right]} \quad (7)$$

$$\widehat{\Psi}_2(t) = \int_0^t \frac{-d\widehat{P}(X \geq s, \Delta = 2)}{\widehat{E}\left[\frac{I(\Delta=0)I(T>s)\pi(s|T;\widehat{\Psi}_1,\widehat{\Psi}_2)}{\pi(T|T;\widehat{\Psi}_1,\widehat{\Psi}_2)}\right]} \quad (8)$$

Now, (7) and (8) have a solution, which can be constructed as follows. First, $\widehat{\Psi}_1(t)$ and $\widehat{\Psi}_2(t)$ are step functions which jump at the unique observed premature and administrative censoring times, respectively. Let $\{C_{(1)}, \ldots, C_{(K)}\}$ be the set of K unique, ordered observed censoring times. Let $N_{1,(k)}$ and $N_{2,(k)}$ denote the number of premature and administratively censored observations at censoring time $C_{(k)}$. Note that when $N_{1,(k)} > 0$ then $N_{2,(k)} = 0$, and vice versa.

Now, we can write $\widehat{\Psi_1}(t) = \sum_{k=1}^K \widehat{\psi}_{1,k} I(C_{(k)} \leq t)$ and $\widehat{\Psi_2}(t) = \sum_{k=1}^K \widehat{\psi}_{2,k} I(C_{(k)} \leq t)$, where the jump sizes $\widehat{\psi}_{1,k}$ and $\psi_{2,k}$ are found by the following procedure:

1. Set $k = K$.

2. If $N_{1,(k)} > 0$, then $\widehat{\psi}_{2,k} = 0$ and solve

$$\widehat{\psi}_{1,k} = \frac{N_{1,(k)}}{\sum_{i=1}^n \frac{I(\Delta_i=0, X_i>C_{(k)})\exp\{q(C_{(k)},X_i)\}}{\prod_{j=k}^K (1-I(X_i>C_{(j)})\exp\{q(C_{(j)},X_i)\widehat{\psi}_{1,j})\times(1-\widehat{\psi}_{2,j})}};$$

   otherwise go to 3.

3. If $N_{2,(k)} > 0$, then $\widehat{\psi}_{1,k} = 0$ and solve

$$\widehat{\psi}_{2,k} = \frac{N_{2,(k)}}{\sum_{i=1}^n \frac{I(\Delta_i=0, X_i>C_{(k)})}{\prod_{j=k}^K (1-I(X_i>C_{(j)})\exp\{q(C_{(j)},X_i)\widehat{\psi}_{1,j})\times(1-\widehat{\psi}_{2,j})}}$$

4. Set $k = k - 1$. If $k = 0$ then stop; otherwise return to 2.

4.3 Estimation of Failure Time Distribution

Motivated by (6), our estimator of $S(t)$ is

$$\widehat{S}(t) = \widehat{E}\left[\frac{I(\Delta = 0)I(T \geq t)}{\pi(T|T;\widehat{\Psi}_1,\widehat{\Psi}_2)}\right] / \widehat{E}\left[\frac{I(\Delta = 0)}{\pi(T|T;\widehat{\Psi}_1,\widehat{\Psi}_2)}\right]$$

$$= \sum_{i=1}^{n} \left[\frac{I(\Delta_i = 0) I(X_i \geq t)}{\pi(X_i | X_i; \hat{\Psi}_1, \hat{\Psi}_2)} \right] / \sum_{i=1}^{n} \left[\frac{I(\Delta_i = 0)}{\pi(X_i | X_i; \hat{\Psi}_1, \hat{\Psi}_2)} \right] \quad (9)$$

This estimator is a step function, which jumps at the observed failure times. From $\widehat{S}(t)$, we can derive the associated step-function estimators for the cumulative distribution function, $F(t)$ and the cumulative hazard function $\Lambda(t)$, as follows:

$$\widehat{F}(t) = 1 - \widehat{S}(t+) \quad (10)$$

$$\widehat{\Lambda}(t) = \int_0^t d\widehat{\Lambda}(s) \quad (11)$$

where

$$d\widehat{\Lambda}(t) = \frac{\widehat{S}(t-) - \widehat{S}(t)}{\widehat{S}(t)} \quad (12)$$

It is important to point out that when $q(t, T) = 0$, then our estimator of the distribution of time to failure is identically equivalent to the Kaplan-Meier estimator (the result of the primary analysis, assuming non-informative censoring). When $q(t, T) = -\infty$, then our estimator is equivalent to the Kaplan-Meier estimator, where each prematurely censored observation is treated as a failure occurring at the next observed failure time. When $q(t, T) = +\infty$, then our estimator is equivalent to Kaplan-Meier estimator, where each prematurely censored observation is treated as a "failure" occurring at c^*.

4.4 Estimation of Other Quantities

4.4.1 Sub-distribution Functions

Estimators for the sub-distribution functions for premature and administrative censoring given failure time T are, respectively,

$$\widehat{F}_1(t|T) = \int_0^t \left\{ \prod_{s \leq u} [1 - \exp\{q(s, T) d\widehat{\Lambda}_1(s)\} [1 - d\widehat{\Lambda}_2(s)] \right\} \exp\{q(u, T)\} d\widehat{\Lambda}_1(u) \quad (13)$$

$$\widehat{F}_2(t|T) = \int_0^t \left\{ \prod_{s \leq u} [1 - \exp\{q(s, T) d\widehat{\Lambda}_1(s)\} [1 - d\widehat{\Lambda}_2(s)] \right\} d\widehat{\Lambda}_2(u) \quad (14)$$

for $t \leq T$. From these equations, estimators for the probabilities that $\Delta = 1$ and $\Delta = 2$ given T are, respectively, $\widehat{F}_1(T|T)$ and $\widehat{F}_2(T|T)$.

4.4.2 Distribution of Failure given Premature Censoring Time

Using Bayes' rule, we can estimate the distribution of failure given that a subject dropped out prematurely at time t. Specifically,

$$d\widehat{F}(s|X=t,\Delta=1)=\frac{d\widehat{F}_1(t|s)d\widehat{F}(s)}{\int_0^s d\widehat{F}_1(u|s)d\widehat{F}(u)}$$

This conditional distribution is very helpful in understanding the implications for varying α and τ.

5 Two Sample Problem

In this section, quantities superscripted by (1) and (2) denote the low and high dose groups, respectively.

5.1 Logrank-Type Statistic

Under the null hypothesis of no treatment effect on the time to failure ($H_0 : \Lambda^{(1)}(t) = \Lambda^{(2)(t)}$ for all $t \in [0, c^*]$),

$$\int_0^{c^*} \frac{P[X^{(1)} \geq t]P[X^{(2)} \geq t]}{P[X^{(1)} \geq t] + P[X^{(2)} \geq t]}\{d\Lambda^{(1)}(t) - d\Lambda^{(2)}(t)\} = 0.$$

When $q^{(1)}(t,T) = q^{(2)}(t,T) = 0$ (i.e., non-informative censoring in both treatment groups) , the numerator of the logrank statistic is proportional to

$$\int_0^{c^*} \frac{Y^{(1)}(t)Y^{(2)}(t)}{Y^{(1)}(t) + Y^{(2)}(t)}\{d\bar{\Lambda}^{(1)}(t) - d\bar{\Lambda}^{(2)}(t)\},$$

where $Y^{(j)}(t)$ equals the number of subjects at-risk at time t in treatment group j and $\bar{\Lambda}^{(j)}(\cdot)$, $j = 1, 2$, are the treatment-specific Nelson-Aalen estimators. Under H_0, this statistic should be close to zero. If this statistic is "sufficiently" large in absolute value then there is "evidence" against the null hypothesis. P-values are constructed using large-sample normal theory.

For fixed $q^{(1)}(t,T)$ and $q^{(2)}(t,T)$, we use the statistic

$$LR = \int_0^{c^*} \frac{Y^{(1)}(t)Y^{(2)}(t)}{Y^{(1)}(t) + Y^{(2)}(t)}\{d\widehat{\Lambda}^{(1)}(t) - d\widehat{\Lambda}^{(2)}(t)\}, \tag{15}$$

where the estimators of the cumulative hazard functions are developed in Section 4. In general, large sample theory can be developed (using similar techniques in Scharfstein and Robins, 2002), but for current purposes, it is complicated to implement. In the next subsection, we develop a parametric bootstrap technique for computing the p-values. This approach should have better finite sample properties than relying on large-sample normal theory.

5.2 P-Values

To compute the p-value, we condition on the observed treatment-specific failure, premature censoring, and administrative times as well as the number of subjects assigned to each treatment group. Such conditioning was inspired by the recent work of Heinz, Gnant, and Schemper (2003).

Under the null hypothesis, an estimator for the distribution of failure is given by

$$\hat{F}^{H_0}(t) = \hat{F}^{(1)}(t)\frac{n^{(1)}}{n^{(1)}+n^{(2)}} + \hat{F}^{(2)}(t)\frac{n^{(2)}}{n^{(1)}+n^{(2)}} \tag{16}$$

Let B be a large number, say 10,000. To compute an approximation to the reference distribution of LR under the null hypothesis and the associated p-value, we use the following parametric bootstrap algorithm.

1. Set $b = 1$.
2. Set $i = 1$.
3. Draw T from $\hat{F}^{H_0}(\cdot)$.
4. If $i \leq N^{(1)}$, set $j = 1$; otherwise set $j = 2$.
5. Draw Δ from a multinomial (levels 0, 1, 2) with cell probabilities $1-\hat{F}_1^{(j)}(T|T)-\hat{F}_2^{(j)}(T|T)$, $\hat{F}_1^{(j)}(T|T)$, $\hat{F}_2^{(j)}(T|T)$.
6. If $\Delta = 0$, set $X = T$. If $\Delta = 1$, draw X from $\hat{F}_1^{(j)}(\cdot|T)/\hat{F}_1^{(j)}(T|T)$. If $\Delta = 2$, draw X from $\hat{F}_2^{(j)}(\cdot|T)/\hat{F}_2^{(j)}(T|T)$.

7. If $i = N^{(1)} + N^{(2)}$, then go to 8; otherwise set i=i+1 and go to 3.

8. Compute LR_b in (13). If $b < B$, then set $b = b + 1$ and go to 2; otherwise stop and go to 9.

9. The distribution of LR_b's is an approximation to the reference distribution of LR under H_0, and a two-sided p-value is computed as the proportion of $|LR_b|$'s greater than or equal to $|LR|$.

6 Conservative Estimator of $\boldsymbol{\beta}$ Using Auxiliary Data

In TOPMAT-EPM-105, many subjects who prematurely withdrew from treatment continued to have follow-up data. For this subset of patients, we define $C_1^\dagger$ as the withdrawal time, which is fully observed. Let $C_2^\dagger$ denote administrative censoring time, and $T^\dagger$ denote the minimum of time of first seizure after $C_1^\dagger$ and c^*. If a subject withdraws prematurely after $C_1^\dagger$ but prior to c^*, then we consider $T^\dagger$ as having occurred at that time. Note that $T^\dagger$ and $C_2^\dagger$ are greater than or equal to $C_1^\dagger$.

Due to the presence of administrative censoring, the observed data for an individual in this cohort is $O^\dagger = (C_1^\dagger, X^\dagger, \Delta^\dagger)$, where $X^\dagger = \min(C_2^\dagger, T^\dagger)$ and $\Delta^\dagger = 1$ if $T^\dagger$ is observed and 0, otherwise. We assume that we observed $n^\dagger$ copies of $O^\dagger$, $\boldsymbol{O}^\dagger = \{O_i^\dagger = (C_{1,i}^\dagger, X_i^\dagger, \Delta^\dagger) : i = 1, \ldots, n^\dagger\}$.

It is important to note that this cohort of subjects has more frequent seizures than those in TOPMAT-EPM-106 and thus the relationship between the treatment withdrawal time and time of next seizure after withdrawal should be stronger than the relationship between premature withdrawal and time of first seizure in TOPMAT-EPM-106.

Formally, we specify a hazard model for $C_1^\dagger$ given $T^\dagger$. In particular, we let

$$\lambda_{C_1^\dagger}(t|T^\dagger) = \lambda_0(t) \exp\{q(t, T^\dagger; \boldsymbol{\beta}^\dagger)\} \quad t < T^\dagger$$

where $q(t, T^\dagger; \boldsymbol{\beta})$ is defined as above.

If $T^\dagger$ were observed on all subjects, we could use the following unbiased, partial-likelihood estimating function to estimate $\boldsymbol{\beta}^*$

$$\int_0^T \{q'(t,T^\dagger;\boldsymbol{\beta}^*) - \frac{E[q'(t,T^\dagger;\boldsymbol{\beta}^*)\exp\{q(t,T^\dagger;\boldsymbol{\beta}^*)\}I(C_1^\dagger \geq t)]}{E[\exp\{q(t,T^\dagger;\boldsymbol{\beta}^*)\}I(C_1^\dagger \geq t)]}\} dN_{C_1^\dagger}(t)$$

where $q'(t,T^\dagger;\boldsymbol{\beta}^\dagger)$ is the derivative of $q(t,T^\dagger;\boldsymbol{\beta})$ with respect $\boldsymbol{\beta}$ evaluated at $\boldsymbol{\beta}^\dagger$, $N_{C_1^\dagger}(t) = I(C_1^\dagger \leq t)$ is the counting process for $C_1^\dagger$.

Since T is not observed on all subjects, the above estimating function is not necessarily observable. However, we can define the following observable estimating function which can be shown to have mean zero:

$$\int_0^{c^*} \frac{1}{\pi(u)} \int_0^u \{q'(t,T^\dagger;\boldsymbol{\beta}^\dagger) - \frac{E[\frac{\Delta}{\pi(T^\dagger)}q'(t,T^\dagger;\boldsymbol{\beta}^\dagger)\exp\{q(t,T^\dagger;\boldsymbol{\beta}^\dagger)\}I(C_1^\dagger \geq t)]}{E[\frac{\Delta}{\pi(T^\dagger)}\exp\{q(t,T^\dagger;\boldsymbol{\beta}^\dagger)\}I(C_1^\dagger \geq t)]}\} dN_{C_1^\dagger}(t) dN_{X^\dagger}(u)$$

where $N_{X^\dagger}(u) = I(X^\dagger \leq u, \Delta = 1)$ is the counting process for observing $T^\dagger$ and $\pi(u) = P(C_2^\dagger \geq u)$.

Thus, it is natural to estimate $\boldsymbol{\beta}^\dagger$ by $\widehat{\boldsymbol{\beta}}^\dagger$ as the solution to

$$E_n\left[\int_0^{c^*} \frac{1}{\hat{\pi}(u)} \int_0^u \left\{q'(t,T^\dagger;\boldsymbol{\beta}^\dagger) - \frac{E_n[\frac{\Delta^\dagger}{\hat{\pi}(T^\dagger)}q'(t,T^\dagger;\boldsymbol{\beta}^\dagger)\exp\{q(t,T^\dagger;\boldsymbol{\beta}^\dagger)\}I(C_1^\dagger \geq t)]}{E_n[\frac{\Delta^\dagger}{\hat{\pi}(T^\dagger)}\exp\{q(t,T^\dagger;\boldsymbol{\beta}^\dagger)\}I(C_1^\dagger \geq t)]}\right\} dN_{C_1^\dagger}(t) dN_{X^\dagger}(u)\right] = 0$$

where $\hat{\pi}(u)$ is the Kaplan-Meier estimator for $C_2^\dagger$ based on data $(X^\dagger, \Delta^\dagger)$. The above equation can be written as follows:

$$U(\boldsymbol{O}^\dagger;\boldsymbol{\beta}^\dagger) = \sum_{i=1}^n \frac{\Delta_i^\dagger}{\hat{\pi}(X_i^\dagger)} \left\{q'(C_{1,i}^\dagger, X_i^\dagger;\boldsymbol{\beta}^\dagger) - \frac{\sum_{j=1}^n \frac{\Delta_j^\dagger}{\hat{pi}(X_j^\dagger)} q'(C_{1,i}^\dagger, X_j^\dagger)\exp\{q(C_{1,i}^\dagger, X_j^\dagger;\boldsymbol{\beta}^\dagger)\}I(C_{1,j}^\dagger \geq C_{1,i}^\dagger)}{\sum_{j=1}^n \frac{\Delta_j^\dagger}{\hat{\pi}(X_j^\dagger)}\exp\{q(C_{1,i}^\dagger, X_j^\dagger;\boldsymbol{\beta}^\dagger)\}I(C_{1,j}^\dagger \geq C_{1,i}^\dagger)}\right\} = 0$$

The estimator can be found by minimizing the quadratic form $U(\boldsymbol{O}^\dagger;\boldsymbol{\beta}^\dagger)'U(\boldsymbol{O}^\dagger;\boldsymbol{\beta}^\dagger)$ subject to the constraint that $\tau^\dagger > c^*$.

To find a confidence region for $\boldsymbol{\beta}^\dagger$, one can use non-parametric bootstrap. That is, construct B new datasets of size $n^\dagger$, where each dataset is constructed by randomly drawing an individual record from the original dataset with replacement. For each dataset, estimate $\boldsymbol{\beta}^\dagger$. From the

B datasets, estimate the joint density using a bivariate non-parametric kernel smoother and then find the contour of this density that contains 95% of the bootstrapped estimates. This confidence region will be conservative when applied to TOPMAT-EPM-106.

References

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Scharfstein, D. and Robins, J. (2002). Estimation of the failure time distribution in the presence of informative censoring. *Biometrika* **89**, 617–634.

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Kun He
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OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	20-505/S-018 and 20-844/S-015
Drug Name:	Topamax ® (topiramate)
Indication:	Seizures
Sponsor:	Johnson & Johnson
Date:	10/29/2002 (Supplement) 7/31/2003 (Amendment to Supplement)
Review Priority:	Standard
Biometrics Division:	Biometrics I (HFD 710)
Statistical Reviewer:	Kun He
Concurring Reviewers:	Kun Jin, , Ph.D.,Team Leader Kooros Mahjoob, Ph.D., Deputy Director
Medical Division:	Neuropharmacological Drug Products (HFD 120)
Clinical Team:	Howard Chazin, M.D., Ph.D., Clinical Reviewer John Feeney, M.D., Team Leader Russell Katz, M.D., Director
Project Manager:	Jacqueline Ware, R. Ph.

Keywords: log-rank test, seizure, topamax

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Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

Although the data and analyses from the current submission achieved statistical significance, there are serious concerns about the interpretation of the results given the large number of unbalanced withdrawals.

1.2 Brief Overview of Clinical Studies

TOPMAT-EPMN-106 was a randomized, double-blind, parallel group study, conducted in USA, Canada, Europe and Latin America. Its primary objective was to compare the safety and efficacy of 2 doses of topiramate (50 mg/day and 400 mg/day) as monotherapy in pediatric and adult subjects with newly diagnosed (within 3 months) epilepsy characterized by partial-onset or generalized seizures or with recurrent epilepsy while off of AEDs. A total of 487 were enrolled resulting 471 randomized with 234 in TPM 50, 236 in TPM 400, and 1 lost to follow-up. There were 4 phases in this study: baseline, open-treatment, double-blind, and long-term extension. The primary efficacy endpoint was the time to first partial onset or generalized seizure during the double-blind phase.

1.3 Statistical Issues and Findings

The primary analysis is log-rank test which gave p-value of .0002 where there were 90 (38%) seizure events out of 234 in TPM 50, and 49 (21%) seizure events out of 236 in TPM 400 groups, respectively.

Unfortunately, log-rank test of all-cause analysis gave p-value of .5706 due to unbalanced withdrawals between two treatment groups, 39 (17%) out of 234 in TPM 50, and 75 (32%) out of 236 in TPM 400, respectively. If the adverse event is counted as failed, there are 103 and 89 failed in TPM 50 and 400 groups, respectively. The log-rank test gave p-value of .2482.

Since all-cause analysis and adverse event as failed are not statistically nominally significant, one issue needs to be addressed is whether there might be potential bias caused by the unbalanced withdrawals, because more withdrawals would have less seizure events. Unless there are data to support that the unbalanced withdrawals wouldn't introduce any bias, one should interpret the result with caution.

The sponsor addressed the issue of withdrawals mainly by simulation, after the Agency informed the issue to the sponsor. Results from "Resampling from Existing Populations" are uninterpretable because it is not appropriate to use a non-withdrawal to replace a withdrawal, and results from "Sample Replacement Using Simulated Data" are unverifiable due to unverifiable simulation

assumption.

The conclusion is that although the data and analyses from the current submission achieved statistical significance, there are serious concerns about the interpretation of the results given the large number of unbalanced withdrawals.

2. Introduction

2.1 Overview

The current submission, J&JPRD's monotherapy program, consists of one pivotal Study PRI/TOP-INT-28 (TOPMAT-EPMN-106) and three supportive studies YI, TOPMAT-EPMN-104 and TOPMAT-EPMN-105. In this review, only TOPMAT-EPMN-106 will be discussed.

TOPMAT-EPMN-106 was a randomized, double-blind, parallel group study, conducted in USA, Canada, Europe and Latin America. Its primary objective was to compare the safety and efficacy of 2 doses of topiramate (50 mg/day and 400 mg/day) as monotherapy in pediatric and adult subjects with newly diagnosed (within 3 months) epilepsy characterized by partial-onset or generalized seizures or with recurrent epilepsy while off of AEDs. A total of 487 were enrolled resulting 471 randomized with 234 in TPM 50, 236 in TPM 400, and 1 lost to follow-up. There were 4 phases in this study: baseline, open-treatment, double-blind, and long-term extension. The primary efficacy endpoint was the time to first partial onset or generalized seizure during the double-blind phase.

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:

http://edr/loadfile.asp?PATH=FILE://\\CDSESUB1\N20505\S_018\2002-10-29&DOCUMENT_ID=2373973&APPL_NO=020505&APPL_TYPE=N

http://edr/loadfile.asp?PATH=FILE://\\CDSESUB1\N20505\S_018\2003-04-04&DOCUMENT_ID=2426913&APPL_NO=020505&APPL_TYPE=N

http://edr/loadfile.asp?PATH=FILE://\\CDSESUB1\N20844\S_015\2003-04-04&DOCUMENT_ID=2426917&APPL_NO=020844&APPL_TYPE=N

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Objective of Study PRI/TOP-INT-28 (TOPMAT-EPMN-106)

The objective of this study was to compare the safety and efficacy of 2 doses of topiramate as monotherapy in pediatric and adult subjects with newly diagnosed (within 3 months) epilepsy characterized by partial-onset or generalized seizures or with recurrent epilepsy while off of AEDs.

3.1.2 Study Design

This randomized, double-blind, parallel-group, international (study compared the safety and efficacy of 2 doses of topiramate as monotherapy for the treatment of newly diagnosed or recurrent epilepsy. The doses chosen to demonstrate a dose-response relationship were hypothesized to be a low, minimally efficacious dose (50 mg/day) versus a high, presumably fully efficacious and generally tolerable higher dose (400 mg/day). Subjects must have weighed at least 25 kg and have had, within 3 months of the first study visit, a new diagnosis of epilepsy (partial-onset or generalized) or a diagnosis of recurrent epilepsy while not taking AEDs.

