Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 18, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Topamax™[topiramate] NDA 20-505

TO: File NDA 20-505
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys the Division's recommendation that NDA 20-505 for Topamax™ be approved.

The evidence submitted is sufficient to support approval of the Topamax™ NDA under labeling (drafted by the Division) that provides for topiramate's use in the management of partial onset seizures in adults.

The conclusion that the Topamax will be effective in use as an adjunctive AED for the management of partial onset seizures is supported by the results of 5 adequate and well controlled clinical investigations that were conducted with patients who were identified as suffering from partial onset seizures with or without secondary generalization. My views of the evidence derived from these 5 clinical trials are summarized in my memorandum to the file of 12/5/95.

Some observations about the Topamax™ NDA review

The Topamax™ NDA has proven to be a very difficult application to evaluate because the sponsor's reports of the untoward events associated with topiramate's use have been incomplete, vague, and difficult, if not at times virtually impossible, to understand from a clinical perspective.

Because of these limitations, I recommended at the end of the first review cycle (December 1995) that the NDA, the fact that the case for topiramate's effectiveness in partial onset seizures had been made notwithstanding, be declared not approvable.

In my memorandum of December 5, 1995 supporting that recommendation, I argued that a conclusion that an NDA is approvable can, logically, only be reached after the agency has determined that a drug product will be "safe for use" under the conditions of use "use prescribed, recommended, or suggested....in [its] labeling..." I could not therefore, I argued, recommend that an approvable action be taken because the risks associated with topiramate's use had not yet been adequately characterized and/or quantitated. Consequently, in my opinion, it would be illogical to offer a definitive conclusion about topiramate's safety for use given the findings of the review team and the lack of adequate reports to show the product was safe for use.

To be clear, I was mindful that it was possible, even likely, that evidence to support a conclusion that topiramate was safe for use might be in the sponsor's possession, but, that possibility was not sufficient in my view to support an approvable action. Thus, I concluded that a decision on the application's approvability ought to be deferred until reports of the analyses required to obtain a valid assessment of topiramate's risks had been submitted to the NDA and reviewed. Accordingly, I recommended that a not approvable action be taken.

The Office Director reached a contrary conclusion (see his 12/29/95 memorandum to me), and issued an approvable action letter (12/29/95)[1].

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[1] My memorandum of 1/2/96 to the Office Director and his response to me of 1/22/96 provide additional information about the basis for these disagreements.

The approvable action letter, at least insofar as its content regarding the deficiencies of the sponsor's analyses of clinical data was concerned, was not very different from that of the not approvable action letter that the Division had forwarded to the Office. Moreover, the approvable letter emphasized that because of the deficiencies found in the sponsor's safety assessments, the agency's determination that the application was approvable was best viewed as both tentative and potentially reversible.

The approvable action letter made a number of requests and suggestions regarding reanalysis of the safety data base. The sponsor was essentially asked to 1) go back to original data sources to gather the information that would allow each untoward clinical event to be categorized and classified under a clinically understandable rubric and 2) to use this new information to explore the relationship between the dose and duration of topiramate's use and the incidence and intensity of the re-categorized events.

After the approvable action letter issued, Division staff, at the sponsor's request, met with representatives of the firm to review the deficiencies identified in the course of the agency's review and to discuss possible strategies the sponsor might employ to obtain a valid and meaningful understanding of the kind and incidence of adverse clinical events associated with the use of topiramate.

The sponsor subsequently conducted a number of new analyses, submitting a formal response to the approvable action letter on June 28, 1996. The Final Safety update to the NDA was submitted on 9/27/96 and case report forms for patients discontinuing because of adverse clinical events were submitted to the file on November 8, 1996.

The review team's analysis of the firm's responses to the approvable Action letter.

Both Dr. McCormick and her supervisor, Dr. Katz, find the firm's efforts to repair the deficiencies in the NDA to be sufficient to allow the NDA to be approved provided that Topamax™ is marketed under the version of product labeling that is attached to the approval action letter being forwarded to the Office.

My personal view is that where epilepsy is concerned it would be imprudent, even reckless, to make such extrapolations. First, epilepsy is a dangerous disease that, if left untreated, may cause serious harm not only to the patient who suffers from the condition, but to others in his/her surround (e.g., the epileptic who experiences a seizure while driving poses a potential threat to everyone on the road). Because the armamentarium already contains a number of effective the addition of a new drug that is of unestablished effectiveness not only perpetrates a fraud on the public, but may cause serious harm because it can (on every occasion it is administered to an epileptic patient in place of an effective delay access to effective treatment. Accordingly, I see no compelling reasons to grant Topamax™, or any for that matter, an

Moreover, from a practical point of view, there is no need to grant such a claim. Topamax™ will be marketed whether or not is granted, and, physicians who choose may decide for themselves whether or not it should be used in a manner that differs from that recommended in approved product labeling. Furthermore, nothing precludes the sponsor conducting, post-approval, the clinical investigations required to

with an active AED is tantamount to malpractice will affect the nature of the study designs and the control conditions that the sponsor may employ, but, these limitations notwithstanding, valid clinical trials can be conducted (I would personally advocate fixed multi-dose comparisons of topiramate and one or more other marketed AEDs that will provide, beyond

performance of the products evaluated).

As to the sponsor's claim regarding

Safety in use

Based on the assessments of them provided in the latest reviews of Drs. McCormick and Katz, the safety analyses submitted to the NDA in response to the approvable action appear to be at the very margin of acceptability. The firm did not do precisely what we asked them to do either in the approvable action letter or advised them to do in the course of the meeting held following the issuance of the approvable action letter. Moreover, to the extent that they did attempt what we asked, they did it in a less than comprehensive manner (see the summary and critique of the firm's efforts provided by Dr. Katz on pages 5 to 8 of his 12/5/95 memorandum). Nevertheless, these limitations notwithstanding, the data

do not show topiramate to be unreasonably unsafe or dangerous.

Accordingly, I am now able, like other members of the Division's review team, to conclude that the reports submitted to the NDA provide no indication that topiramate is unsafe for use under the conditions of use recommended in the labeling developed by the Division's review team. This conclusion should in no way be seen as an acknowledgement, however, that I am satisfied with the quality and depth of the reports the firm has submitted to the application. To the contrary, the poor quality of the sponsor's safety reports has adversely affected the quality of product labeling. Indeed, we would today understand topiramate's adverse effects far better, and labeling would as a consequence provide far more useful information, had the sponsor, from the beginning of its development program, had in place a comprehensive and reliable plan for the collection, recording and analysis of clinical data.

Finally, I note for the record that a regulatory conclusion that topiramate has been shown to be "safe for use" is not a warrant that topiramate is risk free. Rather it is an opinion, based largely on sentiment, that the benefits of topiramate's use are sufficient to justify its use in the face of the risks of use so far identified. Thus, the conclusion offered is a conditional one that may well change if there are serious risks associated with topiramate's use that occur at an incidence too low to be detected in a drug development cohort comprised of 1700 or so subjects.

Dosing Recommendations

The clinical trials conducted to assess topiramate's value as an AED provide robust documentation of the effectiveness of doses of 400 to 800 mg a day. Only the results of a single study (i.e., YD) give any hint that a dose of 200 mg might be effective and then, to a lesser degree than 400 and 600 mg doses. Accordingly, I find no reason to accept the firm's proposal that labeling recommend topiramate at
day.

Labeling

The labeling being forwarded as an attachment to the approval action

letter is largely a product of the Division's review team. The sponsor, however, was given a limited[2] opportunity to review and to offer suggestions for its revision, but only insofar as the wording of the text and the values of numerical estimates that would be necessary to construct labeling to allow topiramate to be marketed as an adjunctive treatment for partial onset seizures in adults. We did not agree to enter into substantive discussions about matters bearing on the two other claims[3] sought by the sponsor because, as I have explained earlier in this review, the Division has concluded that there is a lack of substantial evidence to support either one.

Conclusions

My complaints about the quality of the sponsor's safety reports and analyses notwithstanding, I am persuaded that Topamax™ will, within the meaning of the Act, be safe for use and effective in use, under the conditions of use described in the labeling that the Division has developed. This conclusion is not intended to convey a belief on my part that I, or anyone else for that matter, understand clearly or completely the nature of the untoward cognitive effects being reported in association with topiramate's use. I am now satisfied, however, that these adverse cognitive events, no matter what they actually are, are not so serious and dangerous that they can be deemed sufficient to outweigh the benefits of an unequivocally effective AED such as topiramate.