There were 4 phases in this study: baseline, open-treatment, double-blind, and long-term extension. Only the data collected through the end of the double-blind phase of the study are included in this study report.

The 3-month retrospective baseline phase allowed for the assessment of seizure frequency and AED use prior to study entry. Both the new diagnosis of epilepsy and the diagnosis of recurrent epilepsy (relapse of epilepsy) were established during the 3-month retrospective baseline phase. Seizure history recorded prior to this phase could be used by the investigators to help establish the appropriate diagnosis. All eligible subjects must have had either 1 or 2 well-documented seizures during the retrospective baseline phase. Eligible subjects entered the open-treatment phase within 14 days after screening procedures were performed.

The open-treatment phase was designed to ascertain the ability of each individual subject to tolerate the study medication and to allow for discontinuation of any AED therapy used for temporary or emergency purposes. All subjects who met the entry criteria received topiramate 25 mg/day for 7 days. Subjects were to have no more than 1 seizure between the screening visit and the end of the open-treatment phase. By the end of this phase, subjects who had no unacceptable tolerability problems were randomly assigned to 1 of the 2 topiramate dosage groups, 50 mg/day or 400 mg/day. Subjects who were taking an AED at any time during the baseline phase were required to discontinue this AED prior to randomization.

The double-blind phase was divided into 2 periods, titration and stabilization. The titration period

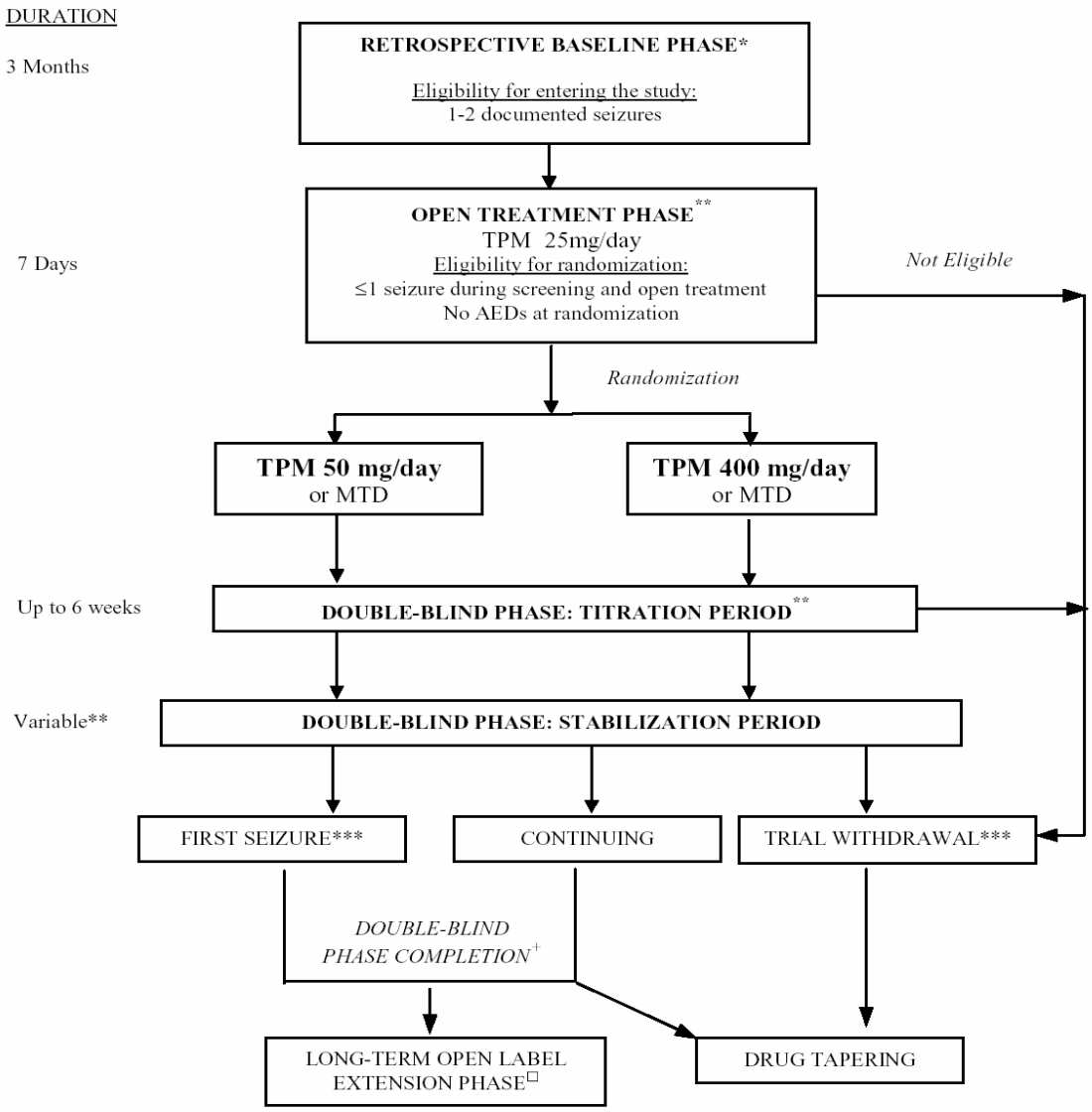
lasted up to 42 days. Topiramate was titrated to either the assigned dose or the maximum tolerated dose. If a subject experienced unacceptable difficulty tolerating topiramate during the initial 21 days of this period, the subject was withdrawn from the study. If a subject experienced tolerability difficulties after Day 21, the dose may have been reduced at the discretion of the investigator according to the recommended dose reduction schedule. A total of 2 50-mg dose reductions were allowed. After a dose reduction, the dose of topiramate could not be increased.

The stabilization period followed titration. During stabilization, the dose of study medication was to remain constant, if possible. Dose reductions were allowed for subjects who had difficulty maintaining the assigned dose (or the maximum tolerated dose). Following dose reduction during the stabilization period, the topiramate dose was not to be increased. Dose reductions for subjects randomized to the 400 mg/day dose group were to occur in 50 mg/day increments; the reduced dose could not be lower than the dose of the titration week prior to the maximum dose achieved during titration. One dose reduction of 25 mg/day was allowed for subjects randomized to the 50 mg/day dose group.

Subjects remained in the double-blind phase until they experienced a first partial-onset or generalized tonic-clonic seizure, until termination of the double-blind phase by the sponsor (6 months after randomization of the last subject), or until withdrawal for protocol-specified reasons, which included adverse events, subject choice, and lost to follow-up.

Subjects who completed the double-blind phase either at the time of their first seizure or at the time of termination of the double-blind phase by the sponsor could continue to receive topiramate in the long-term extension phase. During blinded transition, which lasted up to 49 days, the dosage of topiramate received by the subjects in the topiramate 50 mg/day group was titrated to 400 mg/day or the maximum tolerated dose; subjects in the topiramate 400 mg/day group continued to receive the same topiramate dose as during double-blind phase. Blinded transition was followed by open-label treatment, during which the dose of topiramate was adjusted according to individual tolerability and efficacy, and other AEDs were added if clinically indicated. The maximum daily dose of topiramate was not to exceed 1,600 mg/day for subjects 14 years and older. For subjects less than 14 years of age, the maximum daily dose was 24 mg/kg but was not to exceed 1,600 mg/day. Subjects could continue in the long-term extension phase until study termination by the sponsor or until withdrawal. A diagrammatic representation of the study design is provided in next figure (adapted from Study Report Figure 1).

Figure 1: Study Design for Study TOPMAT-EPMN-106



NOTE: Dose reductions were allowed for subjects who had difficulty reaching or maintaining their assigned dose or maximu tolerated dose. Following dose reduction during the stabilization period, topiramate dose was not to be increased again.

* The first clinic visit occurred up to 14 days prior to starting the open-treatment phase (between Days -21 and -8). At that ti inclusion/exclusion criteria were reviewed and screening procedures were performed.

** Subjects who experienced significant tolerability problems during the open-treatment phase were not eligible for randomization; subjects who experienced significant tolerability problems during the first 21 days of the double-blind phas were withdrawn from the study.

*** Subjects remained in the double-blind phase of the study until i) the subject experienced a first seizure (partial onset or generalized tonic-clonic seizure); ii) the double-blind phase completed; or iii) the subject withdrew from the trial for reaso prespecified in the protocol (adverse events, subject choice, and lost to follow-up).

\+ The double-blind phase was terminated by the sponsor 6 months after the last subject was randomized; enrollment into the study continued until 108 subjects experienced a first seizure.

□ Subjects who experienced a first seizure during the double-blind phase, or who were active in the study at the time the doul blind phase completed, could enter the long-term extension phase.

The study was conducted in US, Canada, Europe, and Latin America. To accommodate various local regulatory requirements, local amendments were issued to the international study protocol TOPMAT-EPMN-106. The administrative changes in the inclusion criteria implemented according to local requirements in Norway included a requirement that eligible subjects be at least 14 years of age; in France and Italy, statements were added regarding the use of hormonal contraception and restrictions on eligibility of postmenopausal and premenarchal female subjects.

The study conduct was initiated based on the original study protocol dated 13 August 1999. The protocol was subsequently amended 6 times; the amendments contained various updates and clarifications to the protocol, as well as modifications to the inclusion/exclusion criteria, study evaluations, including additional laboratory tests, and statistical analysis. The key changes in study design and conduct were as follows.

Protocol Amendment 1, dated 21 January 2000, contained the modified definition of the first seizure as only partial-onset or generalized tonic-clonic seizure and a modified procedure for dose reductions during double-blind phase that excluded the possibility of rechallenge (i.e., of upward titration following dose reduction). Entry criteria were modified so as to i) clarify that the diagnosis of epilepsy, as well as the seizures leading to that diagnosis, were to have occurred during the 3-month
retrospective period, ii) exclude subjects with only myoclonic seizures, and iii) remove clinically significant electrocardiographic abnormalities from the list of exclusion criteria. The purpose of the physical examinations and vital signs measurements at the final follow-up visit was clarified to indicate that they were intended only to follow up previously noted abnormalities. It was also clarified that visual field testing was to be performed only in subjects 12 years of age and older. At the time this amendment went into effect, 33 subjects were enrolled in the study.

Protocol Amendment 2, dated 13 March 2000, contained clarifications to the entry criteria such that prior use of an AED must have occurred only for emergency or temporary use, and that subjects who had uncontrolled epilepsy while taking AEDs were not eligible for enrollment. It was also clarified that sample size calculation was based on the number of subjects with a failure event (108 subjects with a first seizure) needed to achieve sufficient power to demonstrate a significant difference between the treatment groups, and that randomization was to stop when 108 subjects experienced first seizures. The following laboratory tests were added to the chemistry panel: gamma glutamyl transferase (GGT), lactic dehydrogenase (LDH), phosphorus, and uric acid. At the time this amendment went into effect, 63 subjects were enrolled in the study.

Protocol Amendment 3, dated 19 October 2000, increased the duration of the double-blind phase from 2 months to 4 months after the randomization of the last subject. At the time this amendment went into effect, 263 subjects were enrolled in the study.

Protocol Amendment 4, dated 03 May 2001, changed the estimated sample size from approximately 330 to approximately 500 to 560. This estimate of the sample size required to yield 108 first seizures

was updated for administrative reasons, based on the review of blinded seizure data showing that more subjects would have to be enrolled until 108 first seizures have occurred. At the time this amendment went into effect, 430 subjects were enrolled in the study.

Protocol Amendment 5, dated 05 September 2001, increased the duration of the double-blind phase from 4 months to 6 months after the randomization of the last subject. This was motivated, in part, by the new European Union guidance document for AED trials. Analysis of the 6-month seizure-free rate was added to the statistical analysis plan. In addition, quarterly visits for clinical laboratory tests (liver function tests) and serum pregnancy tests were added to the protocol at the request of the FDA. At the time this amendment went into effect, all 487 subjects were enrolled in the study.

Finally, Protocol Amendment 6, dated 04 October 2001, modified study evaluations by adding a chemistry panel at the third visit of the stabilization phase (Visit 8).

Reviewer's remark: In IND review, the Agency pointed out the issue of potential bias to the applicant: "The results of the log-rank test for the time to first seizure may be biased and difficult to interpret if a substantial number of subjects drop out due to toxicity. Please address this issue." The applicant indicated that "we do not foresee this as being an issue. Based on the results of previously conducted monotherapy trials, we do not expect to see a high number of dropouts."

3.1.3 Efficacy Measures

Subjects or their caregivers recorded the date and type of each seizure that occurred in their seizure diaries. A seizure required clinical verification by the investigator. Upon experiencing a seizure, each subject was to contact the investigator, who then evaluated the event in terms of consistency with
epileptic partial onset or generalized tonic-clonic seizures. Verification of each clinical seizure was signed by the investigators, and forms were faxed to the sponsor. The investigator also classified each seizure type described in the diary before the data were recorded on the subject's CRF. Seizures were coded according to International League Against Epilepsy (ILAE) classification (see Appendix 1.1 for details).

The primary efficacy endpoint was the time to first partial onset or generalized seizure during the double-blind phase (excluding taper).

3.1.4 Statistical Analysis Plan

The intent-to-treat population for statistical analysis includes all subjects who enter the core double-blind phase.

The primary efficacy variable is time to first seizure (partial onset or generalized tonic-clonic seizure) during the core double-blind phase (excluding taper). Subjects who do not have seizures

before the end of core double-blind phase are considered censored. Survival analysis techniques will be utilized. Kaplan-Meier estimates for the distribution curves of time of retention will be obtained. A log-rank test will be used to determine the statistical significance between the distribution curves. The significant level for the Log-rank test is 0.05, two sided. Six-month seizure free rate will be analyzed. No interim analysis will be performed. Secondary efficacy analyses will use Cox proportional hazards model to assess the effect of covariates, such as demographic baseline variables.

The sample size calculation is based on the results from previous studies. Due to the fact that the power of the log rank test is driven by the number of failures (number of subjects with a seizure), the time to stop the enrollment of the study is when 108 subjects have seizures during the core double-blind phase. The core double-blind phase will conclude 6 months after the last subject is randomized. The enrollment period is expected to be 14 months, if approximately 24 subjects are enrolled monthly. At the time the enrollment stops, we anticipate there will be about 46 and 62 subjects to have seizures for the high and low dose groups, respectively. The sample size calculation was based on the following assumptions: (1) failure is exponentially distributed with the percentages of seizure free subjects after 16 months of 45% and 30% in the high and low dose groups, respectively; (2) uniform subject entry into the study during accrual period; and (3) loss to follow-up are exponentially distributed with a 15% non-treatment related cumulative dropout rate in each dose group at 16 months. This plan has 92.2% power to detect that the high dose of topiramate is significantly superior to the low dose group at the alpha level of 0.05 (two-sided), or 0.025 (one-sided). Under the assumptions in this paragraph the expected total number of subjects to be enrolled in the study is 330. The actual number of subjects randomized will vary depending on how the actual seizure rate differs from the assumptions.

3.1.5 Study Population

A total of 487 adults and children with a recent (within 3 months) diagnosis of epilepsy or with recurrent epilepsy while off of AEDs who experienced either 1 or 2 well-documented seizures during the 3-month retrospective baseline were enrolled in this trial. Subjects who experienced unacceptable
tolerability problems while receiving topiramate 25 mg/day during the open treatment phase were not eligible for randomization.

As specified in the protocol, the study enrollment was stopped when 108 first seizures were reported. At this time, 462 subjects were enrolled in the study; of those, 440 were randomized. In addition, 25 subjects who were in screening at the time of the 108th first seizure were allowed to enter the study before the enrollment was stopped by the sponsor. As a result, 487 subjects entered the open treatment phase of the study based on their screening evaluations and seizure data collected for the retrospective baseline phase. Of the 487 subjects who entered the trial, 16 withdrew during the open-treatment phase. The remaining 471 subjects were randomly assigned to receive either topiramate 50 mg/day (234 subjects) or topiramate 400 mg/day (237 subjects). Subject 566003, randomized to

topiramate 400 mg/day group, did not have any study visits after randomization and was lost to follow-up;this subject was not included in the intent-to-treat analysis. The remaining 470 subjects were dispensed study medication and had at least 1 study visit after randomization; these subjects were included in the intent-to-treat analysis. The safety analyses in this study report are also based on the intent-to-treat population.

A total of 16 subjects withdrew from the open-treatment phase of the study prior to randomization. Of these, 5 subjects were dispensed the study medication, but did not provide any dosing information. Four of these subjects were lost to follow-up, and 1 withdrew due to subject choice. Of those subjects who received topiramate 25 mg/day (duration of exposure ranging between 3 and 10 days), 4 withdrew due to adverse events and 2 withdrew due to subject choice; 5 subjects were withdrawn for other reasons, including seizures that did not satisfy the protocol-specified eligibility criteria (3 subjects), as well as worsening epilepsy and noncompliance (1 subject each).

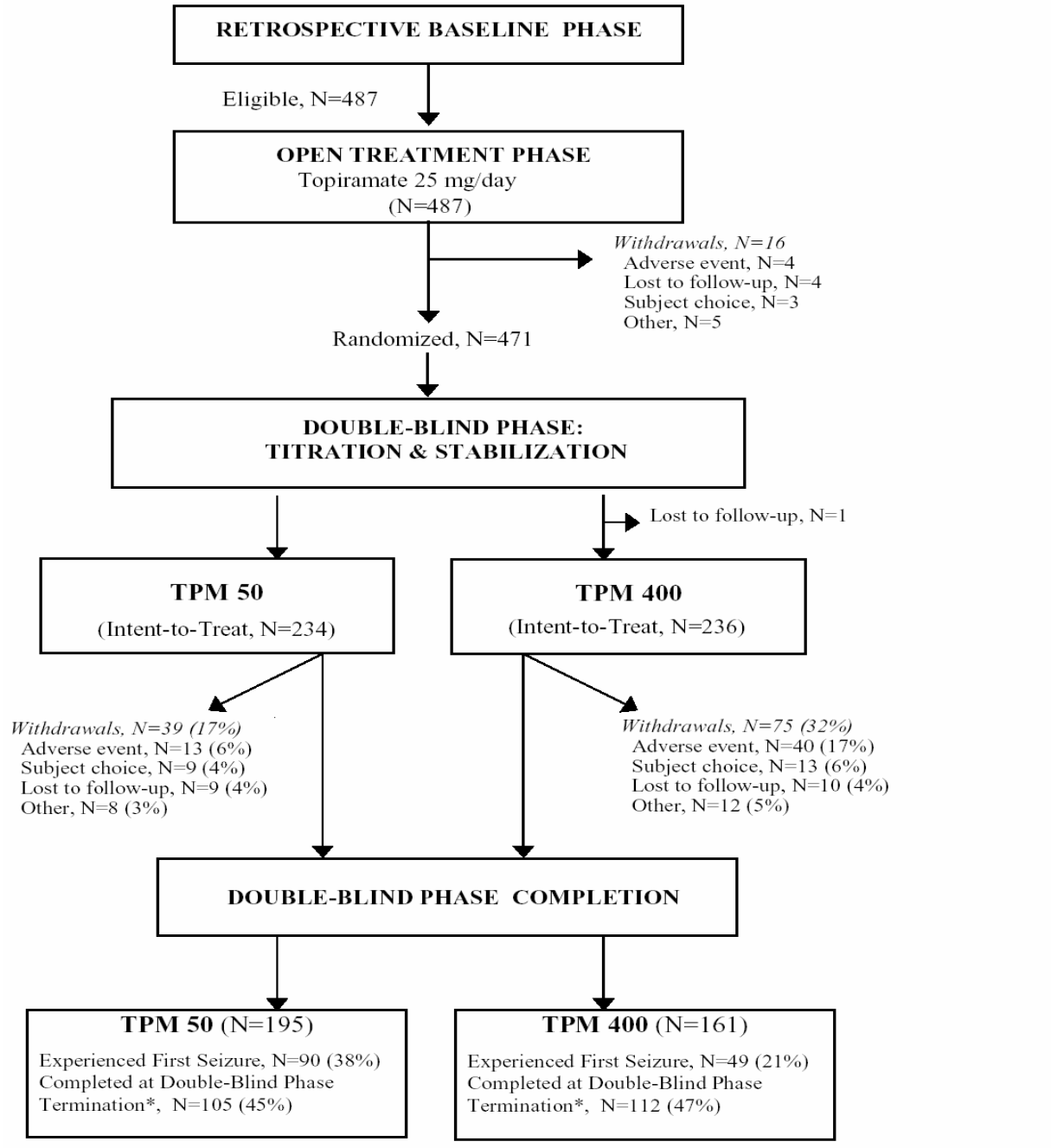
Across the 2 groups, 76% of the subjects completed the study, either at time of termination of the double-blind phase (46%) or at the time of their first seizure (30%). Considerably more subjects in the topiramate 50 mg/day group experienced first seizures (38%), compared to topiramate 400 mg/day group (21%). A total of 114 subjects (24%) withdrew from the study for the protocol-specified reasons that included adverse events (53 subjects; 11%), subject choice (22 subjects; 5%), lost to follow-up (19 subjects; 4%), and other reasons (20 subjects; 4%). Adverse events were reported as the reason for withdrawal for more subjects in TPM 400 group (17%), compared to the TPM 50 group (6%). Next table (adapted from Study Report Table 8) and figure (adapted from Study Report Figure 2) give Study Completion/Discontinuation Information.

Table 3.1.5.1. Study Completion/Discontinuation Information (ITT)

	TPM 50 (N=234)		TPM 400 (N =236)		Total (N=470)	
Completion Status	n	%	n	%	n	%
Completed	**195**	**83**	**161**	**68**	**356**	**76**
Completed at DB phase termination[a]	105	45	112	47	217	46
Completed by having a seizure	90	38	49	21	139	30
Withdrew	**39**	**17**	**75**	**32**	**114**	**24**
Adverse event	13	6	40	17	53	11
Subject choice	9	4	13	6	22	5
Lost to follow-up	9	4	10	4	19	4
Other	8	3	12	5	20	4

[a] Subjects who were active in the study at the time of termination of the double-blind (DB) phase, i.e., 6 months after randomization of the last subject.

Figure 2. Study Discontinuation and Completion Information



* At the time of planned double-blind phase termination (6 months after randomization of the last subject)

The demographic and baseline characteristics for the subjects in the intent-to-treat population are

summarized in next two tables (adapted from Study Report Tables 9a and 9b). Of the 470 subjects in the intent-to-treat population, 233 (50%) were men, and 413 (88%) were white. The median age was 22 years (range, 6 to 83 years); 151 subjects (32%) were 15 years of age or younger (including 14 subjects (3%) who were 7 years of age or younger); 25 subjects (5%) were 65 years or older. The median weight was 64.0 kg (range, 22.3 to 154.5 kg); 192 subjects (41%) had a body weight not exceeding 60 kg, and 96 subjects (20%) weighed more than 85 kg. The treatment groups were well matched with regard to sex, race, age, body weight, and height.