In reaching my affirmative conclusion about the Topamax™ application, I have taken into consideration the fact that the use of currently marketed AEDs is associated with many risks, some quite serious and some even

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[2] A working draft of product labeling the division was prepared to recommend be used was provided to the firm by fax on 12/17/96. At a teleconference on 12/18/96, Division staff and representatives of the firm discussed the Division's labeling. They agreed to provide written suggestions for revisions by the morning of 12/19/96. I agreed that if we found the suggestions acceptable, they would be adopted in the draft forwarded to the Office.

fatal (e.g., felbamate's capacity to cause aplastic anemia is a very good example). I am also influenced by the fact that no marketed AED is fully effective in all epileptic patients and that some epileptic patients respond poorly to all available AEDs. Accordingly, I am predisposed, provided an effective AED can be marketed under labeling that accurately depicts its risks and is candid about the limitations of our knowledge, to have the product enter the armamentarium. Such an approach, importantly, is fully consonant with current agency policy.

Recommendation:

The application should be approved.

Paul Leber, M.D.
12/18/96

MEMORANDUM

DATE: December 5, 1996

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

TO: File, NDA 20-505

SUBJECT: Supervisory Review of Sponsor's Response to Approvable Letter for Topamax

BACKGROUND

R.W. Johnson Pharmaceutical Research Institute was the recipient of an Approvable letter dated 12/29/95 for its NDA 20-505 for topiramate, a new anticonvulsant. That letter raised a number of issues that needed to be addressed prior to approval of the application; those issues are outlined below:

3) Display of individual responses

The sponsor had presented a display of the proportion of patients achieving a 50% reduction in seizure frequency compared to baseline. In the Approvable letter, we asked them to produce cumulative distribution displays that would permit a comparison with placebo of all possible degrees of response.

4) Dose

Although the sponsor had submitted data examining the effectiveness of several doses, we had concluded that the maximal useful dose was 400 mg/day.

5) Safety

By far the most important deficiency in the application was the poorly recorded, reported, described, and analyzed safety data. In particular, the reports described a host of adverse events that could loosely be described as cognitive/behavioral/psychiatric, but that were all poorly described.

Adverse events extremely unlikely to be drug related were frequently reported (e.g., aphasia). These and other examples (including the frequent use of vague terminology such as "thinking abnormal") led the Division to conclude that investigator verbatim reports were being inappropriately coded using standard WHOART terminology which did not accurately reflect patients' actual experiences and/or responses.

In an attempt to rectify and clarify the situation, the letter included steps the Agency wanted the sponsor to take to completely re-evaluate the safety database. These steps were further clarified and discussed in several subsequent meetings with the sponsor. The steps included developing standardized and validated methods to re-classify reports of these events, as well as methodology for determining if case report forms contained the sort of information necessary to perform an adequate re-characterization of the adverse events. The sponsor was to re-calculate incidences for this new set of adverse events which would presumably be more reflective of what patients actually had experienced. The entire

goal was for the sponsor to re-examine the database in an attempt to produce descriptions of events suffered by patients that more accurately reflected the true state of affairs. The suggestion was also made that the sponsor re-interview several of the investigators, who would have access to all the primary data sources (CRFs, hospital and their own personal records, etc.) in an attempt to get the sponsors to adequately characterize each of their patients' responses to treatment. In addition, we asked the sponsor to enlist the aid of an outside expert who would be capable of examining the revised safety report to determine if any specific syndromes or other topiramate-specific adverse events were occurring.

In addition to this re-examination of the safety database, we asked the sponsor to re-evaluate the dose response nature of the adverse events (in the NDA, the sponsor associated adverse events with the doses to which patients were randomized, not with the doses the patients actually received). Finally, we asked the sponsor to provide additional follow-up for patients with significant laboratory abnormalities.

6) Biopharmaceutics

We asked the sponsor to adopt certain dissolution specifications.

Dr. McCormick, medical officer in the division, has reviewed the sponsor's response, which was submitted on 6/28/96, in a detailed document dated 11/18/96. The sponsor's responses (and my comments) to these issues are described below.

1) The sponsor has not performed the reanalysis we have requested. They continue to maintain that their proposed claim is accurate; that is, that topiramate is effective in patients with partial onset seizures with or

First, they have analyzed the studies in which topiramate was given as adjunctive therapy and determined that the effects of topiramate are essentially the same, independent of the specific regimen of concomitant drugs to which it was added. They then reason that if topiramate is effective in the presence of multiple different drugs, as well as different dosing regimens of those drugs, and there are no important documented kinetic interactions with those drugs, then topiramate effects are independent of these other drugs, and therefore, it must have intrinsic anticonvulsant activity;

In addition, the sponsor has now provided experience in approximately 250 patients treated for at least 6 months at a dose of 1000 mg, a reasonably sized cohort.

While there is some appeal to their argument that topiramate must be
the sponsor's conclusion does not follow
from the data. Indeed, it is one reasonable explanation, but there are others, including that topiramate is effective (for reasons unknown) only in the presence of active anticonvulsants, **regardless of**

which specific concomitant treatment with which it is given in combination. The effectiveness of topiramate

use this way.

In this regard, I would reiterate my initial objections to permitting this claim, as I originally wrote in my supervisory memo dated 11/24/95. In brief, my objections were based on the fact that very few patients actually were treated nd the finding was not replicated. I pointed out that the only other recently approved

provided considerably more data on the question. Dr. Leber's memo of 12/5/95 also concluded definitive.

Unfortunately, the sponsor has not provided any additional effectiveness data that speak to the question. While they have responded to the question of additional exposure at the 1000 mg dose, I do not believe that this is the critical issue, and I once again recommend that they not be permitted

3) The sponsor has submitted the cumulative distribution functions we requested. They demonstrate a clear separation between drug and placebo.

4) The sponsor suggests that the dosing range recommended in labelling be 200-400 mg/day, because there is a suggestion (based on global assessments) that 200 mg/day is effective. Because there is no statistical significance on measures of seizure frequency at this dose, we should probably continue to emphasize 400 mg/day as the recommended dose.

5) The sponsor has undertaken a number of steps to re-characterize the safety profile of topiramate.

First, they identified 23 WHOART terms that were used to originally identify adverse events of the type that were of interest. With the help of an outside expert, they reviewed the investigator verbatim terms that had

been coded with these 23 terms. They concluded from this review that 8 of these terms did not accurately portray what the investigators described. As a result, they re-coded the events using the remaining 15 terms, and added 10 WHOART terms they felt more accurately reflected the investigator verbatim reports (in fact, 4 of the original 8 suspect WHOART terms were retained in the "new" group of 10) . This new list of 25 WHOART terms then served as the basis for re-classification and re-quantification of the neuropsychiatric events.

In addition to re-classifying events as described above, the sponsor submitted 2 questionnaires to 6 investigators who had treated a total of 264 patients with topiramate (these were the investigators with the greatest patient experience in the development program), and who had data for 241 patients. One questionnaire was patient specific; that is, these investigators were asked to describe the nature of the adverse events seen in each specific patient they treated. The second questionnaire asked for their global reflections on the adverse effects of topiramate, in their experience.

The sponsor then showed these questionnaires to an outside expert, Dr. James Cereghino, former chief of the Epilepsy Branch of the National Institute of Neurological Disease and Stroke of the NIH, and now a Professor of Neurology at the the Oregon Health Sciences University. It is not clear to me if Dr. Cereghino examined both types of questionnaires, or only those that were patient specific.

An additional step taken by the sponsor was to report a prospective (uncontrolled) study of 15 topiramate treated patients in whom several neuropsychiatric tests were administered.

In general, the sponsor's approach to re-classifying these adverse events in a meaningful way was reasonable, though it fell short for the overall database in the respect that the primary reclassification was based on a re-assignment of investigator verbatim terms, not an examination of more primary documents; e.g., Case Report Forms. An examination of these primary documents presumably would have been more illuminating in understanding what an individual patient had experienced. The re-classification that the sponsor did perform generally served to "un-lump"

terms, so that the new classification is somewhat more descriptive (for example, the investigator term confused (mental slowing) had originally been classified as Confusion; it now is classified as Psychomotor slowing).

Interestingly, the re-characterizations done via questionnaire by the 6 investigators were not included in the re-calculations of adverse event incidences; that re-calculation was done only on the basis of the re-classification performed by the sponsor.

Dr. McCormick's detailed review of the questionnaire data revealed certain common themes, in particular events described as psychomotor slowing, including subjective complaints of slowed thinking and word finding difficulty. Most of the symptoms about which patients complained were not objectively verified, although I am not sure how extensive the attempts to documents these presumed deficits were. She has grouped the types of adverse events into 9 general categories, which encompass the following reaction types; psychomotor slowing, decreased fluency, decreased concentration and attention, memory difficulties, moodiness, psychosis (hallucinations), irritability, depression, and sleepiness. In evaluating the individual patients, at least one investigator referred to a "classical" topiramate titration syndrome, in which patients complained of slowed thinking and word finding difficulty (without demonstrable deficit) which resolved in several weeks, which this investigator attributed to the titration schedule followed in the trials.

Examination of the questionnaires that solicited investigators' global assessments of their experience with topiramate revealed that no investigator identified any specific "syndrome" or panoply of adverse events particularly related to topiramate (even the investigator who characterized certain individual patients as having a "classical" topiramate syndrome did not identify this, or any other syndrome, on the "global" questionnaire).

Dr. Cereghino classified adverse events into 5 distinct categories: 1) paresthesias, 2) ataxia, dizziness, tremor, lightheadedness, 3) difficulty concentrating, slurred speech, confusion, anomia, 4) mood disturbances, fatigue, and 5) hallucinations, suicidal ideation, psychosis. His report

generally describes the investigators' views. As far as I can tell, Dr. Cereghino believes that there is no specific topiramate syndrome or panoply of adverse events that could not be attributed to the patients' underlying disease, concomitant treatment, or interaction of these (or other) factors and topiramate.

The prospective psychometric evaluation provides little useful information, in my view, for the reasons described by Dr. McCormick.

Finally, the sponsor has attempted to re-calculate doses associated with adverse events according to the dose actually received by the patient. Further, they have provided essentially complete follow-up for patients with significantly abnormal lab values (low WBC, RBC, low platelets). The vast majority of these patients experienced a return to (or towards) baseline, usually after discontinuation of the treatment.

In general, I believe that the sponsor has improved somewhat its report and description of the neuropsychiatric adverse events seen in patients treated with topiramate. There is considerable information still unavailable (time course of these events, etc.), but I believe that adequate labelling that will permit the drug to be used safely and effectively can be written.

6) The dissolution specifications will be adopted.

CONCLUSIONS AND RECOMMENDATIONS

The sponsor has addressed all the issues identified in the Approvable letter. However, I believe that they have not adequately addressed the first 2 issues, and I recommend that the Indications section of labelling remain as we proposed in the Approvable letter. Beyond this, I believe we have sufficient information to write labelling that will permit the drug to be used safely and effectively, and recommend that the application be approved.

Russell Katz, M.D.

PURUIS

DEC 29 1995

NDA 20-505

The R.W. Johnson
Pharmaceutical Research Institute
Attention: Stephanie Barba
Director, Regulatory Affairs
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Barba:

Please refer to your August 18, 1994 new drug application (and your resubmission dated December 29, 1994) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topamax™ (topiramate) 25mg., , 100 mg., 200 mg., round

We acknowledge receipt of your additional communications (see ATTACHMENT 1).

We also acknowledge the following submissions as correspondence to your NDA:

October 3, 1995	October 4, 1995	October 5, 1995
October 9, 1995	October 10, 1995	October 17, 1995
October 19, 1995	October 25, 1995	October 30, 1995
November 8, 1995	November 20, 1995	November 27, 1995
November 30, 1995		

Please note, these submissions were received during the final ninety-days of the review cycle and were not considered in our decision. These submissions need not be resubmitted in your response but may be incorporated by reference. Note, however, that the reanalysis of safety requested below needs to be well-organized and coherent; it should therefore incorporate relevant parts of these submissions.

We have completed the review of this application as submitted and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the clinical issues enumerated below. We note that there is need for considerably more analytic effort on your part than is usual in responding to an approvable letter, specifically, to characterize and describe in labeling the adverse effects of topiramate. A consequence of this is that our labeling comments (attachment 2) should be considered preliminary. Although we have considered the application approvable because the effectiveness of topiramate appears to outweigh risks to the extent they have been

presented, there is still considerable uncertainty about those risks and their importance. Accordingly, it remains possible that further analysis could reverse the present conclusion of overall net benefit.

The following clinical issues need to be addressed:

3. Display of individual responses

In addition to describing median reductions of seizure rate, you characterized rates of "responders," patients with a more than 50% decrease in frequency of seizures. Although 50% is a figure of interest, it would be still more helpful to display all patients' responses in a cumulative response curve, in this case plotting the decrease in seizure frequency (as a percent of baseline frequency, from smallest to largest) against the number

of people with a response at least that good. For an example of such a figure, see labeling for tacrine.

4. Dose

We see no evidence that doses above 400 mg/day lead to improved control of seizures in the adjunctive setting; they do, however, appear to lead to an increased rate of at least some adverse effects. We therefore consider the maximal useful dose to be 400 mg/day.

5. Safety

The reports provided in the NDA that address the issue of topiramate's safety provide insufficient details about the risks associated with the use of the drug, in particular those that can be classified as cognitive/psychiatric or neuropsychiatric in type. These neuropsychiatric events were the most prevalent kind of adverse clinical events causing investigators to withdraw patients from treatment with topiramate and were thus troublesome on their face. Our review of the information provided about patients with these events, however, leaves great uncertainty as to the nature, severity and course of the events these individuals suffered. Part of the problem may be due to the use of non-standard terminology. There also appear to be failings in the methods used to classify and categorize events. In many cases we reviewed, the language employed to describe clinical phenomena was too vague to provide an understandable picture of the case; for example, 55 patients were described as having abnormal thinking but it is not clear whether this means they were delusional, formally thought-disordered, confused, etc. In other instances, terminology appeared to be idiosyncratic; e.g., some 30 patients were described as being "aphasic," a term that is usually applied to describe deficits in language comprehension or expression that arise from focal neurological injury--an outcome topiramate seems unlikely to cause. Review of some of these cases indicated that they represented general depression of CNS function. Finally, in some cases, the severity of the event was severely understated; a patient described as "agitated" in fact killed his mother.

The evaluation of neuropsychiatric adverse events needs full scale review and repair.

First, you need to develop standardized and validated methods to classify reports of neuropsychiatric adverse clinical events. In some cases, it will be useful to describe and group closely related events as part of some broader category. You will also need a procedure or protocol for determining the adequacy of a case report (i.e., whether it contains the kind of information that would allow an event to be classified). With this

assessment methodology in place, a determination should then be made as to what proportion of available case report forms contain the kind of information necessary to characterize reported adverse events in language that is informative. If there are sufficient numbers of case reports containing appropriate data, especially for events associated with discontinuation or change in dosage, and those considered serious, the events reported should be classified within exclusive categories that would be readily recognizable by clinicians expert in mental status assessment. Once these classifications are completed, estimates of incidence rates for each kind of event (or related groups of events) and the relationship between incidence and dose or serum concentration, and duration of exposure, should be re-examined. Dose-response should be examined both within randomized study groups (the least confounded by time-related effects) and by actual exposure groups in the full data set.

If the information required to classify cases cannot be extracted from available case report forms, you may have to use alternative sources (e.g., interview clinicians who actually treated patients who participated in the development program, extract information from contemporaneous office or clinic records, etc.) to obtain it. Again, this is particularly critical for adverse events that led to change in therapy.

In addition, there are several other issues related to the assessment of topiramate's safety that need to be addressed.

It has been difficult to determine the ultimate outcome of patients who left studies prematurely because of adverse events. We will need to know how long these events persisted. In addition, the entire database should be examined to determine the time course (time of onset, persistence, response to dose change, etc.) of the important adverse events.

Much of the dose response information has been constructed based upon doses to which patients were randomized, not on doses patients actually received. As you know, many patients did not receive their target doses due to the occurrence of adverse events. For this reason, we ask you to recalculate exposure and duration of treatment data, as well as incidences of adverse events, for doses actually achieved (you may construct ranges for specific doses, but these ranges should be relatively narrow; e.g., 400-499 mg/day, 500-599 mg/day, etc.).

Finally, the number of patients with important laboratory abnormalities has not been clearly stated, and adequate follow-up of some of these patients has not been obtained. Please re-evaluate patients with clinically important abnormalities and obtain and submit detailed follow-up for this group.

BIOPHARMACEUTICS

In addition, we have the following comment on dissolution testing:

Based on data supplied by you, methodology and specifications for all strengths of topiramate tablets are set as follows:

In accordance with the policy described in 21 CAR 314.102(d) and in the Center for Drug Evaluation and Research Manual of Policies and Procedures(MAP)6010.1 (formerly, Staff Manual Guide CAB 4820.6), you may request an informal conference with the Division to discuss what further steps you need to secure approval. The meeting is to be requested at least 15 days in advance. In view of the extensive reevaluation of safety needed, we strongly urge you to seek such a meeting, after considering the contents of this letter. To schedule this conference, please contact:

John S. Purvis
Chief, Project Management Staff
Telephone: (301) 594-5525

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 314.120. In the absence of such action FDA may take action to withdraw the application. Any amendments 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.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

attachments(2)

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 5, 1995

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Topamax™[topiramate] NDA 20-505

TO: File NDA 20-505
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum explicates the basis for my recommendation that R.W. Johnson Pharmaceutical Research Institute's NDA for Topamax (topiramate) be declared **NOT approvable**.