Table 3.1.5.2. Demographic and Baseline Characteristics: Sex, Race, Age, Weight and Height (ITT)

	TPM 50 (N=234)		TPM 400 (N=236)		Total (N=470)	
Sex: n, %						
Male	110	47	123	52	233	50
Female	124	53	113	48	237	50
Race: n, %						
White	203	87	210	89	413	88
Black	13	6	15	6	28	6
Asian	2	1	1	<1	3	1
Other[a]	16	7	10	4	26	6
Age (years): n, %						
≤7	8	3	6	3	14	3
8-11	24	10	31	13	55	12
12-15	42	18	40	17	82	17
16-24	61	26	44	19	105	22
25-34	35	15	41	17	76	16
35-44	27	12	34	14	61	13
45-64	22	9	30	13	52	11
≥65	15	6	10	4	25	5
N	234		236		470	
Mean	27.3		27.9		27.6	
SD	17.79		17.19		17.48	
Median	21.0		24.0		22.0	
Range	6.0 - 83.0		6.0 - 78.0		6.0 - 83.0	
Weight (kg): n, %						
<60	89	38	103	44	192	41
≥60 - ≤85	96	41	86	36	182	39
>85	49	21	47	20	96	20
N	234		236		470	
Mean	67.3		65.2		66.2	
SD	24.31		22.90		23.61	
Median	65.0		62.0		64.0	
Range	22.3 - 154.5		25.0 - 142.7		22.3 – 154.5	
Height (cm)						
N	234		235		469	
Mean	163.4		161.7		162.6	
SD	15.71		15.04		15.39	
Median	167.0		163.0		165.1	
Range	115.0 - 195.6		115.0 - 188.0		115.0 – 195.6	

[a] "Other" included Hispanic, Hispanic/Caucasian, and East Indian.

The median duration since the diagnosis for subjects in both treatment groups was 1 month. All subjects in the intent-to-treat population had experienced either 1 or 2 seizures during the 3-month retrospective baseline phase, as specified in the protocol. The majority of subjects (63%) had only 1 seizure. One or 2 partial onset seizures were reported for 56% of the subjects, compared to 42% subjects with either 1 or 2 generalized seizures. Only 2% of all subjects experienced 2 seizures of different types. The distribution of seizure types and seizure counts was very similar for the 2 topiramate dose groups.

According to the protocol, no more than 1 standard AED could have been used only for emergency or temporary purposes prior to randomization; subjects who had uncontrolled epilepsy while taking AEDs were not eligible for enrollment. Any AEDs were to be completely discontinued by the time of randomization. Approximately, one-half of the subjects in the intent-to-treat population (53% in topiramate 50 mg/day group and 50% in topiramate 400 mg/day group) used an AED before enrollment (Table 9b). The types of AEDs used before randomization were comparable between the 2 treatment groups. AEDs used before randomization by more than 5% of subjects in the intent-to-treat population were phenytoin (20%), valproic acid (10%), and carbamazepine (7%). Twelve subjects (6 subjects in each of the treatment groups) used more than 1 AED before randomization. Of these, only 1 subject (Subject 534001) used 3 AEDs; another subject, Subject 554003, used 2 AEDs concomitantly for 3 days; both cases are described in Section 4.4, Protocol Deviations. The remaining 10 subjects used the 2 AEDs sequentially, not concomitantly, and 1 of the 2 AEDs was used only for short-term treatment (for 1 day in 5 subjects; between 3 to 8 days in the other 5 subjects).

Table 3.1.5.3. Demographic and Baseline Characteristics: Duration of Epilepsy, Baseline Seizure Counts and AED Use Before Randomization (ITT)

	TPM 50 (N=234)	TPM 400 (N=236)	Total (N=470)
Time Since Diagnosis (mos.)			
N	233	236	469
Mean	19.3	27.0	23.2
SD	56.27	72.21	64.83
Median	1.0	1.0	1.0
Range	0.0 - 408.0	0.0 - 456.0	0.0 - 456.0
Seizure Count during 3-month Baseline[c]: n,%			
1 Partial Onset[a]	81 35	78 33	159 34
1 Generalized[b]	67 29	69 29	136 29
2 Partial Onset[a]	45 19	58 25	103 22
2 Generalized[b]	34 15	29 12	63 13
1 Partial Onset[a] + 1 Generalized[b]	7 3	2 1	9 2
Number of AEDs Used Before Randomization: n,%			
0	109 47	119 50	228 49
1	118 50	111 47	229 49
≥2[e,f]	7[f] 3	6 3	13[f] 3
Most Common[d] AEDs Before Randomization: n,%			
Phenytoin	50 21	44 19	94 20
Valproic acid	21 9	28 12	49 10
Carbamazepine	16 7	17 7	33 7
Phenobarbital	9 4	8 3	17 4
Clonazepam	6 3	9 4	15 3
Clobazam	7 3	6 3	13 3
Lamotrigine[g]	6 3	4 2	10 2
Oxcarbazepine[g]	7 3	3 1	10 2
Other antiepileptics[h]	4 2	0	4 1

[a] Includes simple partial, complex partial and partial evolving into secondarily generalized seizures.
[b] Includes generalized tonic-clonic, tonic, and clonic seizures.
[c] Seizures experienced by the subjects during the 3-month retrospective baseline phase of the study.
[d] AEDs used by at least 1% of the subjects in either treatment group. AEDs used by less than 1% of the subjects included fosphenytoin, gabapentin, lorazepam, Comital-L (a combination of phenobarbital, phenytoin, and mephobarbital), and fluoride.
[e] Twelve subjects used more than 1 AED before randomization. Of these, only 1 subject (Subject 534001) used 3 AEDs; another subject, Subject 554003, used both AEDs concomitantly for 3 days; both cases are described in Section 4.4, Protocol Deviations. The remaining 10 subjects used their 2 AEDs sequentially, not concomitantly, and 1 of the 2 AEDs was used only for short-term treatment.
[f] In case of Subject 550001 in TPM 50 group, who received only 1 AED (fosphenytoin) at baseline, topiramate was also coded in error as a baseline AED, bringing the number of subjects using 2 or more AEDs in that group to 7 (Attachment 3.2).
[g] In 9 subjects receiving Trileptal (oxcarbazepine) at baseline, it was coded in error as lamotrigine. An erratum to that effect has been added to the clinical database.
[h] Levetiracetam (3 subjects) and valproate (1 subject).

To summarize, the 2 treatment groups were well balanced with respect to all background disease characteristics, i.e., duration of epilepsy, distribution of seizure counts and types during the 3-month retrospective baseline phase, and number and type of AEDs used before randomization.

3.1.6 Sponsor's Efficacy Results

A total of 470 subjects (234 subjects in topiramate 50 mg/day group and 236 subjects in topiramate 400 mg/day group) were randomly assigned to receive double-blind treatment, dispensed study medication, and had at least 1 study visit after randomization. These 470 subjects were included in the intent-to-treat population for the efficacy analysis.

In error, the first seizure information was not recorded in the clinical database for Subject 532006 in topiramate 400 mg/day group, who completed the study due to first seizure. This subject was included in the efficacy analysis as a censored observation.

Comparison of the Kaplan-Meier survival curves of time to first seizure favored topiramate 400 mg/day over topiramate 50 mg/day (p-value is 0.0002; 2-sided log-rank test). Figure 3.1.6.1 (adapted from Study Report Figure 3) presents the Kaplan-Meier Estimates of Cumulative Rates for Time to First Seizure.

Figure 3.1.6.1. Kaplan-Meier Estimates of Cumulative Rates for Time to First Seizure

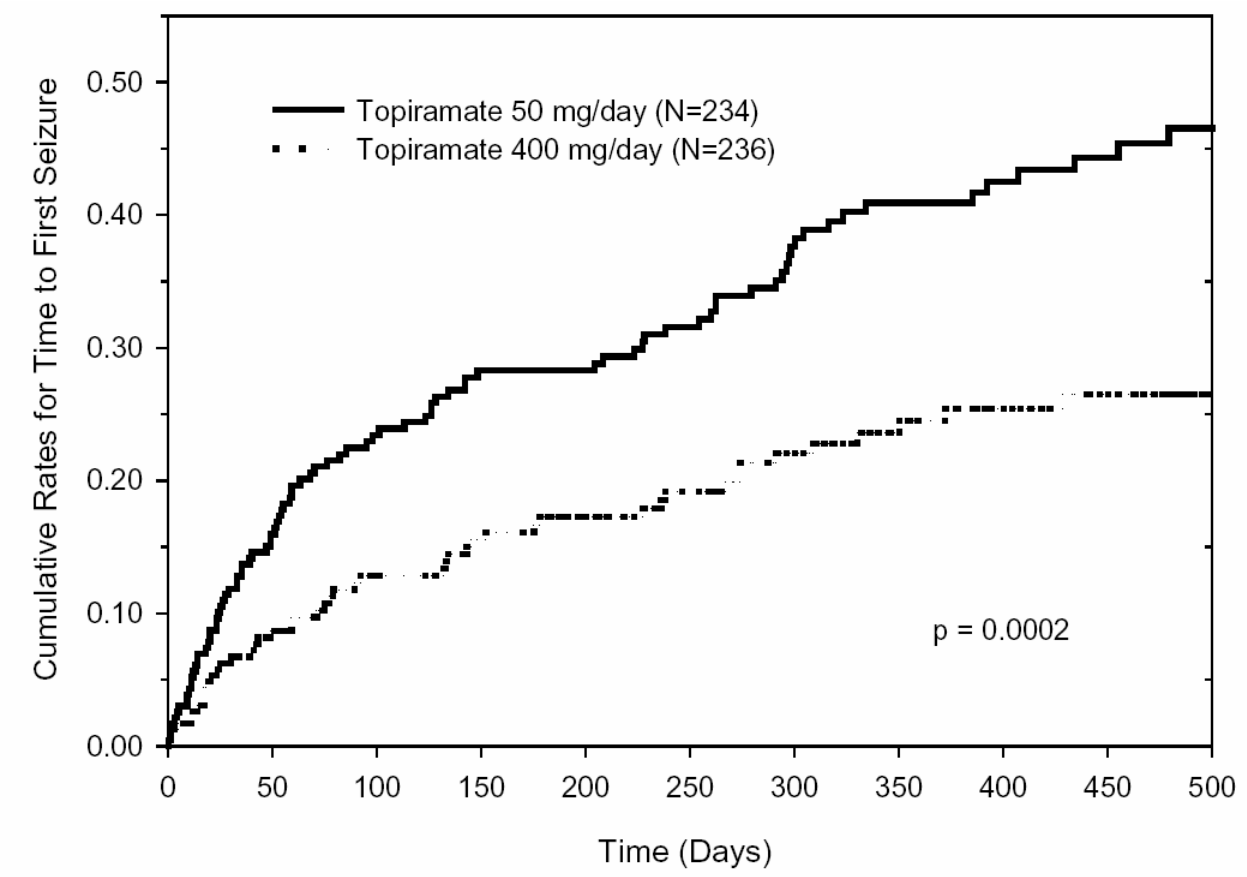


Table 3.1.6.1 (adapted from Study Report Table 13) presents the Kaplan-Meier estimates of

cumulative rates for the time to first seizure for the topiramate 50 mg/day and topiramate 400 mg/day treatment groups at various time point.

Table 3.1.6.1. Kaplan-Meier Estimates of Cumulative Rates for Time to First Seizure

Study Day	TPM 50 (N=234)		TPM 400 (N=236)		p value[a]
	n	Estimate, %	n	Estimate, %	
14	214	6.5	218	2.6	0.046
21	206	9.1	207	4.8	0.071
28	196	11.8	200	6.2	0.039
42	187	15.0	190	7.7	0.015
56	178	18.6	182	8.6	0.003
90	162	22.8	170	11.7	0.002
112	159	24.2	166	12.8	0.002
180	145	28.6	148	17.1	0.003
270	112	34.2	113	19.8	0.001
365	77	41.2	84	24.3	<0.001
455	53	44.6	62	26.3	<0.001

[a] p value for the difference between treatment groups at each time point, obtained using a log-rank test for Kaplan-Meier curves from each of the data sets that were truncated at these time points.

Separation between the 2 groups in favor of the higher dose group with regard to the primary efficacy endpoint occurred early in the titration phase and was statistically significant as early as after 2 weeks post randomization (p = 0.046; 2-sided log-rank test). By following the weekly titration schedule, the subjects in the higher dose group at that time achieved the maximum topiramate dose of 100 mg/day; as shown in Attachment 4.1.3, the mean (SD) average dose achieved by the subjects on Day 14 was 97.1 (12.15) mg/day. The separation between the groups continued to increase for the duration of the double-blind phase; between-group comparisons using truncation of the follow-up duration on Day 14 favored topiramate 100 mg/day over topiramate 25 mg/day (p = 0.046; 2-sided log-rank test). On Day 21 (at the end of the third week, when the dose was titrated upwards in both groups), this comparison showed a trend for significance (p = 0.071; 2-sided log-rank test) in favor of topiramate 150 mg/day vs. topiramate 50 mg/day. Between-group pointwise comparisons were significant at all other time points examined for the remainder of the study. Taken together, these results indicate that topiramate treatment was efficacious in preventing seizures at the dose of 100 mg/day.

3.1.7 Reviewer's Analysis

The reviewer validated the sponsor's analysis according to the protocol. In the following, the reviewer will change Subject 532006 (in topiramate group) from censored observation to seizure observation to correct a recording error, as pointed out by the sponsor. The log-rank test gives p-value .0002 after making the above change.

3.1.7.1 Analysis on Withdrawals

Table 3.1.7.1.1 presents the withdrawals information.

Table 3.1.7.1.1 Withdrawals Information

Withdrawals	TMP 50 (N=234)	TPM 400 (N=236)
Adverse event	13 (6%)	40 (17%)
Subject choice	9 (4%)	13 (6%)
Lost to follow-up	9 (4%)	10 (4%)
Other	8 (3%)	12 (5%)
Total	39 (17%)	75 (32%)

If we count the adverse event as failed, there are 103 and 89 failed in TPM 50 and 400 groups, respectively. The log-rank test gives p-value of .2482.

If we count the lost to follow-up as failed, there are 99 and 59 failed in TPM 50 and 400 groups, respectively. The log-rank test gives p-value of .0006.

If we count all withdrawals as failed (all-cause), there are 129 and 124 failed in TPM 50 and 400 groups, respectively. The log-rank test gives p-value of .5706.

Table 3.1.7.1.2 presents the baseline seizure (partial onset and generalized) for withdrawals and others. Since inclusion criteria allows only 1 or 2 (but no more than 2) documented seizures within the 3 months before enrollment, mean seizures for withdrawals and completes are quite balance.

Table 3.1.7.1.2 Mean Seizure Count During 3-Month Baseline

	TPM 50			TPM 400		
	N	mean	(sd)	N	mean	(sd)
all	234	1.37	(0.48)	236	1.38	(0.49)
withdrawals	39	1.31	(0.47)	75	1.41	(0.50)
completes	195	1.38	(0.49)	161	1.36	(0.48)

The reviewer requested the sponsor to submit any efficacy related follow-up information for withdrawals, for example, whether a patient had seizure or used other medications, the sponsor responded that “For the TOPMAT-EPMN-106 study, the only information we collect after the subjects withdraw from the trial is the persisting adverse event (PAE) information.”

Since all-cause analysis (see Table 3.1.7.2.2) is not statistically nominally significant, one issue needs to be addressed is whether there might be potential bias caused by the unbalanced withdrawals in two treatment groups, because more withdrawals would have less seizure events. Unless there are data to support that the unbalanced withdrawals wouldn't introduce bias, one should interpret the result with caution.

3.1.7.2 Analysis on Truncated Point according to Dose Titration Schedule

Dose Titration Schedule is as follows:

	Open-Treatment	Titration Period (Days)						Stabilization
Dose Group	Days -7 to -1	1 to 7	8 to 14	15 to 21	22 to 28	29 to 35	36 to 42	Period
50 mg/day	25	25	25	50	50	50	50	50
400 mg/day	25	50	100	150	200	300	400	400

NOTE: Topiramate dosages are provided in mg/day.

Table 3.1.7.2.1 presents p-values of log-rank tests using truncated case, i.e., a patient was censored at the selected time point.

Table 3.1.7.2.1 P-values of Truncated Case for Titration Period

Day	TPM 50		TPM 400		p-value
	failed	censored	failed	censored	
14	15	5	6	12	.0457
21	21	7	11	18	.7070
28	27	11	14	22	.0386
35	30	12	15	26	.0229
42	34	13	17	29	.0152

Table 3.1.7.2.2 presents all-cause results for titration period. Although the number of failed in TPM 50 is greater than in TPM 400, none is statistically nominally significant since the number of withdrawals is greater in TPM 400 group than TPM 50 group.

Table 3.1.7.2.2 P-values of Truncated Case for Titration Period (All Cause)

Day	TPM 50 failed	TPM 400 failed	p-value
14	20	18	.7129
21	28	29	.9309
28	38	36	.7808
35	42	41	.8738
42	47	46	.8709

3.1.7.3 Impact of the Protocol Amendments

The Protocol Amendment 2 and 4 are related to increase the sample size, which followed the original Protocol to have 108 failed event. The Protocol Amendment 3 and 5 are related to increase the duration of the double-blind phase from 2 months to 4 months, and from 4 months to 6 months, respectively, after the randomization of the last subject. Table 3.1.7.3 presents log-rank test p-values for 2, 4, and 6 months duration. The impacts of such changes in terms of p-values are small.

Table 3.1.7.3 P-values for 2, 4, and 6 Months Duration

	TPM 50 failed	TPM 400 failed	P-value
2 months	79	44	.0008
4 months	87	48	.0004
6 months	90	49	.0002

3.1.7.4 Analysis on Region

The p-values of log-rank tests show that TPM 400 is superior to TMP 50 in both North America and other countries.

.

Table 3.1.7.4 P-values by Region

Region	TPM 50		TPM 400		p-value
	N	Failed	N	Failed	
North America	108	44	104	22	.0150
Other	126	46	132	27	.0079

3.1.8 Sponsor's Response Dated on August 4, 2003 to the FDA Regarding the Unbalanced Withdrawals

The sponsor performed various sensitivity analyses, including imputation using sample replacement using study data, and sample replacement using simulated data, to examine what potential impact

missing data might have had on the reliability in the primary efficacy analysis.

3.1.8.1 Sample Replacement Using Study Data

Data from the 40 subjects in the TPM 400 group who withdrew from the double-blind phase due to adverse events were replaced with a random sample of: A) subjects from the TPM 50 group, or B) subjects from the TPM 400 group who had at least 1 adverse event but did not withdraw due to an adverse event.

For analyses A and B, the seizure-free duration for the 13 subjects in the TPM 50 group who withdrew due to adverse events was extended from the original date of censoring to 15 February 2002, which is the longest seizure free duration possible. The sensitivity analysis A assumed that the incidence rate of first seizure for subjects who withdrew from the TPM 400 group due to adverse events was the same as that for the subjects in the TPM 50 group. In general, an assumption of equal distribution of populations is not a guarantee of equal observations in random samples from the populations. Thus, to incorporate sampling variation, the following resampling method was used for imputation:

1) in order to consider all available seizure-free information, each subject who withdrew due to an adverse event was matched with a risk set from the TPM 50 group by the time of withdrawal;

2) from the matching risk set, a subject was randomly selected with equal probability, and the time to first seizure and censoring status of the sampled subject were then assigned to the subject with missing data. For example, data for a subject who withdrew at Day 50 from the TPM 400 group were imputed through a random selection of subjects in the TPM 50 group who were seizure-free at Day 50. For each resampled imputation of the 40 TPM 400 subjects who withdrew due to adverse events, the log-rank test was performed. This process was repeated 1,000 times and the 1,000 p values were summarized.

Sensitivity analysis B is to resample from those in the TPM 400 group who had an adverse event but did not withdraw.

The p values for analyses A and B are summarized in Table 3.1.8.1.1. The results support the original conclusion that TPM 400 reduces the incidence rate for first seizure.

Table 3.1.8.1.1 Results of Imputations for Replacing Data From 40 Subjects in the TPM 400 Group Who Withdrew Due to Adverse Events

Analysis	Median p value	Maximum p value	Kaplan-Meier Estimate of Time to First Seizure at Day 500	% of imputations that were statistically significant at p<0.05
A	0.0017	0.0197	46.7%[b]	100%
B	0.0003	0.0039	24.7%[c]	100%

[a] The seizure-free time for the 13 subjects in the TPM 50 group who withdrew due to adverse events was extended from the original date of censoring to 15 February 2002 (i.e., the longest seizure-free duration possible).

[b] Source: Primary efficacy analysis as presented in the clinical study report for Study TOPMAT-EPMN-106 (double-blind phase).

3.1.8.2 Sample Replacement Using Simulated Data

Both sensitivity analyses A and B are based on resampling from existing populations, and therefore are limited because they do not provide a range for which the results are robust. To address this issue, a parametric resampling method for imputation was also conducted. Specifically, those subjects who withdrew were seizure-free at the time of withdrawal, and thus, data for each subject who withdrew were imputed through an exponential distribution, conditional upon the time to discontinuation. For example, if a subject withdrew on Day 50, a random failure time is generated from an exponential distribution with a given seizure rate. The failure time is then compared with the potential duration, which is the duration between Day 50 and 15 February 2002 (i.e., the date of trial completion). If the duration is longer than the random failure time, the subject is considered to have had a seizure at the failure time plus 50; otherwise, the subject's first seizure time is censored on 15 February 2002. Note that the seizure rate for the exponential distribution can be arbitrarily chosen. Therefore, with the parametric method, one can provide a range of seizure rates to determine whether the result of the original log-rank test is robust.

Under the parametric method, 3 sensitivity analyses were performed, which differ in subsetting the missing population. These analyses imputed time to first seizure data for the following subgroups:

C) all 114 subjects from both treatment groups (75 from the TPM 400 group and 39 from TPM 50 group) who withdrew from the double-phase due to any reason,

D) the 53 subjects from both treatment groups (40 from the TPM 400 group and 13 from the TPM 50 group) who withdrew during the double-blind phase due to adverse event(s), and

E) the 40 subjects from the TPM 400 group who withdrew due to adverse events, and the seizure free time for 13 subjects from TPM 50 group who withdrew due to adverse events was extended.

Tables 3.1.8.2.1-3 summarize the results from analyses using the simulated data approach. The first imputation (Table 3.1.8.2.1) showed that by replacing the data from all 114 subjects (75 and 39 subjects from the TPM 400 and 50 groups, respectively) who withdrew (for any reason) from the double-blind phase with computer-generated pseudo-random data, the results favor TPM 400 over TPM 50 (p=0.0296) assuming up to a 50% probability that subjects would have a seizure by Day 500. Notably, the highest probability of having a seizure where a statistically significant difference between the dose groups was found is almost twice the Kaplan-Meier estimated seizure rate of 26% in the TPM 400 group.