My recommendation, which is at variance with that offered by both Drs. McCormick and Sahlroot (joint review of 10/11/95) and Dr. Katz, the Team Leader for Neurology, (memorandum of 11/24/95), does not reflect a disagreement among the review team members and myself about the nature of the numerous deficiencies that exist in the application and/or the steps that the firm will have to take to repair them, but different views about the nature of the regulatory status of the application during the period that it undergoes the requested repairs.[1]

Specifically, although I share the review team's view that data already in the firm's possession may be sufficient to allow them to carry out analyses that will repair the deficiencies we have identified in the application, I find no advantage in announcing an affirmative conclusion about the approvability of the application in advance of reviewing the results of these analyses. Perhaps, the results will not be those we anticipate. In any case, as a practical matter, the total time to approval of the application, if re-analyses document that it can be approved, will not be affected adversely by the nature of the letter issued.

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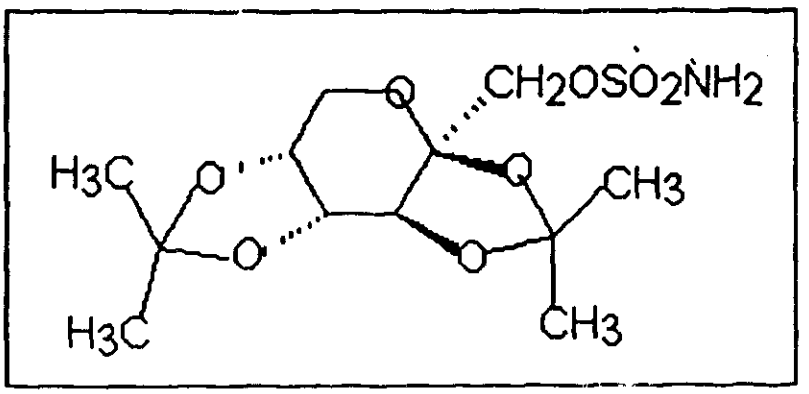
[1] I have discussed my alternative approach for conveying the defects of the application to the firm with both Dr. Katz and Dr. McCormick; each finds it acceptable.

Background:



Topiramate, chemically, a sulfamate-substituted monosaccharide, is a new chemical entity that has been in development under an IND since 1986.

Topiramate is said to resemble acetazolamide (Diamox™), a sulfonamide carbonic anhydrase inhibitor that was among the first of that pharmacologic class to be used as a diuretic. Diamox, incidentally, has long been used, although now only infrequently, as an anti-epileptic.[2]

Of note, particularly if topiramate and acetazolamide share a common mechanism of action, is the fact that tolerance, that cannot be surmounted by increasing drug levels, develops within months to the anticonvulsant effects of acetazolamide.

In preclinical AED screens, topiramate exhibits the capacity to block MES in rats and mice, but not seizures induced by convulsants (e.g., picrotoxin, pentylenetetrazol, or bicuculline); this profile is said to identify a drug that acts by blocking seizure spread without raising the seizure threshold. (Drugs with similar properties include, according to the sponsor, phenytoin and carbamazepine).

Topamax is not now marketed anywhere in the world.

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[2] Initially (circa 1952), presumably, because its administration produced, like ketogenic diets, a metabolic acidosis. However, because acetazolamide continues to exhibit anticonvulsant effects in nephrectomized animals, it is now believed to act by another mechanism, perhaps one related to its capacity to increase of CO2 (which is active against MES) in the brain by direct inhibition of brain carbonic anhydrase.

Application history and my basis for its assessment:

The NDA for topiramate's use in the treatment of patients with partial onset seizures was first submitted on August 29, 1995, but was found to be so poorly organized that it could not be reviewed reliably. Accordingly, the Division refused to file the application; a revised NDA was subsequently re-submitted on December 29, 1995.

My assessment of the NDA is based almost entirely on materials in the administrative file. I have relied, in particular, upon the joint primary medical and statistical review by Drs. McCormick (clinical) and Sahlroot (statistical) and the supervisory memorandum prepared by the Team Leader for Neurology, Dr. Katz. In addition, I have examined personally some of the narrative summaries provided for patients who discontinued for adverse clinical events and I have held discussions about the findings of the review effort with individual members of the review team.

Chemistry:

There are no issues that require comment on my part.

Preclinical Pharmacology/Toxicology

Topiramate teratogenic in mice, rats, and rabbits. These findings are not a barrier to th approval of an antiepileptic drug [AED] provided, however, that the findings are accurately and fully described in product labeling.

Biopharmaceutics

Topamax is an orally administered solid product intended for twice a day (q12h) administration at daily doses of 200 to 600 mg. Topiramate absorption is not affected by food. Plasma topiramate is largely unbound (protein binding <20%) over the range of total plasma concentrations likely to be attained under the dosing regimen recommended.

Approximately 70% of an orally administered dose of topiramate is excreted unchanged in the urine. A very small fraction of topiramate is converted by a number of different pathways to 6 inactive metabolites which, like their parent, are almost entirely excreted in the urine.

The clearance of topiramate is dose proportional; under monotherapy

conditions, its half-life is about 21 hours .

Topiramate's clearance can be increased when it is co-administered with other AEDs; pk studies reported in the NDA (see Oct 5, 1995 Mahmood synopsis) indicate that clearance, although increased, remains dose proportional when topiramate is co-administered with phenytoin, carbamazepine, and primidone. There is some nonlinearity in the presence of valproate (higher doses of topiramate are cleared more rapidly.)

Specifically, when administered with phenytoin, topiramate clearance was increased 2.5 times, and when administered with carbamazepine, it increased 2 fold.

Topiramate, importantly, has no effect on the clearance of carbamazepine or its 10-11 epoxide and only a relatively minor inhibitory effect on phenytoin clearance(20% reduction).

The interaction between topiramate and valproate is modest in both directions; co-administration of the drugs causing a15% increase in the clearance of each.

Renal disease, as would be predicted from the fact that the kidney is the primary route of excretion of both topiramate and its metabolites, reduces its clearance considerably.

Effectiveness in use

Common Clinical Trial Design features and Analytic strategies

The NDA provides results of 6 clinical trials that the review team considers, by design, to be capable of documenting the effectiveness of an AED intended for the management of patients with partial onset seizures.

Add-on trials:

Five of the 6 studies cited employed a so-called add-on placebo controlled design in which patients who fail to show an adequate response to a

presumably adequate course of AED[3] treatment are randomized to receive, in addition to their baseline treatment regimen, either placebo or the experimental AED of interest. An individual's response to the add-on treatment is estimated from the change in seizure frequency (counts/interval) that occurs between the baseline (prerandomization) phase and add-on phases (post randomization) expressed as a percent reduction of the baseline rate (I.e., 100•[e-b]/b).

Estimates of a drug's effects in this design are obtained from the difference in the change in seizure counts observed under the treatment condition and the control (I.e., a between group estimate).

Statistical tests of these differences employed an ANOVA of ranks, however, because the data are not normally distributed, but skewed.

a patient that had only partial seizures, or the development of status epilepticus, etc.). A directionally favorable statistically significant between treatment difference in the distribution of times to discontinuation for therapeutic failure (as defined above) was intended to serve as evidence of topiramate's effectiveness as a monotherapy.

Conduct and Results

Add-on trials

In the table that follows, outcomes under each treatment are presented in terms of Median Percent Reduction in interval Seizure frequency.

study	Rx	Median of % reduction in seizure freq [p value]	Description	Assessment
YD 17 US sites	pbo 200 400 600	11.6 27.2 [0.08] 47.5 [0.009] 44.7 [0.003] {counts/28 d} p. 48 of joint review	N @ entry = 223 12 wk baseline(1 or 2 drug Rx) N @ randomization = 45+45+45+46 = 181 4 wk DB titration, 12 wk DB stabilization N @ completion = 40+41+40+39 = 160	400 and 600 are effective
YE 17 ctr US sites	pbo 600 800 1000	1.7 40.7 [<0.001] 41.0 [<0.001] 36.0 [<0.001] {p 65 of joint review	N @ entry = 12 wk baseline N @ randomization = 47+48+46+47=190 6 (2-12)wk DB titration 12 wk DB stabilization N @ completion = 44+37+39+34 = 154	600 is effective, but no dose response conclusions as high dose not achieved
Y1 4 non-US	pbo 400	1.1 40.7 [0.065]	N @ entry = 8 wk baseline N @ randomization = 24+23 =47 3 wk DB titration 8 wk DB stabilization N @ completion = 22 + 17 = 39	400 is effective
Y2 6 ctr, non-US	pbo 600,	-12.2 [worse] 46.4 [0.004]	N @ entry = 65 8 wk baseline N @ randomization = 30 + 30 = 60 4 wk (2 to 8) DB titration 8 wk DB stabilization N @ completion = 28+25 = 53	600 is effective, actually 500

Y3	pbo 800	-20.6 24.3 [<0.001]	N @ entry = 57 8 wk baseline N @ randomization = 28 +28 = 56 5 wk (2 to 10) DB titration 8 wk DB stabilization N @ completion = 27 +22 =49	Median dose 600 despite nominal assignment: positive

As the table illustrates, the results of the 5 add-on parallel studies uniformly document that topiramate, when used as part of a combination AED treatment program, suppress the incidence of seizures of unspecified types in patients who were selected for study because they exhibited partial onset seizures that occurred alone or in association with other seizure types.

Because the sponsor has failed to provide an analysis that informs us about the actual subtype of seizures that were affected by treatment, the precise action of topiramate cannot be understood or described. Accordingly, it is impossible, despite the nominally positive results reported, to draft labeling at this point in time that will describe the action of topiramate in a manner that is sufficiently informative to allow practitioners to understand what specific kinds of benefits are derived from the use of the drug.

Moreover, beyond failing to provide the kind of information required to draft informative labeling, the lack of analyses bearing on seizure type make it impossible to exclude the possibility, albeit remote, that topiramate, despite

kind) given the experience of a partial onset seizure.

Page
Purged

Overall conclusions about effectiveness

The evidence adduced by the sponsor easily allows a conclusion that topiramate, when used in combination with other AEDs, reduces overall seizure activity in patients who suffer partial onset seizures which occur alone or in combination with other seizure types. One cannot conclude on the basis of the information contained in the application, however, that topiramate is an effective AED within the meaning of the Act. To reach that conclusion, one must know what seizure type or types topiramate suppresses[6]. Because the application fails to provide this critical information, it is not possible to conclude that there is substantial evidence of topiramate's effectiveness in use. I do not disagree with the review team's expectation that the sponsor will be able to provide the required information, however.

Safety for use

It is widely understood that no pharmacologically active substance is likely to be free of risk. Accordingly, a regulatory conclusion that a drug is safe for use is no more than an opinion, albeit one offered by experts familiar with the management of patients with the disease being treated, based on reports of findings made during clinical testing of the drug, that the demonstrated benefits associated with the use of the drug are sufficient to outweigh the risks that have been found to be associated with its use.

Clearly, such a conclusion is highly dependent on the 1) number of patients exposed to drug, 2) the intensity (dose) and duration of exposure of the sample to the drug, 3) the representativeness of the sample vis a vis the population for whom the drug will be recommended upon marketing, 4) the aptness, quality, and reliability of the monitoring processes used to assess the risks to subjects, and 5) the quality and reliability of the data evaluation process applied to the data collected during clinical testing.

The case for topiramate's safety in use as developed in the NDA meets some, but not all, of these enumerated criteria.

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[5] The evidence must speak to the accuracy of a claimed use and the data submitted does not allow the construction of a clinically meaningful claim.

Exposure

In terms of the size of the drug development cohort, there are more than enough patients (N =1679 {1446 with epilepsy})[6] to capture events that occur at least once in short term exposure to as few as one in every three to five hundred patients exposed to topiramate. Our ability to cap the probable upper limit on risk of deaths and serious ADRs is somewhat better because an additional 407 patient exposures are included in the database (from a 7 month Safety Update) for these very serious events.

In tum, because only some 845 patients have been exposed for more than 6 months, our ability to set an upper limit of probable risk for events that occur in chronic use is somewhat less. Similarly, the reduced numbers of exposures (less than 498 at 800 mg/d or more) also limit the warrant of safety provided by experience in this cohort.

Deaths

The number of deaths reported by the sponsor during development of topiramate is 19. Among these, 13 are deemed to be sudden and unexpected; they occurred after as few as 92 to as many as 1788 days on drug. Critically, the rate in terms of events per patient years, circa 5-6/1000, is well within the rate observed for other recent AED drug development cohorts (2.5/1000 for gabapentin, 5.8/1000 for lamotrigine).

Of the remaining 5 deaths, 2 were accidental and witnessed (attributable to seizures , however) and 4 were of medical origin (2 Pulmonary emboli, 1 AdenoCA of cecum, 1 astrocytoma).

Accordingly, the information provided supports a conclusion that the use of topiramate is not associated with an unacceptable risk of drug induced fatality.

Adverse Clinical Events:

In the absence of any valid alternative method, we have long used the

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[6] Exposure through 3/31/95.

incidence of discontinuation for adverse events as a marker for the severity of a drug's adverse reaction profile. By this measure, topiramate is not without disadvantages.

In toto, among all the 1446 epileptic patients in the 3/31/95 database, some 360 withdrew for adverse clinical events. Among 527 topiramate patients enrolled in epilepsy controlled trials, 17% (89) withdrew as compared to 4% (9/216) among placebo assigned patients; the most common class of adverse event leading to discontinuation was neuro-psychiatric (see below).

Other potentially serious complications of topiramate's use included renal calculi (predictable given its activity as a carbonic anhydrase inhibitor) and weight loss.

None of these risks is sufficient to preclude approval of an effective antiepileptic drug product, however.

The problem is that I cannot be confident that anyone (either from the agency review team or the firm) understands the true nature of the events that account for the discontinuations subsumed within the behavioral and/or CNS categories.

Part of the problem is descriptive terminology. I can attest, as someone with both formal post-graduate training and clinical experience in mental status assessment, that the descriptions offered are all too often vague or uninterpretable (i.e., they do not depict a syndrome and/or mental state that clinicians would readily recognize). Whether this is a consequence of the inexactitude of the clinicians observing and recording clinical events, a lack of standardized terminology, or deficiencies in the firm's procedures for classifying clinical events (perhaps, the lack of training of those who did the classification) is unclear to me[7].

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[7] I have discussed this with Dr. McCormick and she, too agrees, that she does not understand what the firm did or how they did it. I have also discussed the matter with Dr. Greg Burkhart, our safety team leader, who has had considerable experience in adverse event classification and tabulation for epidemiologic work. He and I jointly examined some of the narrative summaries submitted, and concurred that although the phenomena described probably involve some kind of CNS depression, the language used is just too vague to permit us to determine whether there are one or several kinds of events being reported. The problem may in part stem from the

Patients (N=55), for example, are described as exhibiting abnormal thinking, but no where is this term defined. I do not know whether this means that patients were delusional, formally thought disordered, or merely confused? Some thirty (N=30) patients are said to be 'aphasic,' but this seems an extremely unlikely result of any drug induced state because aphasia, a broad category for any one of a number of specific deficits in acquired language capacity, is typically attributable to focal, not diffuse, neurological injury and/or impairment.

Thus, the firm's analysis of clinical adverse events leaves unclear what was actually experienced by patients suffering events that can be classified as neuro-psychiatric[8] in origin. To be fair, some case descriptions suggest that topiramate can cause a generalized depression of CNS function (i.e., a reduction in level of alertness, somnolence, bradyphrenia, ataxia, incoordination, perhaps stupor). However, it is certainly possible that topiramate causes other kinds of phenomena, for example, psychosis, agitation, depression. What the patients identified as being aphasic experienced, however, remains a total mystery.

None of these risks, importantly, need constitute an absolute bar to the marketing of an effective AED product, but, when risks are associated with the use of a product, labeling must describe them accurately and in language that is understandable by both prescribers and patients. Moreover, product labeling must provide reasonably precise estimates of the expected incidence of these events, and, when known, factors affecting their incidence (e.g., dose, patient characteristics, etc). The point made is that without this information, a definitive conclusion that topiramate will be safe for use under the conditions of use recommended cannot be made.

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sponsor's usage of public words in a private or idiosyncratic manner (I.e., so-called metonymic usage).

[8] I have so far focused on failures of methodology as the likely explanation for the firm's failure to describe adverse events accurately. However, some cases might have been misclassified for other reasons. Dr. Katz cites (page 21 of this review) as a potential example of the other kind the case of a patient who was classified in the sponsor's tabulations as suffering "agitation" when he had, in fact, actually killed his mother!

Discussion and summation.

In my judgment, the reports provided in the NDA fail to document that topiramate is effective in use or safe for use under any labeling that can/could be drafted currently governing the conditions of that use. This judgment does not carry any adverse implications for the future of the drug. I share the expectation, expressed by both the review team and Dr. Katz, that with appropriate remedial analyses the firm may be able to repair the application.

Nature of the remedial repairs

The goal of the remedial effort is to provide reliable and accurate information about topiramate's benefits and risks that can serve as the basis for comprehensive and accurate product labeling.

Re-analyses of data adduced in the 5 add-on trials should be carried out to determine which seizure type or types are affected by topiramate treatment.

Safety analyses will require greater effort.

First, the firm must develop standardized and validated methods to classify reports of neuropsychiatric adverse clinical events. This should include a protocol for determining the adequacy of a case report(i.e., whether it contains the kind of information that would allow an event to be classified).