Table 3.1.8.2.1 Summary of Simulations: Simulating Data for 114 Subjects Who Withdrew
(Study TOPMAT-EPMN-106; Double-Blind Phase)

Assumed seizure rate at Day 500	Number of 1st seizures for TPM 50 (N=234)	Number of 1st seizures for TPM 400 (N=236)	p value from one simulation
1%	90	48	0.0001
5%	91	51	0.0001
10%	92	55	0.0001
15%	93	58	0.0002
20%	95	59	0.0002
25%	96	63	0.0005
30%	96	66	0.0013
35%	98	69	0.0018
40%	98	73	0.0057
45%	99	77	0.0116
50%	100	82	0.0296
55%	101	86	0.0509
60%	101	90	0.0996
65%	101	91	0.1300
70%	107	94	0.0899
75%	110	98	0.1249
80%	111	100	0.1480
85%	112	105	0.2294
90%	117	108	0.2053
95%	120	112	0.2596
99%	122	116	0.3665

A similar analysis conducted by replacing only the data of those 53 subjects (40 and 13 from the TPM 400 and 50 groups, respectively) who withdrew due to adverse events (D) with computer-generated pseudo-random numbers showed that TPM 400 was superior to TPM 50, assuming an up

to 90% (p=0.0369) probability that subjects would have a first seizure by Day 500. The summary of the p values using this approach is provided in Table 3.1.8.2.2.

Table 3.1.8.2.2 Summary of Simulations: Simulating Data for 53 Subjects Who Withdrew Due to Adverse Events
(Study TOPMAT-EPMN-106; Double-Blind Phase)

Assumed seizure rate at Day 500	Number of 1st seizures for TPM 50 (N=234)	Number of 1st seizures for TPM 400 (N=236)	p value from one simulation
1%	90	48	0.0001
5%	90	48	0.0001
10%	92	50	0.0001
15%	93	51	0.0001
20%	93	52	0.0001
25%	93	52	0.0001
30%	93	54	0.0001
35%	93	56	0.0001
40%	94	59	0.0003
45%	94	62	0.0007
50%	94	64	0.0013
55%	96	68	0.0023
60%	97	69	0.0029
65%	97	70	0.0041
70%	97	71	0.0052
75%	97	72	0.0080
80%	97	72	0.0086
85%	98	74	0.0119
90%	98	79	0.0369
95%	99	81	0.0517
99%	100	83	0.0735

A summary of p values for sensitivity analysis E is shown in Table 3.1.8.2.3.

Table 3.1.8.2.3 Summary of Simulations: Simulating Data for 40 Subjects in the TPM 400 Group Who Withdrew Due to Adverse Events
(Study TOPMAT-EPMN-106; Double-Blind Phase)

Assumed seizure rate at Day 500	Number of 1st seizures for TPM 50 (N=234)	Number of 1st seizures for TPM 400 (N=236)	p value from one simulation
1%	90	48	0.0001
5%	90	49	0.0001
10%	90	50	0.0001
15%	90	51	0.0001
20%	90	52	0.0001
25%	90	55	0.0003
30%	90	57	0.0006
35%	90	57	0.0006
40%	90	58	0.0008
45%	90	59	0.0012
50%	90	62	0.0030
55%	90	64	0.0056
60%	90	66	0.0109
65%	90	66	0.0112
70%	90	69	0.0218
75%	90	70	0.0303
80%	90	72	0.0516
85%	90	75	0.0946
90%	90	77	0.1459
95%	90	80	0.2425
99%	90	81	0.3187

3.1.8.3 Reviewer's Comment

3.1.8.3.1 Resampling from Existing Populations

"Both sensitivity analyses A and B are based on resampling from existing populations." Analysis A is using TMP 50 group non-withdrawals to replace 40 withdrawals due to adverse events in TMP 400 group, and analysis B is using TMP 400 non-withdrawals to replace 40 withdrawals due to adverse events in TMP 400, while 13 withdrawals due to adverse events in TPM 50 are extended from the original censoring date to February 15, 2002. This reviewer is not convinced that using non-withdrawals to replace withdrawals is appropriate because these two groups might be different.

Randomization might achieve the balance of two treatment groups in baseline. After patients are assigned to two groups, they are different since they take different treatments. In addition, non-withdrawal and withdrawal groups might be different even they are in the same treatment group so any characteristics, such as baseline, number of adverse events, etc, might not indicate the real reason why patients withdraw. Therefore, methods of analyses A and B are inappropriate and results are uninterpretable.

3.1.8.3.2 Sample Replacement Using Simulated Data

The result of the simulation, assuming a certain seizure rate at Day 500, is hard to evaluate because it is very difficult to verify simulation assumption. The withdrawal groups might be different than a non-withdrawal so any seizure rate assumptions from other population or other trials are not suitable. Hence, any conclusion made from the simulation under a particular assumption, at most, is only an unverifiable conjecture unless one has a complete follow-up data.

Overall, results from "Resampling from Existing Populations" are uninterpretable, and results from "Sample Replacement Using Simulated Data" are unverifiable.

3.2 Evaluation of Safety

See Clinical Review by Dr. Howard Chazin.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Since the Study was not powered for subgroup analyses, p-values are used to indicate the numerical direction. The p-values of log-rank tests show that TPM 400 is superior to TMP 50 in both male and female.

Table 4.1.1 P-values by Gender

Gender	TPM 50		TPM 400		p-value
	N	Failed	N	Failed	
Male	110	41	123	22	.0011
Female	124	49	113	27	.0739

Since majority subjects are white, no separate analysis on race is performed.

The p-values of log-rank tests show that TPM 400 is superior to TMP 50 in all three age groups.

Table 4.1.2 P-values by Age

Age	TPM 50		TPM 400		p-value
	N	Failed	N	Failed	
≤ 15	74	29	77	12	.0022
15 - 44	123	49	119	28	.0352
> 44	37	12	40	9	.3146

4.2 Other Special/Subgroup Populations

There is no analysis performed for other subgroup.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The primary analysis is log-rank test which gives p-value .0002 where there were 90 (38%) seizure events out of 234 in TPM 50, and 49 (21%) seizure events out of 236 in TPM 400 groups, respectively.

Unfortunately, log-rank test of all-cause analysis gives p-value .5706 due to unbalanced withdrawals between two treatment groups, 39 (17%) out of 234 in TPM 50, and 75 (32%) out of 236 in TPM 400, respectively.

Since all-cause analysis is not statistically nominally significant, one issue needs to be addressed is whether there might be potential bias caused by the unbalanced withdrawals, because more withdrawals would have less seizure events. Unless there are data to support that the unbalanced withdrawals wouldn't introduce any bias, one should interpret the result with caution.

The sponsor addressed the issue of withdrawals mainly by simulation, after the Agency informed the issue to the sponsor. Results from "Resampling from Existing Populations" are uninterpretable because it is not appropriate to use a non-withdrawal to replace a withdrawal, and results from "Sample Replacement Using Simulated Data" are unverifiable due to unverifiable simulation assumption.

5.2 Conclusions and Recommendations

The conclusion is that although the data and analyses from the current submission achieved statistical significance, there are serious concerns about the interpretation of the results given the large number of unbalanced withdrawals.

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Kun Jin
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Kooros Mahjoob
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Topamax ® (Topiramate) **PRIMARY REVIEWER**: Andre Jackson
NDA 20505/S-018 and NDA 20844/S-015 – Monotherapy
NDA 20505/S-022 and NDA 20844/S-019 – Prophylaxis of Migraine Headache
TYPE: Labeling Supplement
FORMULATION: Oral Tablet **STRENGTH:** 25 mg, 100 mg and 200 mg
Sprinkle Capsules 15 mg and 25 mg
APPLICANT: Johnson and Johnson **SUBMISSION DATE:**
February 13, 2004
May 27, 2004.

Review of a Labelling Supplement

BACKGROUND

In each of the efficacy supplements (monotherapy and prophylaxis of migraine headache), there were several drug drug interaction studies. OCPBs reviews of March 19, 2003 and April 23, 2003 provided the reviews of the studies as well as the labeling for all drug drug interactions that were submitted. The Approvable letter for the prophylaxis of migraine headache conveyed the Agency's labeling to the sponsor (October 23, 2003). This labeling also conveyed the text for all of the drug interactions reviewed by OCPB. The Approvable letter for monotherapy (November 26, 2003) did not convey the labeling to the sponsor. The firm has submitted the following labeling in response. OCPB labeling is presented beginning on page 9 and is common for both efficacy supplements.

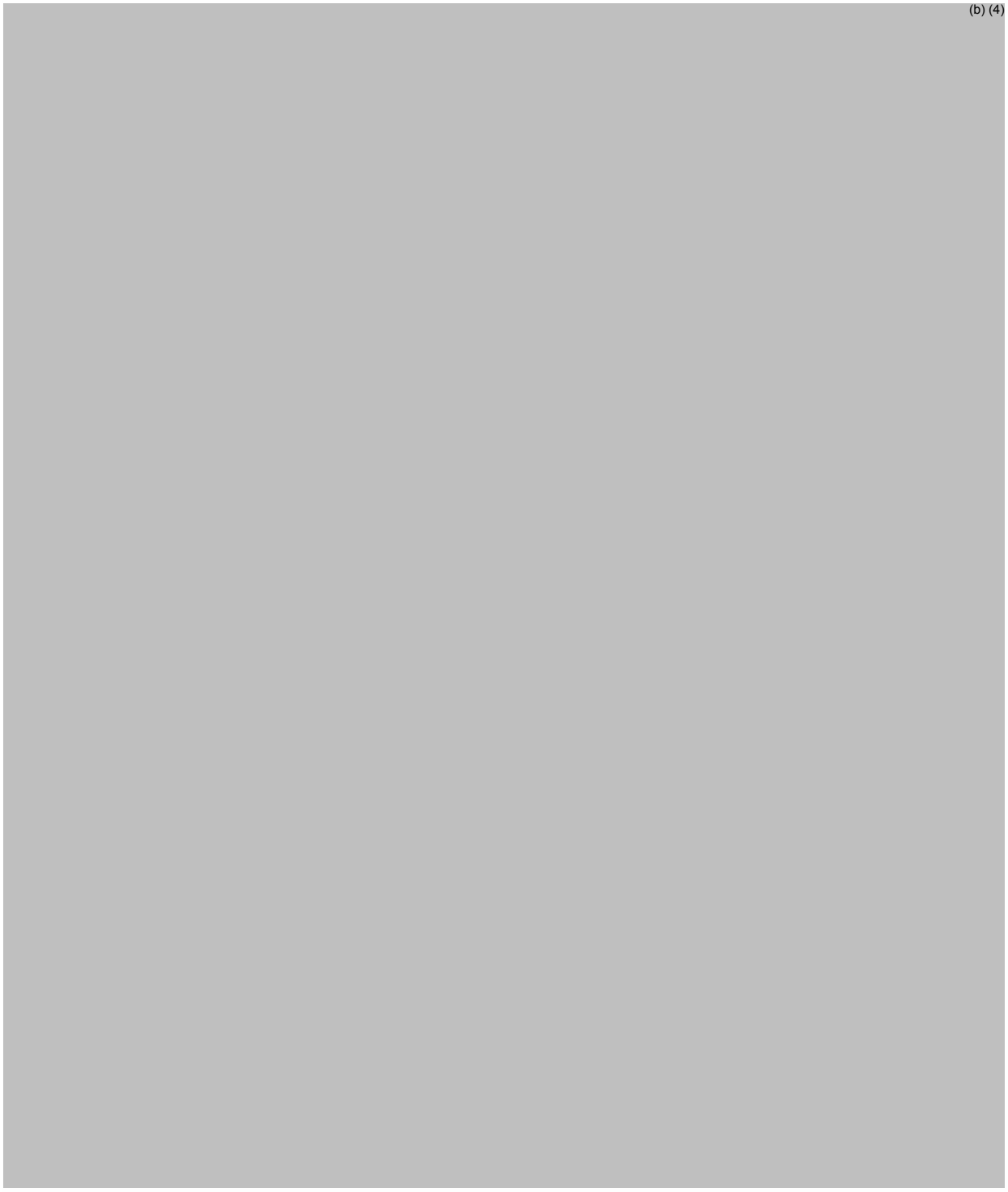
SPONSOR'S LABELLING

6 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

√ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

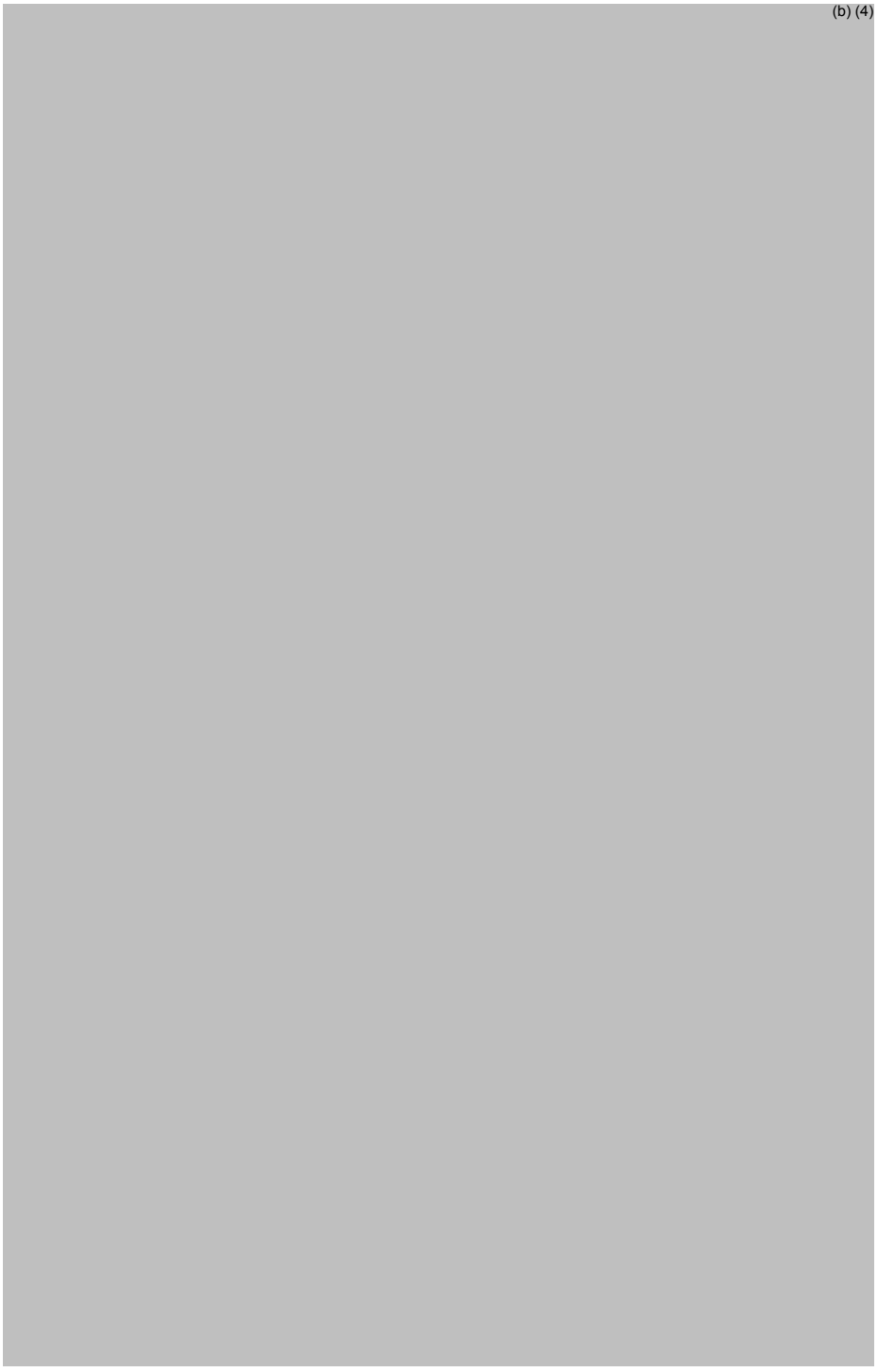


COMMENTS TO THE MEDICAL OFFICER

The firm included Table 4 as a summary of drug-drug interactions between several drugs and Topiramate. OCPB decided to delete Table 4 for the following reasons:

1.Dosing regimens and demographics are not presented in the table.
2.The presentation is not easy to understand.
3.OCPB recommends that the Table be replaced by individual summaries of drug-drug interactions as presented to the Sponsor in the Approvable letter of October 23, 2003.

OCPB PROPOSED LABEL:



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_____ § 552(b)(5) Deliberative Process

SIGNATURES

Andre Jackson_____

RD/FT Initialed by Raman Baweja, Ph.D._____

CC-NDA 20505/S-018 and NDA 20844/S-015; NDA 20505/S-022 and NDA 20844/S-019
, HFD-860(Jackson, Baweja, Rahman, Mehta), Central Documents Room (Biopharm-CDR)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andre Jackson
6/21/04 02:37:11 PM
BIOPHARMACEUTICS

Raman Baweja
6/21/04 04:36:01 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Topamax ® (Topiramate) **PRIMARY REVIEWER**: Andre Jackson
NDA: 20-505/S-018 **TYPE: Efficacy Supplement**
20-844/S-015
FORMULATION: Oral Tablet ;Sprinkles **STRENGTH:** 25 mg, 50, 100, 200, (b) (4) mg
APPLICANT: Johnson and Johnson Submission Date: November 15, 2002

INDICATIONS: Epilepsy
(b) (4)
Migraine Prophylaxis
Generic Name: Topiramate

Executive Summary

Topiramate was approved in 1995 for adjunctive therapy in epilepsy. The current submission contains three phase 3 topiramate monotherapy studies (TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106) to provide the principal safety information related to this new indication. Two of these studies compared the efficacy and safety of 2 topiramate dosage regimens as monotherapy for epileptic subjects: TOPMAT-EPMN-104 evaluated low-dose (25 or 50 mg/day based on body weight) and high-dose (200 or 500 mg/day based on body weight) topiramate regimens in recently diagnosed partial onset epilepsy, and TOPMAT-EPMN-106 evaluated topiramate regimens of 50 and 400 mg/day in newly diagnosed or recurrent epilepsy. The third study, TOPMAT-EPMN-105, compared topiramate monotherapy at dosages of 100 or 200 mg/day to standard monotherapy with carbamazepine 600 mg/day or valproate 1,250 mg/day in newly diagnosed epilepsy. The sponsor has submitted several drug interaction studies to support the safety of Topiramate .

The Clinical Pharmacology/Biopharmaceutics review will evaluate drug effect studies of Topiramate on Lithium, Haloperidol, Amitriptyline, Sumatriptan and Lamotrigine. All studies were conducted by administering Topiramate to determine the effect on the steady-state levels of the compound of interest except for Haloperidol and Sumatriptan.

The important findings related to the effect of Topiramate on the following drugs were:

1.Lithium- Cmax and AUC decreased by 20%

2.Haloperidol- Concluded to be no effect

3. Amitriptyline- 12% increase in AUC(0-24hr) and Cmax

4.Sumatriptan- Concluded to be no effect

5 (a)Lamotrigine- AUC and Cmax decreased by about10% in the presence of Topiramate

5(b) Topiramate –15% increase in AUC and Cmax in the presence of Lamotrigine

The firm conducted several in vitro drug interaction studies for which the following was concluded:

6.In vitro Topiramate does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5.

7.Carbamazepine and Phenytoin do not effect the protein binding of Topiramate

8.Sodium valproate decreased Topiramate binding by about 10% from an initial value of 23% to a final value of 13%. However, Topiramate did not affect the binding of sodium valproate.

All of these findings, both in vivo and in vitro, have been included by OCPB in the label. Please see labeling section.

Recommendation: NDA 20-505/S-018 is acceptable to OCPB. Furthermore, OCPB labeling of all drug-drug interactions and in vitro findings have been included in this review.

TABLE OF CONTENTS

INTRODUCTION AND BACKGROUND

Topiramate is an antiepi1eptic drug developed by Johnson & Johnson Pharmaceutical Research & Development, L.L.C (the sponsor). Topiramate has been approved worldwide as adjunctive therapy for refractory partial onset seizures in adults. On the basis of subsequent add-on, placebo-controlled studies, topiramate was later approved as adjunctive therapy for the treatment of partial onset seizures in pediatric patients (ages 2 and above), as well as refractory generalized epilepsy, including primary generalized tonic-clonic seizures, and Lennox-Gastaut syndrome The dosage recommended for adults with partial onset seizures is 200 to 400 mg/day(400 mg/day in the United States) in 2 divided doses.

In adult studies with the tablet formulation, absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately two hours after a 400-mg oral dose. The bioavailability of topiramate from the tablet formulation is about 80% and is unaffected by food. Variation in plasma topiramate concentrations is low (relative standard deviation = 15-20%), and, therefore, it has predictable pharmacokinetics. The pharmacokinetics of topiramate are linear, with dose proportional increases in plasma concentrations over the 100 to 400 mg b.i.d. (200 to 800 mg/day) dose range. The mean plasma elimination half-life is 21 hours after single or multiple doses, and steady state is thus reached in about four days in subjects with normal renal function. Topiramate is 13-17% bound to human plasma proteins over the concentration range of 1-250 ug/mL.

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis and glucuronidation. Hepatic enzyme-inducing anti-epileptic drugs decrease the plasma concentrations of topiramate.

The clearance of topiramate is independent of age (18-65 years), gender, or race in the absence of underlying renal impairment.

CURRENT SUBMISSION

The firm has conducted drug interaction studies to determine the effect of topiramate on the levels of the following compounds to support specific indications:

Drug	Indication Supported	Study #
A. Lithium	(b) (4)	(b) (4)
B. Haloperidol	(b) (4)	(b) (4)
C. Amitriptyline	Migraine Prophylaxis	TOPMAT-PHI-377
D. Sumatriptan	Migraine Prophylaxis	TOPMAT-PHI-378
E. Lamotrigine	Epilepsy	TOPMAT-PHI-361

The (b) (4) indication for Topiramate was for (b) (4) For migraine and epilepsy it will be prophylactic and monotherapy.

The firm has also conducted several in vitro drug interaction studies.

These were:

Study Objective	Study #
A. Inhibition of cytochrome P450 enzymes by Topiramate	DM01362
B. In Vitro metabolism study of ^{14}C Topiramate using Microsomes expressing human p450	AE-2604
C.Binding of Topiramate to blood cells and plasma Proteins in human blood	99-169A
D.Effects of anticonvulsant drugs phenytoin and carbamazepine and a carbonic Anhydrase inhibitor on the binding of Topiramate to human red cells and plasma protein	2000-384A
E.Interaction study on the protein binding between Topiramate and Valproic acid in human plasma	2000-371A

SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS-CLINICAL PHARMACOLOGY QUESTION BASED REVIEW

Were the studies properly designed to address any drug effect of topiramate on lithium?

Yes, the studies were designed based upon the clinical indication and prescribed dosage regimen for the drug of interest.