With this methodology in place, a determination should then be made as to what proportion of available case report forms contain the kind of information necessary to characterize reported adverse events in language that is informative. If there are sufficient numbers of case reports containing appropriate data, the events reported should be classified within exclusive categories that would be readily recognizable by clinicians expert in mental status assessment. Once these classifications are completed, estimates of incidence rates for each kind of event and the relationship between incidence and dose, and duration of exposure, can be assessed.

If the information required to classify cases cannot be extracted from available case report forms, the firm may have to use alternative sources (e.g., interview clinicians who actually treated patients who participated in the development program, extract information from contemporary office or clinic records, etc.)[9]

Conclusion and Recommendation:

The NDA for topiramate, although it contains reports suggesting that topiramate can eventually be shown to be a safe and effective AED, is not yet at a stage that justifies a regulatory conclusion that it is approvable. This conclusion should be communicated to the firm in a not approvable action letter that both details the basis for the decision and outlines the kinds of repairs that are necessary prior to resubmission.

Toward this end, the Office should issue the not approvable action letter being forwarded in the company of this memorandum.

12/5/95

Paul Leber, M.D.
December 5, 1995

[9] Incidentally, many of these problems might have been avoided had there been in place a requirement, as I have advocated repeatedly, that each clinical investigator write a detailed clinical summary of the course of every patient experiencing any kind of untoward event or syndrome.

MEMORANDUM

DATE: November 24, 1995

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

TO: File, NDA 20-505

SUBJECT: Supervisory Review of NDA 20-505, Topiramate for use in Patients with Partial Seizures

BACKGROUND

NDA 20-505 for topiramate, a carbonic anhydrase inhibitor, was submitted by the R. W. Johnson Pharmaceutical Research Institute on December 29, 1994. The NDA contains the results of 5 adequate and well-controlled trials designed to establish the effectiveness of topiramate as adjunctive treatment in patients with refractory partial seizures. In addition, the results of a single trial designed to establish the effectiveness of topiramate against partial seizures when administered as monotherapy have also been submitted. According to the sponsor, these trials establish the effectiveness of topiramate as a treatment of partial seizures,

Further, safety experience in approximately 1500 patients with epilepsy and approximately 1700 subjects total, has been submitted in support of the application.

Dr. Cynthia McCormick, of this division, and Dr. Todd Sahlroot of the Division of Biometrics, have performed a combined Clinical/Statistical review dated October 11, 1995. Both reviewers have examined the effectiveness data, and Dr. McCormick has examined the safety data. In this memo, I will briefly review the effectiveness and safety data, and convey my recommendations about the NDA.

Before I review the individual studies, it should be noted that the 5 adjunctive therapy studies are of essentially identical design, with several notable exceptions (doses studied, duration of specific phases).

For this reason, I will describe in some detail the design of the first study (YD), but in the description of subsequent studies, I will only describe the differences between each and Study YD.

STUDY YD

Study YD was a double blind, randomized, parallel group, multi-center study in which patients with refractory partial seizures were randomized to receive either 200 mg/day, 400 mg/day, 600 mg/day, or placebo, given orally in a BID regimen.

The study was divided into several phases:

1) **Baseline Phase**-This phase lasted approximately 12 weeks. During this phase, patients were treated with at most 2 anti-epileptic drugs (AEDs) and were observed. During this phase, patients with a diagnosis of epilepsy had to have steady state trough plasma levels of their AEDs that fell within certain well accepted "therapeutic ranges". If patients recorded at least 12 partial onset seizures during this phase, they were randomized into the next phase.

2) **Double Blind Treatment: Titration Phase**-Patients were randomized at this point into one of 4 groups which were designed to ultimately reach a total daily dose of either 200 mg/day, 400 mg/day, 600 mg/day, or placebo. This Titration Phase was to consist of 4, 1 week intervals, in which patients were to receive 100 mg topiramate (or placebo) once a day for the first week, 100 mg (or placebo) BID during the second week, followed by an additional 100 mg bid increment (or placebo) in each of the next 2 weeks. However, if the patient could not tolerate this regimen, a number of maneuvers could be invoked by the investigator. Either the dose could be increased by 100 mg/day (not BID), the length of each interval could be increased to 2 weeks, or the next phase (to be described) could begin after 2 weeks of any dose (not the maximum targeted).

3) **Double Blind Treatment: Stabilization Phase**-During this phase, patients were to be maintained on the maximum dose they achieved during the previous phase. The Stabilization Phase was to last for 12 weeks.

Approximately 180 patients were to be enrolled, with the allowable concomitant AEDs being limited to carbamazepine, phenytoin, valproate, phenobarbital, and/or primidone.

The primary measure of effectiveness was to be seizure frequency, presumably compared to baseline, but the protocol was unclear about which double blind phase would be used for the comparison, or even which seizure types were to be evaluated. Additionally, percent of patients achieving at least 50% reduction in seizure frequency, severity of seizures, physician and patient global ratings, and duration of seizure free intervals were to be evaluated as secondary measures.

Primary seizure data were to be recorded by patients/caretakers in a daily seizure diary.

RESULTS

A total of 223 patients entered the Baseline Phase. A total of 181 at 17 centers were randomized into the Double Blind Titration Phase, with 45 randomized to each group except the 600 mg/day group, into which 46 were randomized. The following chart describes patient flow in the Double Blind Phase:

	Randomized	Discontinued	Completed
Placebo	45	5	40
200 mg/d	45	4	41
400 mg/d	45	5	40
600 mg/d	46	7	39

We do not have information regarding during which period (Titration or Stabilization) patients discontinued.

When Dr. Sahlroot examined the primary data, he noted several discrepancies between his seizure counts and those presented by the sponsor in its analyses. These differences did not affect the outcome, so the data presented here will be those analyzed by Dr. Sahlroot.

The primary outcome measure was change in seizure frequency, compared to baseline. The primary analysis performed was a 2 way ANOVA (treatment, center, and treatment by center interaction) on the ranks of the difference in 28 day seizure frequency between baseline and double-blind treatment. The entire double-blind phase was utilized, and 28 day frequency was calculated as follows: total number of seizures X 28/total number of days in treatment. The sponsor included all seizure types (not just partial seizures). For purposes of calculating the baseline rate, when the baseline period was greater than 12 weeks, only the final 12 weeks of that period were included.

The overall ANOVA was significant at $p<0.01$, and the following table describes the data and p-values for the individual treatment contrasts (baseline Median 28 Day Seizure Frequency varied from 10-11 in the 4 groups):

Median Percent Reduction From Baseline in 28 Day Seizure Frequency

		P-value
Placebo (N=45)	11.6	
200 mg/day (N=45)	27.2	0.080
400 mg/day (N=45)	47.5	0.009
600 mg/day (N=46)	44.7	0.003

Medians are presented as measures of treatment effect (as opposed to means) because the data are not normally distributed. The contrasts for the 400 and 600 mg/day groups compared to placebo are significant in the face of a conservative correction (Bonferroni) for multiple comparisons.

Most patients (75%) were receiving carbamazepine, either in combination or alone.

As Dr. McCormick describes, it is interesting to examine the actual doses achieved for both the total Double-blind phase, as well as for the

Stabilization phase alone. The following doses are described:

	Total Double-blind		Stabilization	
	Mean	Median	Mean	Median
200 mg/day	188	194	200	200
400 mg/day	334	367	391	400
600 mg/day	455	519	556	600

It should be noted that, if the Titration Phase were conducted according to the protocol in all cases, the Mean Daily Dose for the Total Double Blind Phase should be 194, 369, and 531 mg/day for the 200, 400, and 600 mg/day groups, respectively (of course, the full dose should have been achieved in the Stabilization Phase).

SECONDARY MEASURES

The sponsor analyzed several secondary measures. FDA reviewers did not perform independent analyses of this outcomes.

Responder Rate

Responders were defined as patients who had a 50% decrease (or greater) in percent seizure reduction. The following results were obtained:

Treatment	N	%	P-value
Placebo (N=45)	8	18	
200 mg/d (N=45)	12	27	0.620
400 mg/day (N=45)	21	47	0.013
600 mg/day (N=46)	21	46	0.027

Investigator's Global Evaluation

Investigators rated patient improvement at the end of the trial on a 5 point scale: 1=worse, 2=none, 3=minimal, 4=moderate, 5=marked. The following means and p-values were obtained:

	Mean	P-value
Placebo	2.7	
200 mg/d	3 3	0.004
400 mg/d	3.8	<0.001
600 mg/d	3.6	<0.001

Patient's Overall Assessment

Patients assessed the overall effect of the drug at the end of double-blind on the following 4 point scale: 1=poor, 2=fair; 3=good, 4=excellent.