Lithium

Because the (b) (4) patient population may receive concomitant treatment with lithium, investigation of the effect of topiramate on the pharmacokinetics of lithium was done by having subjects that were receiving lithium carbonate 300 mg every 8 hours for 14 days beginning on study Day 1 to be dosed with Topiramate on Day 9 with 50 mg every 12 hours, followed by titration of the topiramate dose to 75 mg every 12 hours on Day 10, and 100 mg every 12 hours from Days 11 to 14.

Was there a significant drug effect of topiramate on the steady-state levels for Lithium? Does this effect warrant a change in Lithium dose?

Table 1: 90% Confidence Intervals for the Ratio of the Means from Day 14 to Day 8 for Lithium Serum and Urine Pharmacokinetic Parameters in Twelve Healthy Subjects Following Multiple Doses of 300 mg Lithium Carbonate Every Eight Hours Before (Day 8) and During (Day 14) Multiple Oral Daily Doses of Topiramate.

				90% Confidence	
				Intervals	
	Geometric	Geometric			
			Estimated		
	Mean	Mean			
			Ratio(%)	Lower	Upper
Parameter	Before	During			
			[During/Before]	Limit(%)	Limit (%)
	Topiramate	Topiramate			
AUC(0-8h) $MEqxhrL^{-1}$	5.56	4.57	82.24	68.92	98.13
Cmax mEq/L	0.94	0.76	80.19	66.65	96.49
Ae mEq	5.91	6.14	103.90	84.36	127.97
CL/F L/hr	1.46	1.79	121.70	102.09	145.19
CLR L/hr	1.06	1.23	115.57	94.74	140.97

There was a significant drug-drug interaction between topiramate and lithium. However, the interaction lowered the lithium AUC at steady-state by 18 % and Cmax by 20%. However since the levels were lowered a dose adjustment is not required. However, the administration of topiramate to patients on chronic lithium therapy may result in the normal lithium dose not being as efficacious.

Were the studies properly designed to address any drug effect of topiramate on haloperidol?

Yes, the studies were designed based upon the clinical indication and prescribed dosage regimen for the drug of interest.

Haloperidol

Topiramate is currently being investigated as a potential treatment for (b) (4). Because the (b) (4) patient population may commonly receive concomitant treatment with haloperidol, investigation of the effect of topiramate on the pharmacokinetics of haloperidol was undertaken. Subjects received a single 5-mg oral dose of haloperidol on Day 1, and a 72-h profile of haloperidol plasma pharmacokinetics was performed. Following completion of the 72-h profile, there was a 4-day washout period. On Day 8, topiramate administration began at 50 mg every 12 hours, with titration to 75 mg every 12 hours on Day 9 and 100 mg every 12 hours on Days 10 through 16. On Study Day 14 subjects received a single 5-mg oral dose of haloperidol, and a subsequent 72-h pharmacokinetic profile was obtained.

Was there a significant drug effect of topiramate on the plasma levels for haloperidol? Does this effect warrant a change in haloperidol dose?

Table 2: Results from ANOVA for Haloperidol – Day Effect and 90% Confidence Intervals for the Ratio of the Means from Day 14 to Day 1 (Protocol [redacted])

(Protocol [redacted])

	Day Effect (with vs. without topiramate)			Geometric Mean		Day 14 vs. Day 1		
Parameter	F-value	df	p-value	Day 1	Day 14	Ratio (%)	Lower Limit (%)	Upper Limit (%)
C_{max}	0.03	(1,11)	0.874	1.43	1.44	101.05	90.03	113.42
AUC(0-*)	14.06	(1,11)	0.003[a]	30.13	33.93	112.61	106.38	119.19
AUC(0-∞)	10.16	(1,11)	0.009[a]	35.75	39.58	110.74	104.55	117.28
CL/F	10.16	(1,11)	0.009[a]	2331.29	2105.26	90.30	85.26	95.64

[a] Denotes signficance at the 5% level

Topiramate following multiple dosing of 100 mg/12 hrs did not have an effect on Haloperidol single dose pharmacokinetics, therefore no adjustment in Haloperidol dose is required.

Were the studies properly designed to address any drug effect of topiramate on amitriptyline?

Yes, the studies were designed based upon the clinical indication and prescribed dosage regimen for the drug of interest.

Amitriptyline

Amitriptyline is a commonly prescribed tricyclic antidepressant. This compound inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Interference with the reuptake of norepinephrine or serotonin may contribute to the antidepressant activity of amitriptyline.

The demethylated metabolite of amitriptyline is also a tricyclic with antidepressant activity. Topiramate is currently being evaluated as potential treatment for [redacted] and prophylaxis of migraine headache. Because these patients may receive concomitant treatment with amitriptyline, an investigation of the effects of multiple oral daily topiramate dosing on the pharmacokinetics of amitriptyline was undertaken.

Eligible subjects received 25 mg of amitriptyline administered once daily on Days 1 through 8. Topiramate dosing was initiated at a dosage of 25 mg administered twice daily on Days 9 and 10 for a total daily dosage of 50 mg. The topiramate daily dosage was titrated to 100 mg on Days 11 and 12, to 150 mg on Days 13 and 14, and to 200 mg on Days 15 through 20. Amitriptyline was administered concomitantly with topiramate at a constant dosage of 25 mg per day on Days 9 through 20.

Table 3. Amitriptyline Pharmacokinetic Least Squares Mean Parameters on log scale following Daily Oral Administration of 25 mg of Amitriptyline to Healthy Subjects Before and During Daily Topiramate Dosing .

	Without Topiramate	With Topiramate	W/WO ratio
AUC(0-24) ng/mlx hr	5.85	5.98	1.12
Cmax ng/ml	3.32	3.43	1.12
Cl/F ml/hr	7.08	6.96	0.88

Table 4. 90% Confidence Intervals for Ratio of Means for Amitriptyline

AUC(0-24) ng/mlx hr	89-142
Cmax ng/ml	85-147

The firm proposed to drop subject # 110 from the analysis. However perusal of the individual subject results indicated that although his results were somewhat different the amitriptyline data was similar to that for subject # 113 which would lead one to believe that for this component that this may be representative data. For example on day 7 before topiramate dosing #110 was lower but similar to #113. On the other hand, on day 20 some of subject #110 values were higher than #113. Inclusion of subject #110 resulted in a 12% increase in AUC(0-24) and Cmax for amitriptyline in the 18 normal subjects (6 male; 6 female) receiving 200 mg/day of Topiramate.

The outcome of this drug interaction study shows that due to variability steady-state amitriptyline subjects can show large changes in AUC and Cmax when dosed with Topiramate. However since the means were within 10% even when the variable subject was included an adjustment in dosage is not warranted**.** The label should state that some subjects may experience a large increase (8 fold) in amitriptyline concentration in the presence of Topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response..

Were the studies properly designed to address any drug effect of topiramate on sumatriptan?

Yes, the studies were designed based upon the clinical indication and prescribed dosage regimen for the drug of interest.

Sumatriptan

Sumatriptan is used in the acute treatment of migraine and it is anticipated that topiramate may be administered concomitantly as a prophylaxis for migraine. Therefore, it is important to investigate the effect of topiramate on the pharmacokinetics of sumatriptan.

Subjects were randomized to receive 2 single oral doses of sumatriptan while others were randomized to receive 2 single subcutaneous injections of sumatriptan. Each group included at least 5 women and at least 5 men. Subjects received either a single 100-mg oral dose or a single 6-mg subcutaneous injection of sumatriptan on Day 1 according to their assigned treatment group. This was followed by a 6-day washout. On Day 8, subjects received 50 mg of topiramate every 12 hours, followed by 75 mg topiramate every 12 hours on Day 9, and 100 mg of topiramate every 12 hours on Days 10 through 14. On Day 14, subjects received a second dose

of sumatriptan either as a single 100-mg oral dose or as a single 6-mg subcutaneous injection, according to their assigned treatment group. Subjects participated in the study for approximately 15 days.

Was there a significant drug effect of topiramate on the single oral dose plasma levels for sumatriptan that would warrant a dosage adjustment for sumatriptan in the presence of topiramate?

Table 5 : Statistical Comparison of Sumatriptan Pharmacokinetic Parameters Following Oral Administration of Sumatriptan Without (Day 1) and With (Day 14) Concomitant Topiramate (n=12) (Study TOPMAT-PHI-378)

Parameter	LSM[a] (Day 14)	LSM[a] (Day 1)	Comparison; Day 14: Day 1 (%)	
			Ratio[b]	90% CI
$AUC_{(0-\infty)}$ (ng*h/mL)	222.1	245.7	90	85, 96
$AUC_{(0-*)}$ (ng*h/mL)	217.2	240.6	90	85, 96
C_{max} (ng/mL)	51.48	48.48	106	90, 125
CL/F (L/h)	450.2	406.9	111	104, 118
$t_{½}$ (h)	2.28	2.16	106	95, 118

[a]Geometric least squares mean.
[b]Geometric least squares mean ratio.

Subcutaneous Dosing With Sumatriptan

Table 6**:** Mean (SD) Sumatriptan Pharmacokinetic Parameters Following Subcutaneous Administration of Sumatriptan Without (Day 1) and With (Day 14) Topiramate Coadministration (n=12) (Study TOPMAT-PHI-378)

Day	Statistics	$AUC_{(0-\infty)}$ (ng*h/mL)	$AUC_{(0-*)}$ (ng*h/mL)	C_{max} (ng/mL)	CL/F (L/h)	$t_{½}$ (h)
1	Mean[a]	96.5	92.5	56.88	63.6	1.87
	SD	15.0	15.2	11.66	9.8	0.34
	CV%	15.6	16.4	20.5	15.4	18.3
14	Mean[a]	93.8	89.9	58.34	65.7	1.66
	SD	15.9	16.2	15.17	11.5	0.44
	CV%	17.0	18.1	26.0	17.5	26.3

[a] Arithmetic means.

Note: T_{max} was 0.50 hours for all subjects following subcutaneous dosing.

The drug interaction studies indicated that there was no drug-drug interaction between Sumatriptan and Topiramate following either oral or subcutaneous administration of Sumatriptan. Therefore no adjustment in Sumatriptan is required during the use of Topiramate for Migraine Prophylaxis.

Were the studies properly designed to address any drug effect of topiramate on lamotrigine?

Yes, the studies were designed based upon the clinical indication and prescribed dosage regimen for the drug of interest.

Lamotrigine

The objectives of this study were to determine within the same group of patients with epilepsy: a) the steady-state pharmacokinetics of lamotrigine while on lamotrigine monotherapy, b) the steady-state pharmacokinetics of lamotrigine while concomitantly administered topiramate at three escalating doses of 100, 200, and 400 mg/day, c) the steady-state pharmacokinetics of topiramate at the three escalating topiramate doses while on a fixed-dose lamotrigine therapy, and d) the steady-state pharmacokinetics of topiramate while on topiramate monotherapy.

This Phase I study was an open-label, sequential treatment study designed to evaluate the steady-state pharmacokinetics of lamotrigine and topiramate administered as monotherapy and combination therapy in subjects with epilepsy. Subjects were required to be receiving lamotrigine monotherapy at a stable dose for five weeks prior to study enrollment and to have epilepsy that was not optimally controlled by the lamotrigine. Following enrollment, subjects received escalating doses of topiramate; dose titration began at 50 mg/day for 2 weeks, followed by escalations in steps of 50 mg/day every 2 weeks until the maximum dose of 400 mg/day or an individual subject's maximum tolerated dose was achieved. Subjects maintained a constant dose

of lamotrigine throughout the combination treatment period. The dose of lamotrigine was then tapered at a rate of approximately 25% per week. The dose of topiramate was adjusted only if necessary during the lamotrigine tapering period. After the tapering of lamotrigine was completed, subjects remained on topiramate monotherapy for 14 days.

1. Lamotrigine AUC and Cmax values decreased approximately 10% in the presence of steady-state Topiramate plasma concentrations.

2. Topiramate AUC and Cmax values increased approximately 15% in the presence of Lamotrigine .

Since a therapeutic plasma concentration range has not been established for lamotrigine, dosing of Lamotrigine is based on therapeutic response therefore during the switch to monotherapy with Topiramate, therapeutic response should be closely monitored. The goal of the transition regimen is to effect the conversion to monotherapy with Topiramate under conditions that ensure adequate seizure control. Therefore if there is a decrease in response during the course of the transition regimen, then the dose of Lamotrigine may have to be increased**.**

In Vitro

Is there any indication that topiramate can cause induction/inhibition of any CYP enzymes?

At 50 uM and 100 uM (17-34 ug/ml) there was a slight 20% inhibitory effect on CYP2B6 and CYP2A6. Topiramate did not effect other CYP enzymes. These concentrations are near the observed Cmax of 27 ug/ml following a 400 mg oral dose/12 hrs.

Is the protein binding and red cell partioning of topiramate linear or nonlinear?

The binding of KW-6485 (topiramate) to blood cells and to plasma proteins in human blood was investigated in vitro using ^{14}C-KW-6485. The binding of KW-6485 to plasma proteins was as low as 15 to 41 % in the blood concentration range of topiramate of 0.5 to 200 μg/mL, and decreased with the increase of plasma concentrations of topiramate. The Scatchard-plot analysis indicated the existence of two classes of binding sites with association constants of 1.31×10^7 $(mol/L)^{-1}$ and 1.48×10^3 $(mol/L)^{-1}$ and relative capacities of 0.0486 μmol/L and 1.89×10^2 μmol/L, respectively. The binding to blood cells also decreased with increase of the concentration of topiramate in the same concentration range as above. The association constants in high and low affinity sites were 3.46×10^6 $(mol/L)^{-1}$ and 1.43×10^2 $(mol/L)^{-1}$ with relative capacities of 25.3 μmol/L and 8.74×10^3 μmol/L, respectively.

Although there is apparent non linearity in plasma protein binding and red cell partitioning, Topiramate exhibits linear kinetics following multiple dosing.

Do the outcomes of the other in vitro plasma protein binding and red cell drug interaction studies warrant any changes in labeling?

Two interaction studies related to plasma protein binding and red cell partioning of Topiramate were done with carbamazepine(CBZ), phenytoin (PHT), valproic acid (VPA), and acetazolamide (ACZ). There was no significant effect of Topiramate on valproic acid binding and also there was only a modest 10% increase in free fraction of topiramate when valproic acid was added to Topiramate.

When Topiramate KW-6485 was added at a concentration of 5 μg/mL to human blood, the blood/plasma partition ratio (B/P) and the plasma protein binding (fb) were 2.13±0.15 (mean±S.D., n=6) and 18.5±3.5 %, respectively. In the case of addition of KW-6485 (5 μg/mL) and ACZ (150 μg/mL) to the human blood, the B/P of KW-6485 was halved to 1.03±0.05 thus indicating ACZ to inhibit the binding of KW-6485 to blood cells. On the other hand, when CBZ (45 μg/mL) or PHT (75 μg/mL) was added to the blood sample with the same KW-6485 concentration, the B/P of KW-6485 were 2.21±0.10 and 2.18±0.11, respectively and the fb were 17.1±3.6 % and 15.7±1.9 %, respectively. Both CBZ and PHT had no effect on the bindings of topiramate to human plasma protein and human blood cells.

FDA PROPOSED LABELLING

(b) (4)

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√ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Comments:

1. The original label lists protein binding as 13-17% for a concentration range of 1-250 ug/ml which is somewhat different from that presented in the current study which was as low as 15 to 41 % in the blood concentration range of topiramate of 0.5 to 200 µg/mL, and decreased with the increase of plasma concentrations of topiramate.

SIGNATURES

Andre Jackson_____
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

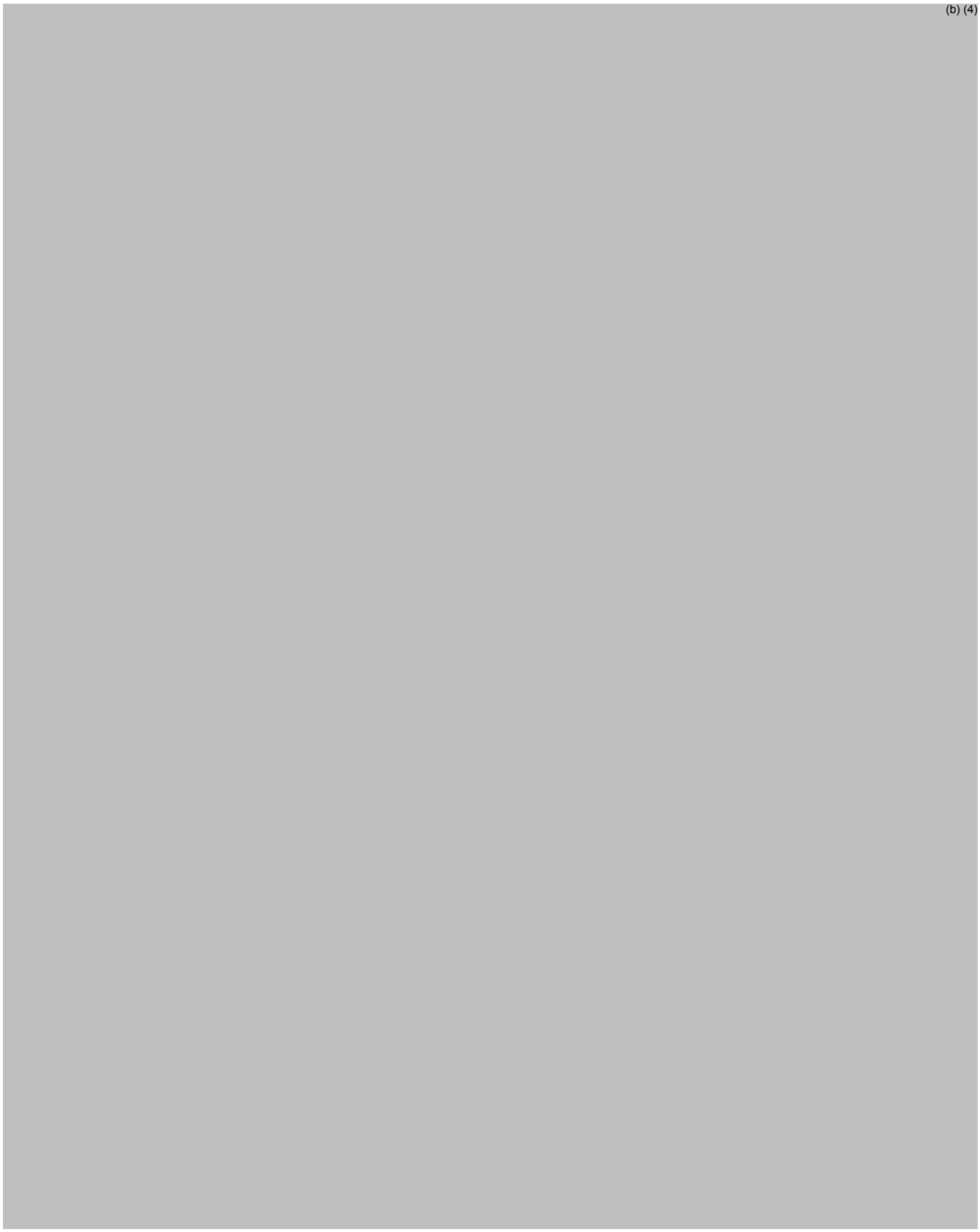
RD/FT initialized by Ray Baweja, Ph.D._____

Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: NDA 20-505/S-018 N20-844/S-015,HFD-120, HFD-860(Mehta, Sahajwalla, Baweja, Jackson)

APPENDIX

(b) (4)



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_____ § 552(b)(5) Deliberative Process

Individual Study Report- TOPMAT-PHI-377- Amitriptyline

Study Introduction and Objectives

Amitriptyline is a commonly prescribed tricyclic antidepressant.

Amitriptyline is rapidly absorbed with maximum plasma concentrations typically observed within 2 to 4 hours after dosing. The oral bioavailability of this compound is approximately 47%. Amitriptyline plasma concentrations decline in a biphasic decline manner after peak concentrations are reached. Approximately 95% of the total drug concentration is bound to plasma proteins. The apparent oral clearance and terminal half-life values range from 1100 to 1950 mL/min and 19 to 29 hours, respectively.

Amitriptyline exhibits a high intrinsic clearance and is primarily eliminated by hepatic metabolism. This compound undergoes N-demethylation, a biotransformation pathway purportedly mediated by the cytochrome P450 3A (CYP3A) isoforms, to form nortriptyline. Hydroxylation of amitriptyline and nortriptyline correlates with the debrisoquin hydroxylation phenotype, indicating a role for CYP2D6 in the elimination of both compounds.

The demethylated metabolite of amitriptyline is also a tricyclic with antidepressant activity. Maximum plasma concentrations of nortriptyline are typically achieved at 8 to 24 hours after oral administration of the parent compound. The half-life of nortriptyline is variable, ranging from 23 to 56 hours. Following a single 50 mg dose of amitriptyline, the mean ratio for metabolite to parent area under the plasma concentration-time curve is approximately 0.80.

Topiramate is currently being evaluated as potential treatment for bipolar disease and prophylaxis of migraine headache. Because these patients may receive concomitant treatment with amitriptyline, an investigation of the effects of multiple oral daily topiramate dosing on the pharmacokinetics of amitriptyline was investigated. The pharmacokinetics of topiramate was also assessed for comparability to historical control data obtained from healthy subjects.

Study Design

Eligible subjects received 25 mg of amitriptyline administered once daily on Days 1 through 8. Topiramate dosing was initiated at a dosage of 25 mg administered twice daily on Days 9 and 10 for a total daily dosage of 50 mg. The topiramate daily dosage was titrated to 100 mg on Days 11 and 12, to 150 mg on Days 13 and 14, and to 200 mg on Days 15 through 20. Amitriptyline was administered concomitantly with topiramate at a constant dosage of 25 mg per day on Days 9 through 20.

Sample Collection and Handling

Samples were collected on Day 8 and Day 20 of amitriptyline dosing at the following times: 0 (predose), 0.5,1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours post dose for measurement of amitriptyline and nortriptyline concentrations. In addition, steady-state predose (trough) concentrations of each compound on Day 7 and Day 19 were determined.

Topiramate samples were collected on Day 20 at the following times: 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post dose for measurement of topiramate concentrations.

Subject demographic data are presented in the following Table A10.

Table A10. Demographic data.