The following means and p=values were obtained:

	Mean	P-value
Placebo	2.2	
200 mg/d	2.6	0.030
400 mg/d	2.8	0.007
600 mg/d	2.6	0.053

Seizure Duration and Seizure Severity were not adequately documented, and, therefore, were not analyzed.

STUDY YE

Study YE was essentially identical in design to Study YD, except that patients were randomized to receive either placebo, 600 mg/day, 800 mg/day, or 1000 mg/day orally in a BID regimen.

RESULTS

A total of 242 patients entered the Baseline Phase, with 190 patients being randomized into the Double Blind Titration Phase. The following chart describes patient flow in the Double Blind Phase:

	Randomized	Discontinued	Completed
Placebo	47	3	44
600 mg/d	48	11	37
800 mg/d	48	9	39
1000 mg/d	47	13	34

The following results were seen for the comparisons of the individual doses with placebo on the primary measure, Change in 28 Day Seizure Frequency, as computed by Dr. Schlroot; the results of the overall ANOVA yielded a p-value of 0.0001:

Median Percent Reduction From Baseline in 28 Day Seizure Frequency

		P-value
Placebo (N=47)	1.7	
600 mg/d (N=48)	40.7	0.0001
800 mg/d (N=48)	41.0	0.0001
1000 mg/d (N=47)	36.0	0.0001

Again, as in the first study, the majority of patients (71%) were taking carbamazepine, either alone or in combination.

The following table describes the actual (Mean and Median) daily doses achieved in the trial:

	Total Double Blind		**Stabilization**	
	Mean	Median	Mean	Median
600 mg/day	431	520	544	600
800 mg/day	611	690	739	800
1000 mg/day	611	740	799	1000

SECONDARY MEASURES

The following results represent the sponsor's analyses; FDA reviewers have not performed independent analyses of these secondary outcomes.

Responder Rate

Treatment	N	%	P-value
Placebo (N=47)	4	9	
600 mg/d (N=48)	21	44	<0.001
800 mg/d (N=48)	19	40	0.001
1000 mg/d (N=47)	18	38	0.001

Investigator's Global Evaluation

	Mean	P-Value
Placebo	2.4	
600 mg/d	3.5	<0.001
800 mg/d	3.5	<0.001
1000 mg/d	3.5	<0.001

Patient's Overall Assessment

	Mean	P-value
Placebo	1.9	
600 mg/d	2.6	<0.001
800 mg/d	2.6	<0.001
1000 mg/d	2.4	0.015

STUDY Y1

This study was of essentially identical design as the first 2, except it compared only 2 groups; topiramate 400 mg/day and placebo. FUrther, the Baseiine Phase was only slated to be 8 weeks long, the Titration was

designed to be 3 weeks, and the Stabilization Phase was to be 8 weeks long. In order to be eligible for the double-blind portion of the trial, patients had to experience at least 8 partial onset seizures during baseline.

RESULTS

A total of 52 subjects were enrolled in 4 centers in Europe; 47 patients were randomized. The following table describes patient flow in the Double Blind Phase:

	Randomized	Discontinued	Completed
Placebo	24	2	22
400 mg/day	23	6	17

The following chart describes the results, confirmed by Dr. Sahlroot, of the analysis of the primary outcome measure:

Median Percent Reduction From Baseline in 28 Day Seizure Frequency

	Baseline	Change	P-value
Placebo (N=24)	10	1.1	
400 Mg/d (N=23)	18	40.7	0.065

The mean and median daily dose achieved in the topiramate group in the entire double blind phase were 312 and 353 mg/day, respectively, while the mean and median during the stabilization phase were 387 and 400 mg/day, respectively. As in the other studies, most patients (64%) were taking carbamazepine, either alone or in combination.

SECONDARY MEASURES

Again, no attempt was made by FDA reviewers to independently confirm the sponsor's analyses of the secondary measures.

Responder Rate

Treatment	N	%	P-value
Placebo (N=24)	2	8	
400 mg/d (N=23)	8	35	0.033

Investigator's Global Evaluation

	Mean	P-value
Placebo	2.2	
400 mg/d	3.5	0.002

Patient's Overall Assessment

	Mean	P-value
Placebo	1.6	
400 mg/d	2.3	0.021

STUDY Y2

In this trial, of similar design to the study above, patients were randomized to receive either 600 mg/day of topiramate (given orally as a BID regimen) or placebo.

Results

A total of 65 patients entered the Baseline phase in 6 centers in Europe;

60 were randomized into the Double Blind Phase. The following chart describes patient flow in the Double Blind Phase:

	Randomized	Discontinued	Completed
Placebo	30	2	28
600 mg/d	30	5	25

The following table describes the results of the analysis of the primary outcome measure, as corroborated by Dr. Sahlroot:

Median Percent Reduction From Baseline In 28 Day Seizure Frequency

	Baseline	Change	P-value
Placebo (N=30)	15	-12.2	
600 mg/d (N=30)	16.8	46.4	0.004

Most patients (63%) were receiving carbamazepine, either alone or in combination.

The mean and median doses during the entire double blind phase were 430 and 505 mg/day, respectively, while the mean and median for the stabilization phase were 519 and 600 mg/day, respectively.

SECONDARY MEASURES

Again, FDA reviewers did not independently analyze the secondary outcomes.

Responder Rate

Treatment	**N**	**%**	**P-value**
Placebo (N=30)	3	10	
600 mg/day (N=30)	14	47	0.001

Investigator's Global Evaluation

	Mean	P-value
Placebo	2.5	
600 mg/d	3.3	0.002

Patient's Overall Assessment

	Mean	P-value
Placebo	1.6	
600 mg/day	2.3	0.01

STUDY Y3

This study is of essentially identical design as the previous 2, except that the Titration Phase was to be 5 weeks, and patients were randomized to receive either 800 mg/day of topiramate, or placebo.

Results

A total of 57 patients entered the baseline phase; 56 were randomized into the Double Blind Phase. The following chart displays patient flow in the Double Blind Phase:

	Randomized	Discontinued	Completed
Placebo	28	1	27
800 mg/d	28	6	22

The following chart displays the results of the analysis of the primary outcome measure, as performed by Dr. Sahlroot:

Median Percent Reduction From Baseline in 28 Day Seizure Frequency

		P-value
Placebo	-20.6	
800 mg/d	24.3	0.0008

Again, most subjects (82%) were taking carbamazepine, either alone or in combination.

The mean and median daily doses achieved in the total double blind phase were 448 and 449 mg/day, respectively, while the mean and median in the Stabilization Phase were 568 and 600 mg/day, respectively.

SECONDARY MEASURES

Once again, FDA reviewers did not perform independent analyses of these measures.

Responder Rate

Treatment	**N**	**%**	**P-value**
Placebo (N=28)	0	0	
800 mg/d (N=28)	12	43	0.001

Investigator's Global Evaluation

	Mean	P-value
Placebo	2.3	
800 mg/d	3.7	<0.001

Patient's Overall Assessment

	Mean	P-value
Placebo	1.8	
800 mg/d	2.4	0.009

2 Pages
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SAFETY

The NDA ostensibly contains complete safety information on a total of 1697 people exposed to at least one dose of topiramate (1446 patients with epilepsy, 251 subjects without epilepsy). In addition, presumably complete information about deaths and serious adverse events has been collected for an additional 407 patients followed prospectively (cutoff date for this latter cohort is March 31, 1995), so that the sponsor claims that the NDA contains complete death and serious adverse event data from a cohort of 2104 exposed subjects.

As can be determined from Pages 22-3 of the Clinical Statistical Review, 845 patients have received topiramate for at least 6 months, with 245 having been treated for longer than 2 years. From the cohort of 1446 patients with epilepsy treated with topiramate, we can see that 628 patients have been treated for greater than 6 months with 500 mg/day as their most frequent dose. (It would be useful to know how many patients have been exposed to doses of 400 mg/day for at least 6 months, since 400 mg/day has been shown to be an effective dose. However, data for this lower dose cohort has not been presented by the sponsor, although, obviously, the number will be greater than 628). The total number of patients receiving a mean dose of at least 800 mg/day for whom complete safety data have been presented is 498, with 421 having received this dose most frequently for at least 6 months.

DEATHS

A total of 19 deaths in patients receiving topiramate have been reported in the NDA, for a crude mortality of 0.9% (19/2104). All deaths occurred in patients receiving topiramate in long term extension protocols. The shortest duration of treatment in this cohort of19 was 92 days, with a

mean duration of exposure of 558 days (range 92-1768 days).