	All Subjects (N=18)
Age (years)	
Mean (SD)	32.7 (5.29)
Median	33.0
Range	21.0 to 40.0
Sex	
Male	9 (50%)
Female	9 (50%)
Race	
White	0
Black	3 (17%)
Asian	0
Hispanic	15 (83%)
Weight (kg)	
Mean (SD)	69.4 (7.69)
Median	68.9
Range	51.8 to 81.4
Height (cm)	
Mean (SD)	164.7 (7.90)
Median	165.1
Range	149.9 to 177.8
Frame Size	
Small	1 (6%)
Medium	17 (94%)

Bioanalytical Methods

Studied Period (years): Clinical Conduct: 25 March 1999 to 27 April 1999
Analysis of the serum samples was conducted 08 September 1999 to 13 September 1999.
Theoretical storage time: March 25, 1999-September 13, 1999~6 months

Table DM-ADS1: Human Plasma Assay Validation Information for Amitriptyline and Nortriptyline (TOPMAT-PHI-377)

Title:	Determination of Amitriptyline and Nortriptyline in Human Plasma by LC-MS/MS.
Type of Assay:	LC-MS/MS
Regression Method:	Weighted linear regression (1/concentration^2)
Range of Standard Line:	0.500 to 200 ng/mL
Limit of Quantitation (LOQ):	0.500 ng/mL
Specificity:	No interfering peaks were observed in the chromatograms at the elution times of amitriptyline, nortriptyline, or internal standards.
<u>Amitriptyline</u>	
Interday Precision:	% CV ≤5.05 for all standards
Interday Accuracy:	% Dev ≤4.0 for all standards (% Dev from theoretical value at all concentrations)
Quality Controls (QCs):	Prepared at 0.500, 1.50, 20.0, and 150 ng/mL
Precision (QCs):	% CV ≤15.06
Accuracy (QCs):	% Dev ≤3.6 (% Dev from theoretical value at all concentrations)
Bench-Top Stability:	Extracted samples stored under injection conditions are stable for at least 51.25 hours (carried out on low, medium, and high QCs).
Freeze/Thaw Stability:	Amitriptyline plasma samples are stable upon subjection to at least four freeze/thaw cycles (carried out on low, medium, and high QCs).
<u>Nortriptyline</u>	
Interday Precision:	% CV ≤4.05 for all standards
Interday Accuracy:	% Dev ≤1.8 for all standards (% Dev from theoretical value at all concentrations)
Quality Controls (QCs):	Prepared at 0.500, 1.50, 20.0, and 150 ng/mL
Precision (QCs):	% CV ≤8.66
Accuracy (QCs):	% Dev ≤2.7 (% Dev from theoretical value at all concentrations)

Bench-Top Stability:	Extracted samples stored under injection conditions are stable for at least 51.25 hours (carried out on low, medium, and high QCs).
Freeze/Thaw Stability:	Nortriptyline plasma samples are stable upon subjection to at least four freeze/thaw cycles (carried out on low, medium, and high QCs).
Acceptability Criteria:	Validation conformed to acceptability criteria in PPD Development Method Validation Report Project Code ABEW (refer to RWJPRI Document No. EDMS-USRA-6059742).[a]
Assay Implementation:	All analysis days met PPD Development acceptance criteria for standard curves and QCs (refer to RWJPRI Notebook TOPMAT-PHI-377)

Statistical Analysis

Analysis of variance (ANOVA) models were fitted to log-transformed Cmax and AUC0-24h values for amitriptyline, with the co-administration of topiramate (before and during topiramate) as the predictor and subject as a block effect. The effect of topiramate co-administration was tested at a 5% level of significance. Ninety-percent confidence intervals for the ratio of the mean Cmax and AUC0 24h values of amitriptyline obtained during topiramate administration to those obtained before topiramate administration were constructed using the estimated least square means and the intra-subject variability from ANOVA modeling

RESULTS

Table A11 : Amitriptyline Pharmacokinetic Parameters Following Daily Oral Administration of 25 mg of Amitriptyline to Healthy Subjects Before and During Daily Topiramate Dosing . Subject #110 excluded.

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng*h/mL)	CL/F (mL/min)
Before Topiramate				
N	17	17	17	17
Mean	34.6	3.9	449.2	1173.6
SD	12.9	0.90	197.3	685.1
% CV	37.3	22.8	43.9	58.4
Median	34.0	4.0	500.7	832.2
During Topiramate				
N	17	17	17	17
Mean	37.5	3.9	485.0	1266.3
SD	19.9	1.09	266.2	940.2
% CV	53.0	27.61	54.9	74.2
Median	37.5	4.0	475.7	875.9

Table A12: Nortriptyline Pharmacokinetic Parameters Following Daily Oral Administration of 25 mg of Amitriptyline to Healthy Subjects Before and During Daily Topiramate Dosing . Subject #110 excluded.

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng*h/mL)
Before Topiramate			
N	17	17	17
Mean	17.3	6.5	335.4
SD	12.1	1.81	243.1
% CV	70.2	27.9	72.5
Median	12.9	6.0	239.8
During Topiramate			
N	17	17	17
Mean	20.8	6.7	400.91
SD	16.5	2.52	347.7
% CV	79.4	38.0	86.7
Median	14.5	6.0	247.1

Table A13. Amitriptyline Pharmacokinetic Least Squares Mean Parameters on log scale following Daily Oral Administration of 25 mg of Amitriptyline to Healthy Subjects Before and During Daily Topiramate Dosing ..

Subject #110 included

	Without Topiramate	**With Topiramate**	**W/WO ratio**
AUC(0-24) ng/mlx hr	5.85	5.98	1.12
Cmax ng/ml	3.32	3.43	1.12
Cl/F ml/hr	7.08	6.96	0.88

Subject #110 excluded

	Without Topiramate	**With Topiramate**	**W/WO ratio**
AUC(0-24) ng/mlx hr	6.0	6.0	1.00
Cmax ng/ml	3.46	3.46	1.00
Cl/F ml/hr	6.93	6.93	1.00

Table A14: Point Estimates and Ninety-Percent Confidence Intervals for the Ratio of Means for Amitriptyline and Nortriptyline Pharmacokinetic Parameters[a]

		With versus Without Topiramate		
Drug	Parameter	Ratio (%)	Lower Limit (%)	Upper Limit (%)
Amitriptyline	C_{max}	99.59	82.65	119.99
	AUC_{0-24h}	100.90	88.23	115.39
Nortriptyline	C_{max}	113.46	102.38	125.74
	AUC_{0-24h}	110.20	100.42	120.93

[a] Analysis based on a sample size of 17 subjects

Table A15. 90% Confidence Intervals for Ratio of Means for Amitriptyline with Subject #110 included.

AUC(0-24) ng/mlx hr	89-142
Cmax ng/ml	85-147

Comments:

1. The firm proposed to drop subject # 110 from the analysis. However perusal of the individual subject results indicated that although his results were somewhat different the amitriptyline data was similar to that for subject # 113 which would lead one to believe that for this component that this may be representative data. For example the day 7 before topiramate dosing #110 was lower but similar to #113. On the other hand, on day 20 some of subject #110 values were higher than #113. Inclusion of subject #110 resulted in a 12% increase in AUC(0-24) and Cmax for amitriptyline in the 18 normal subjects (9 male; 9 female) receiving 200 mg/day of Topiramate.

Day 8:

110*	0.87	0.69	1.20	1.69	1.80	1.81	2.33	2.06	1.91	1.46	1.06	0.75	0.61	0.58
111	7.12	7.29	7.74	8.57	12.3	14.7	22.6	22.5	19.5	13.9	10.5	7.39	6.36	5.75
112	7.35	5.80	8.81	11.2	16.7	20.3	23.6	31.9	14.8	15.4	10.4	7.40	5.94	5.59
113	2.69	2.64	2.46	3.21	5.25	8.05	10.3	11.8	9.24	7.63	4.61	3.23	2.68	1.94

Day 20:

110*	0.92	0.71	0.81	2.72	10.2	15.5	20.5	19.9	17.7	12.3	7.39	5.35	4.26	4.41
111	5.71	6.91	6.77	7.16	11.0	16.3	21.1	18.0	13.4	10.8	10.0	6.98	5.90	4.71
112	7.37	6.63	6.33	6.58	7.01	7.22	7.30	6.78	6.27	4.89	4.33	2.99	2.87	3.61
113	3.91	3.10	3.10	5.22	7.77	8.79	15.1	14.0	10.1	5.84	4.67	3.03	3.08	2.45

Individual Study Report- TOPMAT-PHI-378- Sumatriptan

Study Introduction and Objectives

Topiramate is being investigated as prophylactic treatment for therapeutic benefit in subjects with migraine disorder. Sumatriptan is used in the acute treatment of migraine and it is anticipated that topiramate may be administered concomitantly. Therefore, it is important to investigate the effect of topiramate on the pharmacokinetics of sumatriptan.

On subcutaneous dosing of sumatriptan, systemic clearance is 1,194 +/- 149 mL/min (mean +/- SD), distribution half-life is 15 +/- 2 minutes, terminal half-life is 115 +/- 19 minutes, and volume of distribution (central compartment) is 50 +/- 8 liters. Cmax (maximum concentration) following a 6-mg subcutaneous injection is approximately 71 ng/mL (range, 49 to 110 ng/mL), and occurs (Tmax) at 12 minutes (range 5-20 minutes). The bioavailability is 97% +/- 16%. Following oral dosing with 100 mg sumatriptan, Cmax is approximately 51 ng/mL (range, 28 to 100 ng/mL), Tmax is approximately 2 hours, and elimination half-life (t½) is approximately2.5 hours. Bioavailability of an oral dose is approximately 15%, primarily due to presystemic metabolism and partly due to incomplete absorption, and is not significantly affected by food. On single dosing, sumatriptan is dose proportional in its extent of absorption (area under the concentration-time curve [AUC]) over a dose range of 25 to 200 mg, but the Cmax after 100 mg is approximately 25% less than expected based on a 25 mg dose. Protein binding of sumatriptan is low, approximately 14-21%. The drug is largely metabolized to an inactive metabolite (indole acetic acid) by monoamine oxidase (MAO); predominantly the A isoenzyme. The 200 mg/day topiramate dose used in this study is based on the limit of tolerability in healthy volunteers, and is anticipated to have clinical relevance to the plasma topiramate concentrations to be used for treatment of migraine. Healthy volunteers receiving 200 mg/day topiramate monotherapy will achieve plasma topiramate concentrations comparable to those achieved from a 400 mg/day dose in patients with epilepsy receiving topiramate as adjunctive therapy to concomitant enzyme inducing antiepileptic drugs. The 100-mg oral dose and the 6-mg subcutaneous dose of sumatriptan used in this study are the standard doses prescribed for clinical use.

The objective of this study was to determine the effect of topiramate on the single dose pharmacokinetics of sumatriptan when sumatriptan was given as an oral tablet or subcutaneous injection.

Study Design

This was an open-label study in 24 healthy adult men and women, between the ages of 18 to 40 years. Twelve subjects were randomized to receive 2 single oral doses of sumatriptan and twelve were randomized to receive 2 single subcutaneous injections of sumatriptan. Each group included at least 5 women and at least 5 men. Subjects received either a single 100-mg oral dose or a single 6-mg subcutaneous injection of sumatriptan on Day 1 according to their assigned treatment group. This was followed by a 6-day washout. On Day 8, subjects received 50 mg of

topiramate every 12 hours, followed by 75 mg topiramate every 12 hours on Day 9, and 100 mg of topiramate every 12 hours on Days 10 through 14. On Day 14, subjects received a second dose of sumatriptan either as a single 100-mg oral dose or as a single 6-mg subcutaneous injection, according to their assigned treatment group. Subjects participated in the study for approximately 15 days.

Sample Collection and Handling

Venous blood samples, 7 mL each, were collected by direct venipuncture or through an indwelling peripheral venous heparin lock catheter into a 7 mL B-D Vacutainer® "green top" tube (sodium heparin as the anticoagulant). The tube bore a subject identification label provided by the sponsor. Thirteen samples (predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose) were collected following dosing with sumatriptan alone (Day 1), for measurement of sumatriptan serum concentrations. Thirteen samples (predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose) were collected for measurement of sumatriptan serum concentrations and eleven samples (predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours postdose) were collected for measurement of topiramate plasma concentrations following coadministration of sumatriptan and topiramate on Day 14.

Table A15.: Demographic and Baseline Characteristics (Study TOPMAT-PHI-378)

	All Subjects (N=24)
Age (yrs)	
N	24
Mean (SD)	25.0 (5.40)
Median	23.0
Range	(18-38)
18-20	4 (17%)
21-30	16 (67%)
31-40	4 (17%)
Sex	
Male	14 (58%)
Female	10 (42%)
Race	
White	22 (92%)
Asian	1 (4%)
Other	1 (4%)
Height (cm)	
N	24
Mean (SD)	170.33 (9.433)
Median	168.90
Range	(152.4 – 186.7)
Weight (kg)	
N	24
Mean (SD)	72.13 (12.630)
Median	68.65
Range	(53.2 – 96.4)
Frame Size	
Small	3 (13%)
Medium	14 (58%)
Large	7 (29%)

Note: All subjects completed the study.

Bioanalytical Methods

Studied Period (years): Clinical Conduct: 27 May 1999 21 June 1999
Sample analysis 01 September 1999 24 September 1999
Theoretical storage time :May 27, 1999-September 24, 1999~4 months

Table DM-ADS1: Human Serum Assay Validation Information for Sumatriptan (TOPMAT-PHI-378)

Title:	Validation of a High Performance Liquid Chromatographic Mass Spectrometric Method for the Determination of Sumatriptan in Human Serum (refer to RWJPRI Project Notebook TOPMAT-PHI-378).
Type of Assay:	LCMS, positive ion
Regression Method:	Weighted linear regression calculated ($1/concentration^2$)
Range of Standard Line:	1.00 to 139.97 ng/mL
Limit of Quantitation (LOQ):	1.00 ng/mL
Specificity:	No significant interference at the retention times of sumatriptan and amitriptyline (internal standard) was observed in human serum.
Interday Precision:	% CV ≤4.7 for all standards (N = 3)
Interday Accuracy:	% Dev ≤6.9 for all standards (N ≥2) (% Dev from theoretical value at all concentrations)
Quality Controls:	Prepared at 1.00, 3.00, 39.99, and 109.98 ng/mL
Precision (Quality Controls):	% CV ≤9.4
Accuracy (Quality Controls):	% Dev ≤2.9 (% Dev from theoretical value at all quality control concentrations)
Stock Solution Stability:	Stock stability at -22 °C for sumatriptan and amitriptyline in methanol was demonstrated for 101 and 201 days, respectively.
Long Term Stability:	Long-term storage stability was demonstrated for 76 days at -22 °C (carried out on quality control samples).
Processed Sample Stability:	Processed sample stability was demonstrated for 100.0 hours at room temperature (carried out on quality control samples).
Bench Top Stability:	Bench top stability was demonstrated for 9.1 hours at room temperature (carried out on quality control samples).
Freeze/Thaw Stability:	Sumatriptan serum samples are stable upon subjection to at least three freeze/thaw cycles (carried out on quality control samples).
Acceptability Criteria:	Validation conformed to Phoenix acceptability criteria (refer to RWJPRI Drug Metabolism Notebook TOPMAT-PHI-378).
Assay Implementation:	All analysis days met acceptance criteria for standard lines and quality controls (refer to RWJPRI Drug Metabolism Notebook TOPMAT-PHI-378).

Statistical Analysis

For sumatriptan, statistical comparisons of pharmacokinetic parameters were performed separately for each route of administration. For each route of administration, ANOVA models were fit to the data to test for sex by treatment interaction. Since the sex by treatment interaction terms were not significant for any of the PK parameters, the comparison for 2 treatments was carried out by pooling the data from both sexes together. For each route, parameters estimated before and during topiramate dosing were compared using analysis of variance (ANOVA). ANOVA models were fit to the log-transformed pharmacokinetic parameter of interest (Cmax, AUC(0-□), AUC(0-*), t½, CL/F) with subject and treatment (sumatriptan alone [Day 1] or sumatriptan combined with topiramate [Day 14]) as factors. The treatment effect was tested at a 2-sided 5% level of significance using the residual error term.

RESULTS

Oral Dosing With Sumatriptan:

Table A16**:** Mean (SD) Sumatriptan Pharmacokinetic Parameters following Oral Administration of Sumatriptan Without (Day 1) and With (Day 14) Topiramate Coadministration (n=12) (Study TOPMAT-PHI-378)

Day	Statistics	$AUC_{(0-\infty)}$ (ng*h/mL)	$AUC_{(0-*)}$ (ng*h/mL)	C_{max} (ng/mL)	CL/F (L/h)	$t_{½}$ (h)	T_{max}[b] (h)
1	Mean[a]	254.2	249.1	50.44	422.3	2.21	1.25
	SD	67.2	67.1	14.90	127.8	0.48	0.50, 4.00
	CV%	26.4	26.9	29.5	30.3	21.7	--
14	Mean[a]	227.5	222.6	53.73	462.1	2.35	1.25
	SD	50.3	49.7	16.49	114.6	0.55	0.50, 3.00
	CV%	22.1	22.3	30.7	24.8	23.6	--

[a] Arithmetic means.
[b] Values presented for T_{max} are median and range.

Table A17**:** Statistical Comparison of Sumatriptan Pharmacokinetic Parameters Following Oral Administration of Sumatriptan Without (Day 1) and With (Day 14) Concomitant Topiramate (n=12) (Study TOPMAT-PHI-378)

Parameter	LSM[a] (Day 14)	LSM[a] (Day 1)	Comparison; Day 14: Day 1 (%) Ratio[b]	90% CI
$AUC_{(0-\infty)}$ (ng*h/mL)	222.1	245.7	90	85, 96
$AUC_{(0-*)}$ (ng*h/mL)	217.2	240.6	90	85, 96
C_{max} (ng/mL)	51.48	48.48	106	90, 125
CL/F (L/h)	450.2	406.9	111	104, 118
$t_{½}$ (h)	2.28	2.16	106	95, 118

[a]Geometric least squares mean.
[b]Geometric least squares mean ratio.

Subcutaneous Dosing With Sumatriptan

Table A18**:** Mean (SD) Sumatriptan Pharmacokinetic Parameters Following Subcutaneous Administration of Sumatriptan Without (Day 1) and With (Day 14) Topiramate Coadministration (n=12) (Study TOPMAT-PHI-378)

Day	Statistics	$AUC_{(0-\infty)}$ (ng*h/mL)	$AUC_{(0-*)}$ (ng*h/mL)	C_{max} (ng/mL)	CL/F (L/h)	$t_{½}$ (h)
1	Mean[a]	96.5	92.5	56.88	63.6	1.87
	SD	15.0	15.2	11.66	9.8	0.34
	CV%	15.6	16.4	20.5	15.4	18.3
14	Mean[a]	93.8	89.9	58.34	65.7	1.66
	SD	15.9	16.2	15.17	11.5	0.44
	CV%	17.0	18.1	26.0	17.5	26.3

[a] Arithmetic means.

Note: T_{max} was 0.50 hours for all subjects following subcutaneous dosing.

Historical comparison of Sumatriptan Effect on Topiramate

Topiramate pharmacokinetic data from this study were compared to historical data from previous studies in which healthy subjects or epileptic patients received the same dosing regimen of topiramate (100 mg q12h). Clearance data from Protocol YB[9], conducted in healthy subjects, and Protocols MS-216[10] and MS-218[11], conducted in epilepsy patients, are summarized in Table 7.

Table A19**:** Comparison of Topiramate Apparent Oral Clearance Data from this Study to Historical Pharmacokinetic Data (Study TOPMAT-PHI-378)

Study	Mean Apparent Clearance (CL/F) (mL/min)	Range of Apparent Clearance (CL/F) (mL/min)
YB	31.0 (10)	18.0-46.9
MS-216	33.2 (3)	27.7-36.6
MS-218	25.9 (8)	19.0-33.8
TOPMAT-PHI-378	20.8 (4.0)	15.6-31.1

Comments:

1.The results from this study shows that topiramate does not effect the pharmacokinetics of sumatriptan.

2.The historical comparison indicates an effort by the firm to determine any possible effect of sumatriptan on topiramate. Unfortunately the results are inconclusive since the ranges for all of the studies overlap for the studied despite the subject population.

Individual Study Report- TOPMAT-PHI-361- Lamotrigine

Study Introduction and Objectives

As it was anticipated that topiramate may be used as adjunctive therapy to lamotrigine, this study was designed to determine if a pharmacokinetic interaction occurred. The study was also designed to evaluate the pharmacokinetics of topiramate in the presence of lamotrigine.

The objectives of this study were to determine within the same group of patients with epilepsy: a) the steady-state pharmacokinetics of lamotrigine while on lamotrigine monotherapy, b) the steady-state pharmacokinetics of lamotrigine while concomitantly administered topiramate at three escalating doses of 100, 200, and 400 mg/day, c) the steady-state pharmacokinetics of topiramate at the three escalating topiramate doses while on a fixed-dose lamotrigine therapy, and d) the steady-state pharmacokinetics of topiramate while on topiramate monotherapy.

Study Design

This Phase I study was an open-label, sequential treatment study designed to evaluate the steady-state pharmacokinetics of lamotrigine and topiramate administered as monotherapy and combination therapy in subjects with epilepsy. Subjects were required to be receiving lamotrigine monotherapy at a stable dose for five weeks prior to study enrollment and to have epilepsy that was not optimally controlled by the lamotrigine. Following enrollment, subjects received escalating doses of topiramate; dose titration began at 50 mg/day for 2 weeks, followed by escalations in steps of 50 mg/day every 2 weeks until the maximum dose of 400 mg/day or an individual subject's maximum tolerated dose was achieved. Subjects maintained a constant dose of lamotrigine throughout the combination treatment period. The dose of lamotrigine was then tapered at a rate of approximately 25% per week. The dose of topiramate was adjusted only if necessary during the lamotrigine tapering period. After the tapering of lamotrigine was completed, subjects remained on topiramate monotherapy for 14 days.

Table A20: Time and Events Schedule (Protocol TOPMAT-PHI-361)

(Protocol TOPMAT-PHI-361)

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
Week	-2	-1	-1	4	8	12	16	18	19	20	21	Taper	Term
Day			-1	7	7	7	7	1	1	1	7		
Lamotrigine Dose[a]	X	X	X	X	X	X	X	.5	.25	0	0		
Topiramate Dose[b]	0	0	0	100	200	300	400	400	400	400	400		
Blood Sample (lamotrigine)	X[c]	X[c]	X[d]	X[d]	X[d]		X[d]	X[e]	X[e]	X[c]	X[d]		
Blood Sample (topiramate)				X[e]	X[e]		X[e]	X[c]	X[e]	X[c]	X[e]		
Urine Sample (lamotrigine & topiramate)[f]			X	X	X		X				X		
Medical History	X												
Physical Examination		X			X								X
Electrocardiogram		X											X
Pregnancy Test (if female)		X											
Clinical Laboratory Tests		X			X								X
Adverse Events[g]				X	X	X	X	X	X	X	X	X	X
Vital Signs		X	X	X	X	X	X				X	X	X
Seizure Count			X	X	X	X	X	X	X	X	X	X	X
Dispense Study Medication			X	X	X	X	X	X	X	X	X		
Collect Unused Study Medication				X	X	X	X	X	X	X	X	X	X

[a] Subjects were to receive a stable dose of lamotrigine for at least five weeks before the start of the study and during the study through Week 16; tapering of the lamotrigine dose began at Week 17 with subjects receiving 75% of their prior dose, followed by 50% during Week 18 and 25% during Week 19; subjects were not to receive lamotrigine during Weeks 20 and 21.

[b] Subjects began receiving topiramate on Week 1 Day 1 with a dose of 50 mg/day; the dose was titrated upward in steps of 50 mg/day every two weeks until the subject's maximum tolerated dose or the maximum dose of 400 mg/day was achieved; thereafter subjects maintained a stable dose of topiramate until tapering began after Visit 11 (or when the subject prematurely discontinued the study).

[c] Single pre-dose trough blood sample collected before the morning dose.

[d] Serial blood samples collected at 0, 1, 2, 3, 4, 6, 8, and 12 hours after dosing.

[e] Single blood sample collected 12 hours after dosing.

[f] Urine collected at 0 to 4, 4 to 8, and 8 to 12 hours after dosing.

[g] Adverse events were also evaluated by telephone on Day 7 of Weeks 2, 6, 10, and 14.

Table A21: Demographic and Baseline Characteristics (All Subjects in Protocol TOPMAT-PHI-361)

Characteristic	Topiramate (N=13)
Age (yr)	
N	13
Mean	33.5
SD	11.87
Median	32.0
Range	19.0 to 57.0
Sex [n (%)]	
Male	5 (38)
Female	8 (62)
Race [n (%)]	
White	13 (100)
Black	0 (0)
Asian	0 (0)
Other	0 (0)
Weight (kg)	
N	13
Mean	73.8
SD	17.87
Median	68.0
Range	44.4 to 104.5
Height (cm)	
N	13
Mean	169.6
SD	7.52
Median	167.0
Range	160.5 to 186.5

Characteristic	Topiramate (N=13)
Monthly Seizure Rate	
N	13
Mean	19.9
SD	40.86
Median	7.1
Range	0.0 to 151.2
Seizure Type [N (%)][a]	
Other[b]	6 (46)
Tonic-Clonic	2 (15)
Myoclonic	1 (8)
Atypical Absence	0 (0)
Absence	0 (0)
Tonic	0 (0)
Clonic	0 (0)
Drop Attack	0 (0)
Any Generalized Seizures	2 (15)
Any Seizure Type	8 (62)

[a] Number and percent of subjects who had each type of seizure recorded during the baseline period. Individual subjects may have experienced more than one seizure type during the baseline period.

[b] "Other" included complex partial, simple partial, and secondarily generalized seizures.

Thirteen subjects enrolled in the study, and 11 subjects (85%) completed the study. Two subjects (15%) withdrew because of adverse events. Subject 202 experienced mental slowing and outbursts of temper and withdrew from the study after 30 days of topiramate dosing. This subject received a maximum dose of 100 mg/day topiramate; the subject also received 300 mg/day lamotrigine throughout the study. Subject 203 experienced dyspnea and withdrew after 39 days of topiramate dosing. This subject received a maximum dose of 150 mg/day topiramate; the subject also received 300 mg/day lamotrigine throughout the study. In addition, Subject 201 completed the study but experienced adverse events that the investigator described as resulting in study discontinuation.

Sample Collection and Handling

Single blood samples were collected prior to the initiation of topiramate therapy at Visits 1 and 2 for determination of trough concentrations of lamotrigine. At Visits 3, 4, 5, 7, and 11, serial blood samples were collected for determination of lamotrigine concentrations at 0, 1, 2, 3, 4, 6, 8, and 12 hours after dosing. At Visits 4, 5, 7, and 11, serial blood samples were collected for determination of topiramate concentrations at 0, 1, 2, 3, 4, 6, 8, and 12 hours after dosing. Single blood samples for determination of trough lamotrigine and topiramate concentrations were collected before dose administration at Visits 8, 9, and 10. Urine was collected for determination of topiramate concentrations at Visits 3, 4, 5, 7, and 11 at 0 to 4, 4 to 8, and 8 to 12 hours after dosing.

Bioanalytical Methods

Studied Period (years): Clinical Conduct: 7 July 1997 - 21 October 1999

Sample Analysis: Lamotrigine in plasma: 7 June 2000 – 19 July 2000; Topiramate in plasma: 19 May 2000 – 30 May 2000; Topiramate in urine: 30 June 2000 – 14 July 2000

Theoretical storage time : Lamotrigine plasma-July 7, 1997-July 19, 2000-~3 years
Topiramate plasma-July 7, 1997-May 30, 2000~2 years 10 months

Table DM-ADS1: Human Serum Assay Validation Information for Lamotrigine (TOP-INT-12)

Title:	Lamotrigine Measurement in Human Plasma/Serum by Reversed Phase HPLC.
Type of Assay:	HPLC/UV detection
Range of Standard Curve:	0.50 to 20.00 µg/mL
Limit of Quantitation (LOQ):	0.50 µg/mL
Specificity:	Confirmed with blank human serum and plasma
Interday Precision:	% CV for lamotrigine <7.5 for all standards
Interday Accuracy:	% Dev for lamotrigine <9.0 for all standards (% Dev from theoretical value at all concentrations)
Quality Controls (QCs):	Prepared at 1.5, 7.5, and 17.5 µg/mL
Precision (QCs):	% CV <5.9 lamotrigine
Freeze/Thaw Stability (QCs):	The effect of freeze/thaw cycles was demonstrated using twelve freeze/thaw cycles. No effect was seen.
Acceptability Criteria:	Validation conformed to Medical Toxicology Laboratory acceptability criteria (refer to RWJPRI Notebook TOP-INT-12)
Assay Implementation:	All analysis days met acceptance criteria for standard curves and QCs (refer to RWJPRI Notebook TOP-INT-12).

Statistical Analysis

The concentrations of lamotrigine in plasma and topiramate in plasma and urine at each applicable visit were summarized. No imputations were performed for missing data concentrations or missing times. If a concentration or a time point was missing for a particular data point, that point was not used in the pharmacokinetic parameter calculations. Symbols for the following text are:

Cmin_Nor- Dose normalized trough concentrations
Cmax_Nor- Dose normalized Cmax

AUC_Nor- Dose normalized AUC
Ae_Nor- Dose normalized amount excreted

The following pharmacokinetic parameters of lamotrigine in plasma were calculated and summarized for the indicated visits for the concentrations:

Visits 1, 2, 8, 9, and 10: C_{min}, C_{min}_Nor

Visits 3, 4, 5, and 7: C_{max}, T_{max}, AUC, C_{min}, C_{max}_Nor, AUC_Nor, C_{min}_Nor, CL_{oral}

Visit 11: C_{max}, T_{max}, AUC, C_{min}

The following pharmacokinetic parameters of topiramate in plasma and urine:

were calculated and summarized at the indicated visits:

Visits 4, 5, 7, and 11: C_{max}, T_{max}, AUC, C_{min}, C_{max}_Nor, AUC_Nor, C_{min}_Nor, CL_{oral}, A_e, A_e_Nor, CL_R

An ANOVA was performed for the log-transformed pharmacokinetic parameter of interest. Only subjects who completed the study were included in this analysis. This analysis included subject as a random effect and visit as a fixed effect. From this ANOVA, least squares means for each visit, estimated visit differences, and 90% confidence intervals for visit differences were calculated. These log-transformed results were transformed back to the original scale by exponentiation to obtain least square geometric means, ratios of the visit means, and 90% confidence intervals for these ratios. Later visits were compared to earlier visits with the earlier visit as the reference. If the limits of the 90% confidence interval for the ratio of the visit means fell entirely within 80% to 125%, it was concluded that the pharmacokinetic parameters were not altered by the presence of the other antiepileptic drug and that the steady state was maintained.

The first objective was to determine the steady-state pharmacokinetics of lamotrigine while on lamotrigine monotherapy. An ANOVA was performed for the dose-normalized trough concentrations (Cmin_Nor) at Visits 1, 2, and 3 for lamotrigine.

The second objective was to determine the steady-state pharmacokinetics of lamotrigine while concomitantly dosed with topiramate at each of three escalating topiramate doses. An ANOVA was performed for the dose-normalized pharmacokinetic parameters (Cmax_Nor, AUC_Nor,

Cmin_Nor, and CLoral) at Visits 3, 4, 5, and 7 for lamotrigine. The primary comparison was based on AUC_Nor.

The third objective was to determine the steady-state pharmacokinetics of topiramate at each of three escalating topiramate doses while on a fixed dose lamotrigine therapy. An ANOVA was performed for the dose-normalized pharmacokinetic parameters (Cmax_Nor, AUC_Nor, Cmin_Nor, Ae_Nor, CLoral, and CLR) at Visits 4, 5, and 7 for topiramate in plasma. The primary comparison was based on AUC_Nor.

The last objective was to determine the steady-state pharmacokinetics of topiramate while on topiramate monotherapy. An ANOVA was performed for the dose-normalized pharmacokinetic parameters (Cmax_Nor, AUC_Nor, Cmin_Nor, Ae_Nor, CLoral, and CLR) at Visits 7 and 11 for topiramate in plasma. The primary comparison was based on AUC_Nor.

RESULTS

Change in Lamotrigine pharmacokinetic values in the presence of topiramate on the following visit days during the course of the study, visits 7 vs. 3, and when Lamotrigine was being tapered at a rate of approximately 25% per week, visits 7 vs. 11.

	AUC	**Cmax**
Visit 7 vs Visit 3 **Lamotrigine + Topiramate 400 mg vs Lamotrigine alone**	**-10.1%**	**-8.3**

	AUC	**Cmax**	**Cmin**
Visit 7 vs Visit 11 **Lamotrigine + Topiramate 400 mg vs Topiramate alone**	**+14.8%**	**+16.8%**	**8.6%**

Table A22: Results of Statistical Comparisons of Pharmacokinetic Parameters of Lamotrigine Obtained when Lamotrigine Given Alone (Visit 3) and in Combination with Topiramate (Visits 4, 5, and 7) (Subjects Who Completed the Study; Protocol TOPMAT-PHI-361)

Metric	Visit	Geometric LSMean	Ratio vs. Visit 4	90% CI vs. Visit 4	Ratio vs. Visit 5	90% CI vs. Visit 5	Ratio vs. Visit 7	90% CI vs. Visit 7
Dose-normalized AUC	3	0.2172	108.0%	96.6%, 120.7%	98.8%	88.3%, 110.4%	89.9%	80.4%, 100.5%
	4	0.2345	NA	NA	91.5%	81.8%, 102.3%	83.2%	74.5%, 93.1%
	5	0.2145	NA	NA	NA	NA	91.0%	81.4%, 101.7%
	7	0.1952	NA	NA	NA	NA	NA	NA
Dose-normalized C_{max}	3	0.0243	113.2%	101.9%, 125.8%	93.6%	84.2%, 104.1%	91.7%	82.5%, 101.9%
	4	0.0275	NA	NA	82.7%	74.4%, 91.9%	81.0%	72.9%, 90.0%
	5	0.0227	NA	NA	NA	NA	98.0%	88.1%, 108.9%
	7	0.0223	NA	NA	NA	NA	NA	NA
Dose-normalized C_{min}	3	0.0149	117.8%	101.7%, 136.5%	104.8%	90.5%, 121.4%	98.6%	85.2%, 114.3%
	4	0.0176	NA	NA	88.9%	76.8%, 103.0%	83.7%	72.3%, 96.9%
	5	0.0156	NA	NA	NA	NA	94.1%	81.2%, 109.0%
	7	0.0147	NA	NA	NA	NA	NA	NA
CL_{oral}	3	4.6043	92.6%	82.8%, 103.6%	101.2%	90.6%, 113.2%	111.3%	99.5%, 124.4%
	4	4.2649	NA	NA	109.3%	97.8%, 122.2%	120.1%	107.4%, 134.3%
	5	4.6616	NA	NA	NA	NA	109.9%	98.3%, 122.9%
	7	5.1231	NA	NA	NA	NA	NA	NA

Note: Geometric lsmeans are the antilogs of the lsmeans of the natural logarithmic transformed endpoints from an ANOVA model. The model included terms for subject and visit and the natural logarithm of the PK parameters as the dependent variable.
NA = Not Applicable, CI = Confidence interval for ratio of visit means.

Comments:

1. Several of the low (0.5 ug/ml) concentrations for the calibration curve were greater than 20% (i.e. runs 4,5,6, and 10). There were 12 curves run. It appears that the assay is not robust at 0.05 ug/ml. This did not seem to have a major impact on the study since the lowest plasma levels were approximately 1.2 ug/ml.

2. There appeared to be a large increase in lamotrigine AUC and Cmax on the first day of therapy (i.e. day 4).

3. As dose of topiramate is increased the AUC and Cmax for Lamotrigine decreased from visits 4-7**.**

4. Lamotrigine AUC and Cmax values decreased approximately 10% in the presence of steady-state Topiramate plasma concentrations.

5. Topiramate AUC and Cmax values increased approximately 15% in the presence of Lamotrigine .

NONCLINICAL ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION (ADME) STUDIES OF TOPERIMATE UTILIZING HUMAN BIOMATERIALS

Study DMO1362- Determination of the Potential for RWJ-17021 to Inhibit Cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) in vitro in Human Liver Microsomes.

RWJ-17021 (0.25 – 100 μM) was evaluated for its ability to inhibit human liver microsomal cytochrome P450 enzyme activities. Enzyme activities associated with CYP1A2, CYP2A6,

CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 were determined using enzyme-specific probe compounds incubated with pooled human liver microsomal samples.
Two or more drugs may compete for the active site of a single human liver CYP enzyme. Alternatively, a drug may be an inhibitor of a specific CYP enzyme without necessarily being a substrate for that enzyme.

Methods

Human liver microsomes pooled from 10-15 donors, and human liver microsomes pooled from 5-6 donors with high enzyme activities associated with specific CYP isoforms were used for the studies. The microsomes were isolated and characterized for CYP enzyme activities by the research laboratory and stored at -80°C until use.

The total CYP content and isoenzyme-specific activities of the human liver microsomes are shown in the table below.

CYP Enzyme	CYP 1A2 Pool	CYP2C19/2B6 Pool	CYP2C9 Pool	CYP2D6 Pool	CYP3A4 Pool	Control Pool
CYP1A2	141.1	41.7	37.1	74.7	84.6	48.2
CYP2A6	2614.4	2088.0	1296.2	1283.5	2075.1	1456.0
CYP2C19	48.0	134.8	21.6	55.1	29.7	38.8
CYP2B6	149.8	244.8	53.3	55.2	134.9	60.2
CYP2C9	209.2	329.1	304.6	248.6	199.3	147.7
CYP2D6	153.9	172.5	245.1	280.8	125.5	224.9
CYP2E1	1689.0	1679.0	1878.7	1786.8	1517.2	2133.0
CYP3A4/5	5065.3	7077.7	1786.9	1671.5	5347.8	3107.0
CYP4A11	1181.0	970.4	1214.0	1143.0	708.0	785.0
Total CYP Content	0.47	0.5	0.28	0.31	0.54	0.40

The concentration of the substrates used for the characterisation of the different enzymes were: 7-ethoxyresorufin (10 µM); coumarin (50 µM); S-mephenytoin (400 µM); tolbutamide (1 mM); dextromethorphan (80 µM); chlorzoxazone (500 µM); testosterone (250 µM); and lauric acid (100 µM).

The corresponding enzyme reaction are: 7-ethoxyresorufin *O*-deethylation for CYP1A2, Coumarin 7-hydroxylation for CYP2A6, S-mephenytoin 4'-hydroxylation and *N*-demethylation for CYP2C19 and CYP2B6, Tolbutamide methyl-hydroxylation for CYP2C9, Dextromethorphan *O*-demethylation for CYP2D6, Chlorzoxazone 6-hydroxylation for CYP2E1, Testosterone 6ß-hydroxylation for CYP3A4/5 and Lauric Acid 12-hydroxylation for CYP4A11.

Enzyme activity is expressed in pmol/mg protein/min.
Total CYP content is expressed in nmol/mg protein.

The effect of topiramate on the metabolism of each of the substrates was studied using human microsomes to assess its impact on each of the enzyme systems.

Effect of topiramate on various CYP enzyme activities

Isoform and Reaction	RWJ-17021 (µM)							
Catalyzed	0	0.25	1	5	10	25	50	100
(CYP1A2) 7-ethoxyresorufin *O*-deethylation	100.0	107.5	105.5	94.0	101.9	97.4	97.6	92.2

(CYP2A6) Coumarin 7-Hydroxylation	100.0	92.9	88.2	97.2	95.2	98.6	91.3	82.3
(CYP2B6) S-mephenytoin *N*-Demethylation	100.0	105.5	95.1	103.2	99.2	96.0	80.7	72.3
(CYP2C9) Tolbutamide methyl-hydroxylation	100.0	107.4	109.6	99.2	101.2	99.7	101.7	97.4
(CYP2C19) S-mephenytoin 4'-hydroxylation	100.0	98.9	91.9	100.7	96.8	106.5	101.4	101.1
(CYP2D6) Dextromethorphan *O*-demethylation	100.0	95.6	100.5	100.3	97.6	98.1	98.8	95.5
(CYP2E1) Chlorzoxazone 6-Hydroxylation	100.0	93.4	84.8	83.0	87.7	83.6	94.0	93.7
(CYP3A4/5) Testosterone 6ß-Hydroxylation	100.0	101.7	100.8	103.4	96.7	105.2	107.3	103.7

Known CYP isoform-selective inhibitors, 10 µM α-naphthoflavone (CYP1A2), 50 µM tranylcypromine (CYP2A6 and CYP2C19), 200 µM 7-ethoxy-4-trifluoromethyl coumarin (CYP2B6), 20 µM sulfaphenazole (CYP2C9), 1 µM quinidine (CYP2D6), 50 µM diethyl-dithiocarbamate (CYP2E1) and 1 µM ketoconazole (CYP3A4/5), were included in this study as positive controls.

Table SD1: Positive Controls for Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 Activities in Pooled Human Liver Microsomes.

Inhibitor Concentration	**Enzyme**	**% Inhibition**
10 µM α-Naphthoflavone	CYP1A2	88.4
50 µM Tranylcypromine	CYP2A6	98.0
200 µM 7-ethoxy-4-trifluoromethyl coumarin	CYP2B6	37.9
20 µM Sulfaphenazole	CYP2C9	84.8
50 µM Tranylcypromine	CYP2C19	57.1
1 µM Quinidine	CYP2D6	67.3
50 µM Diethyl-dithiocarbamate	CYP2E1	65.1
1 µM Ketoconazole	CYP3A4/5	94.0

Conclusion:

When RWJ-17021 was incubated with human liver microsomes, a slight inhibitory effect of approximately 19-28% was observed on CYP2B6 (S-mephenytoin *N*-demethylation) enzymatic activity, at the highest concentrations (50 and 100 µM). There was also a slight indication of an inhibitory effect (~18% inhibition) observed on CYP2A6 (coumarin 7-hydroxylation) enzymatic activity, but only at the highest concentration (100 µM). Enzyme activities associated with CYP1A2 (7-ethoxyresorufin *O*-deethylation), CYP2C9 (tolbutamide methyl-hydroxylation), CYP2C19 (S-mephenytoin 4'-hydroxylation), CYP2D6 (dextromethorphan *O*-

demethylation), CYP2E1 (chlorzoxazone 6-hydroxylation) and CYP3A4/5 (testosterone 6□-hydroxylation) were not inhibited by RWJ-17021 at concentrations up to 100 μM.
These in vitro concentrations are greater than the reported highest observed concentrations in humans.

In Vitro Metabolism study of ^{14}C-Topiramate using Microsomes Expressing Human P450 (II) –Report No. AE-2604.

OBJECTIVE

Human P450 subfamilies involved in metabolism of ^{14}C-KW-6485 were estimated using microsomes expressing human P450. In addition, whether KW-6485 inhibits enzymatic reaction mediated by human P450 subfamilies or not was examined.

Methods

[a)] Control microsomes for each subfamily

CYP1A1, 1B1, 2C8, 2D6-Val, 2E1, 3A4
Reductase [phosphate buffer solution (pH 7.4) was used]

CYP2A6, 2C9-Arg, 2C9-Cys
Reductase [Tris buffer solution (pH 7.4) was used]

CYP1A2, 2B6, 2C19, 2D6-Met
Control (vector) [phosphate buffer solution (pH 7.4) was used]

Conclusions

Inhibition of each P450 model substrate metabolism in microsomes prepared from B-lymphoblastoid cell lines expressing cDNA's encoding each human P450 by Topiramte and each positive control.

Cytochrome P450 enzymes	% of Control			
	KW-6485 2 μM	KW-6485 20 μM	KW-6485 200 μM	Positive control **
Control *	100.0	100.0	100.0	——
1A1	111.3	106.7	99.2	2.2
1A2	99.7	95.7	98.6	11.7
1B1	97.4	92.1	93.2	0.7
2A6	102.7	92.7	93.3	20.1
2B6	109.9	104.2	99.5	9.2
2C8	95.7	98.8	101.3	40.9
2C9-Arg	100.4	96.3	91.1	59.6
2C9-Cys	101.7	100.6	102.3	60.9
2C19	104.7	99.3	99.4	19.4
2D6-Met	84.1	85.0	85.6	6.9
2D6-Val	93.8	87.4	66.9	3.1
2E1	100.2	101.5	100.3	6.2
3A4	104.9	96.2	101.1	17.7

* : Without test article

** : Concentration of positive control

CYP1A1, 1A2, 1B1 : α-Naphthoflavone (5 μM)

CYP2E1 : Diethyldithiocarbamate (100 μM)

Other CYPs : SKF-525A (300 μM)

Binding of Topiramate to Blood Cells and Plasma Proteins in Human Blood

Methods- Study No. 99-169A

Measured radioactivity was divided by specific activity to calculate concentration. Blood cell concentration ($C_{blood\ cell}$, μg eq./mL) was calculated using the following equation. Plasma protein-bound drug concentration (C_{bound}, μg eq./mL) was calculated by subtracting unbound drug concentration ($C_{unbound}$, μg eq./mL) from plasma concentration (C_{plasma}, μg eq./mL).

$$C_{blood\ cell} = \frac{C_{blood} - C_{plasma} \times (1 - Ht)}{Ht}$$

2.9. Analysis of blood cells distribution and protein binding

From the radioactivity concentrations measured in the paragraph 2.8., blood/plasma partition ratio (B/P), unbound fraction (fu), bound fraction (fb), bound/unbound drug ratio (fb/fu), and blood cell/unbound drug distribution coefficient (D)[2)] were calculated as follows:

$$B/P = C_{blood}/C_{plasma} \quad fu = C_{unbound}/C_{plasma} \quad fb = 1–fu \quad fb/fu = C_{bound}/C_{unbound}$$

$$D = C_{blood\ cell}/(fu \cdot C_{plasma}) = \frac{(C_{blood} / C_{plasma}) / fu - (1 - Ht) - fb(1 - Ht) / fu}{Ht}$$

Conclusion

Unbound drug concentration indicates nonlinearity to blood concentration, when blood concentration was relatively low (C_{blood} < 5 ug/ml), but it increased almost proportionally at C_{blood}>10 ug/ml. The clinical doses of KW-6485 are 200-400 mg/day. If dose is gradually increased from 200 mg/day in clinical practice, unbound plasma concentration of KW-6485 which is considered to relate to pharmacological effect or toxicity does not sharply increase, and is almost proportional to blood concentration, because blood cells distribution is saturated.

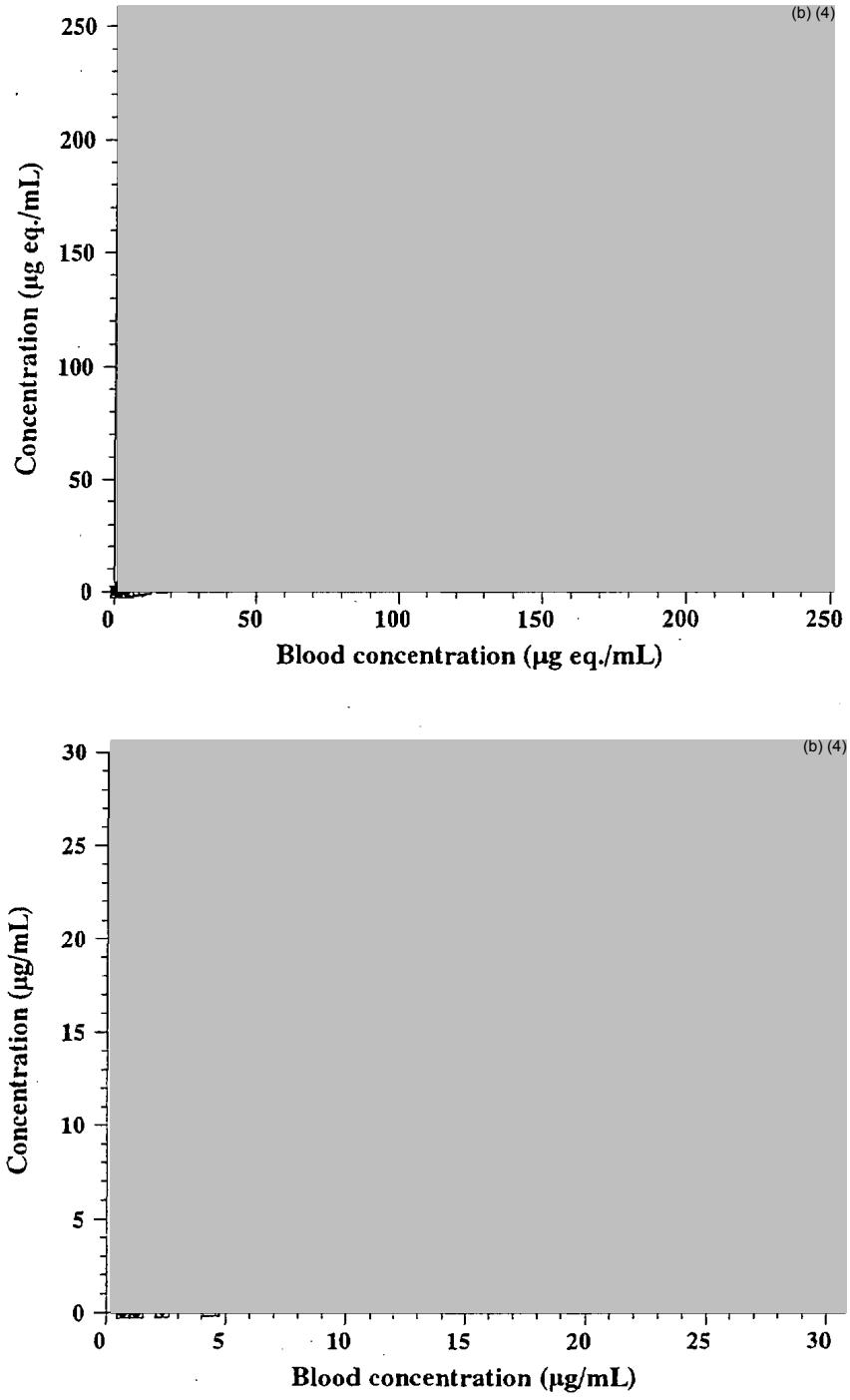

Fig. 6 Relationships between blood concentration and blood cells, plasma, free drug or bound drug concentrations

Symbols represent the actual values in this experiment. Lines represent fitting curves calculated from the binding parameters

Effects of Anticonvulsant Drugs and a Carbonic Anhydrase Inhibitor on the Binding of Topiramate to Human Blood Cells and Plasma Protein- STUDY NO. 2000-384A

INTRODUCTION

Topamax is an anticonvulsant and is reported to bind to blood cells in a saturable manner and to show low plasma protein. The following interactions with other anticonvulsant drugs were reported in concomitant use in epilepsy; the decreases in the area under the plasma concentration to time curve (AUC), maximum plasma concentration (Cmax), and mean plasma concentration (Cav) of KW-6485 by about 40% in combination with carbamazepine (CBZ), the decrease in the apparent total concentration of KW-6485 by 48 % in combination with phenytoin (PHT), the decrease in AUC and Cmax of KW-6485 by about 14% in combination with valproic acid (VPA). However, the causes have not been investigated. Since KW-6485 slightly inhibits carbonic anhydrase, the combination with acetazolamide (ACZ), a typical carbonic anhydrase inhibitor, may change the binding of KW-6485 to blood cells due to inhibition of the binding to carbonic anhydrase on the erythrocyte membrane. The present study investigated the effects of above-mentioned 4 drugs (ACZ, CBZ, PHT and VPA) on the bindings of KW-6485 to human blood cells and plasma protein in vitro , in order to investigate causes of altered pharmacokinetics of KW-6485 by CBZ, PHT and VPA and to investigate the interaction between KW-6485 and ACZ.

METHODS

The blood/plasma partition ratio (B/P) and the plasma protein binding (fb) were calculated by $B/P = C_{blood}/C_{plasma}$ and $fb = 1 - (C_{unbound}/C_{plasma})$, respectively.

The concentrations of KW-6485 in blood, plasma and unbound fraction (C_{blood}, C_{plasma} and $C_{unbound}$) were calculated by dividing measured value of each fraction by their specific radioactivity. The concentration in blood cells ($C_{blood\,cell}$) was calculated using the following equation, and the concentration of KW-6485 bound to plasma protein (C_{bound}) was calculated by subtracting $C_{unbound}$ from C_{plasma}.

$$C_{blood\,cell} = \frac{C_{blood} - (1 - Ht) \times C_{plasma}}{Ht}$$

CONCLUSION

When KW-6485 was added at a concentration of 5 μg/mL to human blood, the blood / plasma partition ratio (B/P) and the plasma protein binding (fb) were 2.13±0.15 (mean ± S.D., n=6) and 18.5±3.5%, respectively. In the case of addition of KW-6485 (5 μg/mL) and ACZ (150 μg/mL) to the human blood, the B/P of KW-6485 was halved to 1.03±0.05 thus indicating ACZ to inhibit the binding of KW-6485 to blood cells. On the other hand, when CBZ (45 μg/mL) or PHT (75 μg/mL) was added to the blood sample with same KW-6485 concentration, the B/P of KW-6485 were 2.21±0.10 and 2.18±0.11, respectively and the fb were 17.1±3.6% and 15.7±1.9%, respectively. Both CBZ and PHT had no effect on the bindings to human plasma protein and human blood cells. When KW-6485 (5 μg/mL) and sodium valproate (VPA-Na) (500 μg/mL) were added to the human blood, the B/P of 2.20±0.09 of KW-6485 was not affected. In contrast, fb significantly decreased from 18.5±3.5% to 12.2±2.5% and the free fraction concentration of KW-6485 in plasma increased from 2.33±0.08 μg/mL to 2.38±0.08 μg/mL. However, such a slight increase was considered to have no clinical significance.

STUDY NO.2000-371-A

Interaction Study on the Protein Binding between Topiramte and Valproic Acid in Human Plasma (No. 2000-371A)

PURPOSE OF THE STUDY

Topiramate is an anticonvulsant drug. The concomitant therapy of KW-6485 and valproic acid (VPA) in patients with epilepsy revealed pharmacokinetic interactions between the two drugs; the concomitant therapy caused about a 15% decrease in the maximum plasma concentration and area under the plasma concentration-time curve (AUC) of KW-6485 compared with the values during KW-6485 monotherapy, and an 11.3% decrease in the AUC of VPA compared with the value during VPA monotherapy. In the in vitro study evaluating the effects of anticonvulsant drugs on the binding of KW-6485 to human blood cells and plasma protein, the addition of VPA (plasma concentrations of sodium valproate: 500 and]ug/mL) resulted in a decrease in the protein binding of KW-6485 (plasma concentration of KW-6485: about 2.8 ug/mL). This interaction in protein binding was considered to partly explain the changes in pharmacokinetics observed in the concomitant therapy. The present study was performed to investigate in more detail the protein-binding interaction between KW-6485 and VPA in human plasma. The therapeutic plasma level used as the middle concentration (sodium valproate: 100 ug/mL, KW-6485: 10 ug/mL), and the low and high concentrations were set at 10 times lower and 5 times higher than the middle concentration, respectively.

METHODS

Study 1. Effects of KWA-6485 on the protein binding of VPA

The plasma and protein-unbound fraction were collected and treated in a manner described below:

Plasma: 5 mL of a liquid scintillation cocktail Hionic Fluor was added to 100 μL of the incubated plasma, well agitated, and then subjected tc radioactivity determination.

Unbound fraction: 800 μL of the remaining incubated plasma was centrifuged with a Centrifree micropartition device ((b) (4)) at 2000 x g for 12 or 15 min at room temperature. 5 mL of a liquid scintillation cocktail Hionic Fluor was added to 100 μL of the filtrate, well agitated, and then subjected to radioactivity determination.

Study 2. Effects of VPA on the protein binding of KW-6485

The study was in a manner similar to study 1. Topiramate concentrations were 1, 10 or 50 ug/ml while VPA-Na concentrations were 0, 10, 100 and 500 ug/ml.

CONCLUSIONS

The influence of KW-6485 on the binding of valproic acid (VPA) to human plasma proteins and the influence of VPA on the binding of KW-6485 to human plasma protein were investigated in *in vitro* using ^{14}C-labeled compounds.

1) The free fractions (fu) of KW-6485 in human plasma were 77.6±3.0, 75.9±1.1, 79.4±1.4% (mean±S.D., n=6) at 1, 10 and 50 μg/mL of KW-6485, respectively. When VPA-Na was added at a concentration of 500 μg/mL to these plasma, the fu of KW-6485 significantly increased to 87.6±1.7, 86.4±1.5, 88.8±1.7%, respectively ($p < 0.0001$).
2) The fu values of VPA-Na in human plasma were 7.09±0.23, 13.3±0.3, 53.3±0.7% (mean±S.D., n=5 or 6) at 10, 100, 500 μg/mL of VPA-Na in the presence of KW-6485 at 50 μg/mL, respectively. These values were not different from the values of control group (no addition of KW-6485) (7.24±0.20, 13.7±0.5, 53.9±1.0%).

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/s/

Andre Jackson
3/19/03 01:53:26 PM
BIOPHARMACEUTICS

Raman Baweja
3/19/03 03:41:48 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: June 18, 2003

TO: Jacqueline Ware, Pharm.D, Senior Regulatory Project Manager
Howard Chazin, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Associate Director
Good Clinical Practice Branch I &II, HFD-46/47
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA #: 20-505/SE1-018 (Tablets)
20-844/SE1-015 (Sprinkle Capsules)

APPLICANT: Ortho-McNeil Pharmaceutical, Inc./Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (JNJPRD)

DRUG: Topamax (topiramate)

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Topamax Monotherapy in Treatment of Partial Seizure

CONSULTATION REQUEST DATE: January 10, 2003

ACTION GOAL DATE: August 30, 2003

I. BACKGROUND:

Topamax (topiramate) tablets and sprinkle capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2-16 years with partial onset seizures, or primary tonic-clonic seizures and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome. For adults (17 years of age and over), the recommended total daily dose of Topamax as adjunctive therapy is 400 mg/day in two divided doses. In current labeling, it was stated that a

daily dose of 200 mg/day has consistent effects and is less effective than 400 mg/day for adults with partial onset seizures. Based on the study results of TOPMAT-EPMN-106 (A Randomized, Double-Blind, Parallel Group, Monotherapy Study to Compare the Safety and Efficacy of Two Doses of Topiramate in the Treatment of Newly Diagnosed or Recurrent Epilepsy) submitted in this NDA application, the sponsor has requested the use of Topamax as montherapy in adults and children 6 years of age and older with newly diagnosed epilepsy.

The study was conducted at both U.S. and non-U.S. sites. It was a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of treatment with Topamax versus placebo in subjects with a newly diagnosed or recurrent epilepsy. The primary objective of this study was to examine the efficacy and safety of two doses (low dose of 25 or 50mg/day; high dose of 200 or 500 mg/day based on subject's weight) of Topamax when used as monotherapy in subjects with a newly diagnosed (within three months) epilepsy (partial onset or generalized) or recurrent epilepsy while off anti-epileptic drugs (AEDs).

The inspection assignment was issued in January 2003 to review the conduct of Drs. Nash, Grinspan and Sarisjulis. These investigators enrolled a large number of subjects in the protocol.

II. INSPECTIONAL FINDINGS

The following sites were inspected:

NAME	Location	Assignment Date	Dates of EIR received	Classification
M. Nash	Decatur, GA	1/11/03	5/15/03	VAI
A. Grinspan	Rio Cuarto, Argentina	1/16/03	5/19/03	VAI*
N. Sarisjulis	La Plata, Argentina	1/16/03	5/30/03	VAI*

* final classification pending; the letter to the investigators are currently with the Office of Chief Counsel for review.

NASH, M.D.

At this site, 23 subjects were enrolled in the study and 14 subjects withdrew from the study. Reasons for discontinuation included lost to follow up (3 subjects), adverse event (subject 531002: seizure; subject 531021: extreme fatigue and headaches; subject 531022: migraine and anxiety; subject 531023: fatigue and confusion), withdrawal of consent (3 subjects), non-compliance (2 subjects) and treatment failure (1 subject).

An audit of 9 subjects' records was conducted. No Form FDA-483 was issued. However, we note that the site did not retain seizure diaries for majority of study subjects. According to the protocol, the seizure diaries are dispensed during the visits as each subject or subject's caregiver recorded the date and type of each seizure experienced during the trial. Primary efficacy end

point is time to first seizure during the core double-blind phase. The study coordinator stated that the patients would often forget to bring the cards and if they had not experienced seizures the cards would be blank. Based on the fact that the site did not maintain seizure diaries for majority of subjects, it is difficult to determine whether these subjects indeed did not have any seizures.

I communicated with the Review Division Medical Officer about this finding of missing seizure diaries. The review division requested the FDA field investigator to check if there were seizure diaries for four subjects (subject #531001, 530002, 531003 and 531022) who reported seizure during the trial as per data listing.

Subject #531001 and 531003 had seizure diaries. Subject 531002 was instructed to bring the seizure diaries at visit 2 and 3 but the subject did not return the diaries. Subject died from stroke on (b) (4) and the site reported as a SAE. Subject 531022 had no seizure diaries. However, the site filled out first seizure notification form to the sponsor stating date of verified seizure occurred on 5/22/01. It was also noted on early termination visit sheet that subject had a seizure and was protocol deviation because the subject was non-compliant (missed 2 doses due to side effects) resulting in first seizure and subject was terminated from the study. I have conveyed the inspectional observation to the Review Division to consider whether it may have any impact on study outcome.

GRINSPAN, M.D.

At this site, 46 subjects were screened; 44 subjects were randomized and 42 subjects completed the double-blind phase of the study. An audit of 26 subjects' records was conducted.

Limitation to this inspection was the source documents including informed consent were written in Spanish. The majority of exhibits provided in the EIR were in Spanish. Our FDA field investigator was able to understand the language and stated that the Spanish version of informed consent did not include an explanation of whom to contact for answers to pertinent questions about the research and subjects' rights. No other major objectionable conditions noted in the EIR. Data appear acceptable.

SARISJULIS, M.D.

At this site, 16 subjects were screened and randomized. All subjects completed the double-blind phase of the study. An audit of 9 subjects' records was conducted.

Similar limitation to this inspection was noted as the source documents including informed consent were written in Spanish. The majority of exhibits provided in the EIR were in Spanish. The Spanish version of informed consent did not include an explanation of whom to contact for answers to pertinent questions about the research and subjects' rights. No other major objectionable conditions noted in the EIR. Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Except for the issue of missing diaries at Dr. Nash's site as I have mentioned above, overall, the data from these sites that had been inspected appear acceptable for use in support of this supplemental NDA.

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection completed but EIR still pending

_____
Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

cc:
NDA 20-505/SE1-018
NDA 20-844/SE1-015
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/c/r/s
HFD-47/Khin
HFD-47/Friend
HFD-45/RF

rd: NK:6/16-6/18/03

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/s/

Ni Aye Khin
6/19/03 02:20:42 PM
MEDICAL OFFICER

This clinical inspection summary (DSI paper version) was initialed and concurred by Dr. A. El-Hage on 6/19/03.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-505/S-018 & 20-844/S015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Calder, Courtney

From: Calder, Courtney
Sent: Thursday, February 10, 2005 11:34 AM
To: 'mkaufman@prdus.jnj.com'; 'cglamkow@prdus.jnj.com'
Subject: Topamax Phase IV Commitment comments

Dear Ms. Glamkowski and Mr. Kaufman,

We have reviewed your protocol for a juvenile rat toxicology study of topiramate (NDAs 20-505/S-018 and 20-844/S-015; submissions dated 11/24/04) and have the following comments:

The study design is generally appropriate. However, the proposed group sizes are marginal for neurobehavioral assessments and could fall below acceptable numbers in the event of significant accidental or drug-induced animal loss. Details of the neurobehavioral testing procedures were not provided and, thus, the adequacy of these tests could not be fully evaluated. It is recommended that a complex multiple-T water maze, such as the Biel or Cincinnati maze, be used and that measurement of the auditory startle reflex include assessments of habituation and pre-pulse inhibition. In addition to those proposed, motor activity measures should include total activity and stereotypy. For those developmental or behavioral assessments to be performed during the treatment period, it was not clear when in relationship to daily dosing the assessments would be made. It is recommended that these be performed just prior to daily dosing. It is also recommended that measurement of serum bicarbonate be included in the clinical pathology analysis.

If you have any questions, please contact me.
Sincerely,
Courtney

****

Courtney R. Calder, Pharm.D., LT USPHS
Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 594-5315
Fax: (301) 594-2859
Email: calderc@cder.fda.gov

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/s/

Courtney Calder
2/10/05 05:36:31 PM
CSO

David, Paul A

From: David, Paul A
Sent: Wednesday, May 21, 2003 7:17 AM
To: Tania Hillmer [PRDUS] (E-mail)
Cc: David, Paul A
Subject: Topamax: Monotherapy Efficacy Supplements

Good Morning Tania,
I'm not sure if you are the correct person in J&J to direct this request for additional information regarding the Topamax monotherapy of partial onset seizures efficacy supplements, NDAs 20-505/S-018 & 20-844/S-015. However, since we have corresponded on previous Topamax issues, I am hoping that you will either forward the e-mail to the appropriate person or respond directly to the e-mail.

Our reviewing statistician has the following request for additional information:

Please submit the withdrawal information for Study EPMN-106. Specifically, there were 39 subjects in TPM 50, and 75 subjects in TPM 400 who withdrew from the study. We need any available follow-up information after withdrawing; for example, whether the patients had rescue medicine (what and when), whether the patients had seizures, etc.

If the information can be conveyed electronically, I would appreciate it. Please send a response to both myself and Dr. Jacqueline Ware, the PM for this project, since I will be out of the office next week.
Thanks for your assistance,

Paul David, R.Ph.
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120
ODE1; CDER; FDA
Telephone: 301-594-5530
Fax: 301-594-2859
David@cder.fda.gov

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/s/

Paul David
5/21/03 07:13:54 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW ISSUES IDENTIFIED

NDA 20-505/S-018
NDA 20-844/S-015

Ortho-McNeil Pharmaceuticals, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Catherine M. Glamkowski
Associate Director, Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Glamkowski:

Please refer to your October 29, 2002 new drug applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topamax (topiramate) Tablets and Topamax (topiramate capsules) Sprinkle Capsules.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications have been filed under section 505(b) of the Act on December 30, 2002 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. We note that Topamax has not yet been evaluated in a juvenile animal toxicology study. Since one of the primary safety concerns in the pediatric age group is for possible effects on the developing CNS, we are considering requesting a Postmarketing Commitment in which we would ask that you thoroughly evaluate the potential for developmental neurotoxicity in a repeated-dose juvenile rat study. This evaluation would include detailed neurohistopathology examinations and extensive longitudinal neurobehavioral assessments (measures of physical development, sensory function, locomotor activity, learning, and memory). In addition, male and female sexual maturation and reproductive function would be evaluated. The protocol for such a study could be submitted for review prior to initiation.

2. We have concerns about the number and timing of amendments made to Protocol EPMN-106. Therefore, we have listed in a separate section below (Item 1) several requests for information.

3. We have been unable to locate, in the current applications, any pharmacokinetic information and/or data specific to monotherapy use of topiramate in children. We acknowledge that you have submitted summary pharmacokinetic information and data relevant to monotherapy use of topiramate in adults, which was originally submitted with the original topiramate NDA. Because your proposed monotherapy indication includes children and adults, we are looking

for pharmacokinetic information in children that supports the monotherapy doses of topiramate proposed in the labeling included in these applications. This issue was discussed at the March 12, 2002 preNDA meeting, and we were under the impression that this information would be included in these new applications at the time of submission. Therefore, we have listed in a separate section below (Item 2) a request for information.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

In follow-up to Items 2 and 3 above, we also request that you submit the following information:

1. For Protocol EPMN-106:
   - All complete protocol amendments with signatures, date, and any internal meeting minutes or documents where decisions/discussions regarding the protocol amendments and their implementation occurred.

   - A detailed list of people who performed the blinded review, the date that the blinded review was performed, a list of the specific variables checked and a description of the exact analyses performed in the blinded review.

   - Information on whether the firm or the CRO performed any unblinded efficacy analyses prior to the official unblinding date or if they were aware of the results of such analyses.

   - The SAS codes for validating the Tables 9a and 9b: Demographic and Baseline Characteristics, and SAS codes for the primary efficacy analysis. This information can be provided in either paper or electronic format.

   - Create and submit several variables in a separate efficacy data set:
     (a) a variable to identify the order of randomization of all patients;
     (b) a variable to identify the first 330 randomized patients;
     (c) a variable to record failed or censored for the first 330 randomized patients, using 2-months as the duration of the double-blind phase after the 330^{th} patient was enrolled, and perform the primary analysis for the first 330 patients with "failed" and "censored" as defined in (c). Please include the SAS code when this new data set is submitted.

2. Identify where, in the current submission for these applications, the pharmacokinetic information and/or data in children, which supports the monotherapy doses of topiramate proposed in the labeling, is located. If this information is not in the current submission, we ask that you submit it as soon as possible and inform us in advance of the expected timing.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
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