Dr. McCormick has examined the reports of these deaths in detail. She has classified 13 of the 19 as being Sudden Unexplained Deaths in Epilepsy (SUDE), using relatively conservative definitions used by the Division in reviewing previous NDAs for AEDs. In essence, otherwise healthy patients with epilepsy who are found dead, for whom no other obvious cause of death is apparent, and who have not been observed to have had a seizure, are classified as victims of SUDE. In particular, patients who have been found to have drowned or been in "epilepsy related accidents" are included in this cohort, despite the fact that they are usually classified (and were in this NDA by the sponsor) as being accidental deaths, often assumed to be the result of an unwitnessed seizure. Several of the 13 had autopsies, none of which identified a specific cause of death. In this cohort, the range of duration of treatment with topiramate was 92-1768 days, and the daily dose at the time of death ranged from 200-1600 mg/day (5/13 were receiving greater than 1000 mg/day at the time of death).

The estimated exposure in patient-years for the entire cohort for whom mortality data are known is approximately 2600 patient-yrs, yielding an incidence density of mortality due to SUDE of 13/2600, or 5/1000 pt-yrs. As Dr. McCormick notes, this rate approximates those of other recently approved AEDs (Gabapentin-2.5/1000 pt-yrs, Lamictal-5.8/1000 pt-yrs).

Of the remaining deaths, 2 of interest were presumably due to pulmonary embolism, although this was documented in only one case. In one case, a 63 year old man chronically ill with heart failure, neuropathy, ataxia, paraproteinemia (all prior to topiramate therapy) was admitted to the hospital with pneumonia after 990 days of topiramate treatment. His condition worsened, and on day 1069 of treatment died of acute respiratory failure; dose of topiramate at the time of death was 400 mg/day. No autopsy was performed.

In the second case, a 40 year old man was found on lab testing to have a platelet count of 774,000 and thrombophlebitis after approximately 400 days of topiramate treatment (daily dose of 1300 mg at that time). One week later he died of a massive pulmonary embolism, documented at surgery. Interestingly, one month prior to his death, a platelet count could

not be determined, due to clumping of the platelets.

DISCONTINUATIONS

Of the total 1446 patients with epilepsy treated with topiramate, 723 (50%) discontinued treatment. Of these, 360, (25% of the total) withdrew due to adverse events. Of the 527 patients with epilepsy enrolled in controlled trials, 89 (17%) withdrew due to adverse events (compared to 9/216, or 4% of placebo patients).

In the entire cohort of 1446 (of whom 360 withdrew due to adverse events), the most common reasons for discontinuation were related to effects on behavior, cognitive function, and/or psychiatric symptoms. The classification by the sponsor of these various events was inconsistent, variable, and inaccurate at times. Nonetheless, the most common terms listed by the sponsor as reasons for withdrawal are listed below. The incidences listed below are not mutually exclusive; many patients had several events listed as reasons for withdrawal.

	N	%(of total cohort of 1446)
Confusion	59	4.0
Thinking abnormal	55	3.8
Somnolence	49	3.3
Fatigue	49	3.3
Memory difficulty	44	3.0
Depression	43	3.0
Ataxia	35	2.4
Dizziness	40	2.8
Anorexia	34	2.4
Impaired concentration	30	2.0
Aphasia	30	2.0
Nervousness	27	1.9
Emotional Lability	25	1.7

Headache	22	1.5
Anxiety	21	1.5

In the controlled trials, adverse events that were associated with discontinuation paralleled those in the entire cohort, with Impaired Cognition being responsible for the greatest number of discontinuations (27/527, or 5%), followed by Anxiety (15/572, or 3%) and Diplopia (16/527, or 3%). In the controlled trials, these events appeared to be related to treatment with higher doses, although the numbers of patients receiving a given dose, and the number of events at a given dose, were relatively small. For example, 15/214 (7%) of patients receiving 1000 mg/day discontinued due to Impaired Cognition, compared to 12/313 (4%) of patients receiving lower doses, with the incidence in the 400, 600, and 800 mg/day dose groups each between 3-5%. With regard to Anxiety, the incidence of withdrawal due to this adverse event was 11/214 (5%), while at lower doses the incidence varied from 1-1.6%. The dose response data for Diplopia are essentially identical to that for Anxiety.

SERIOUS ADVERSE EVENTS

A total of 221/1446 (15%) of topiramate treated patients were considered by the sponsor to have suffered a serious adverse event, by the usual definition. By far the largest percentage of these events can be characterized as cognitive/psychiatric adverse events.

Cognitive/Psychiatric Serious Adverse Events

Under the rubric of Cognitive Adverse Events, the sponsor has included the following terms: Thinking Abnormal, Confusion, Concentration Impaired, Aphasia, Slowed Thinking, Amnesia. A search of the CANDA by Dr. McCormick revealed that 62% of the total 1446 topiramate exposed epilepsy population reported at least one episode of at least one of these events (these were not all serious). In her view, based on a reading of CRFs, at least some number of these reports were misleading, but presumably were based on the sponsor's inability to code an event accurately. As she notes in her review, we have requested a detailed re-assessment of these events from the sponsor.

According to the table in the clinical/statistical review on pages 183-188, 44/1446 (3%) of patients had at least one serious psychiatric event that, according to Dr. McCormick, could reasonably be attributed, at least in part, to treatment with topiramate. Events with at least 2 reports were, in decreasing frequency, Psychosis (15/1446 or 1%), Depression (7/1446 or .5%-3 suicide attempts), Personality Disorder (5/1446 or .3%), Confusion, Aggressive Behavior, Agitation, Emotional Lability, Anorexia, Nervousness, and Somnolence. Other events had only one report each. No clear relationship to duration on therapy or dose (although simple inspection suggests that Psychosis ordinarily occurred at the high end of the dosing range) emerges for these events. Importantly, Dr. McCormick points out a particularly egregious miscoding of a Psychiatric event on page 193 of her review. Specifically, a patient was coded as having experienced "Agitation", when, in fact, after psychiatric evaluation, he killed his mother. This example, as well as others, reinforced Dr. McCormick's conclusion that potentially serious miscoding took place to an unknown degree, and additional evaluation was requested of the sponsor.

Similar difficulties arose in the interpretation of the sponsor's categorization of the adverse events subsumed under the term Personality Change.

Dr. McCormick has compared the crude rates of Depression in topiramate treated patients to those of 3 recently approved AEDs (p.192 of the clinical/statistical review). This comparison suggests that the risk of experiencing depression while on topiramate is approximately 3 times greater than for these other drugs, although such comparisons performed among several studies can be quite misleading for many reasons.

Weight Loss/Anorexia

Of the 485 topiramate treated patients in controlled trials who had pre and post-baseline weights measured, 281/485 (58%) lost 5 kg or less, while 101/485 (21%) lost between 5-10 kg, and an additional 30/485 (6%) lost at least 10 kg, for a total of 412/485 (85%) of topiramate treated patients with weight loss. This compares with a total of 80/206 (39%) of

placebo patients for whom pre and post-baseline weights are available who lost weight, 78 of whom lost at most 5 kg. In the controlled trials, 57 topiramate treated patients reported anorexia, compared to 8 placebo patients. The sponsor has suggested that the weight loss seen in topiramate treated patients is correlated with the anorexia, as well as with increasing topiramate dose.

Renal Calculi

A total of 32/2086 (1.5%) of topiramate treated patients described in the 4 month Safety Update reported 43 episodes of kidney stones. A total of 27 (84%) of these patients were males ages 21-54. The overall annualized incidence rate was 123/10,000 persons, which compares to the sponsor's estimate of 235/10,000 persons for acetazolamide (the prototypical carbonic anhydrase inhibitor) and 7-21 cases/10,000 persons background rate. No obvious correlation with dose or duration of treatment emerged, and 8 cases required hospitalization, and were therefore considered serious.

OTHER ADVERSE EVENTS

Controlled trials

In placebo controlled trials (adjunctive treatment), the following adverse events occurred with an incidence of at least 2 X that of placebo:

Event	Topiramate		Placebo	
	N	%	N	%
Dizziness	165	31	33	15
Somnolence	149	28	21	10
Thinking Abnl	112	21	5	2
Paresthesia	96	18	10	5
Nervousness	93	18	16	7
Confusion	84	16	9	4
Ataxia	84	16	15	7
Amnesia	69	13	7	3
Concentration Impaired	69	13	4	2

Depression	61	12	11	5
Weight Decrease	61	12	6	3
Diplopia	59	11	12	6
Vision Abnl	58	11	6	3
Emotional Lability	58	11	7	3
Anorexia	57	11	8	4
Aphasia	54	10	1	.5
Speech Disorder	53	10	5	2

The adverse events reported in the monotherapy study generally mirror those seen in the adjunctive studies, but these data are less meaningful given that: 1) the numbers are small (only 24 patients randomized to each treatment, and 2) very few patients actually achieved monotherapy. For these reasons, the adverse event profile of topiramate when given as monotherapy cannot be considered to have been adequately evaluated.

The dose response of the adverse event pattern is difficult to discern, given that the sponsor has presented adverse event incidences at the intended doses, but not for the doses actually achieved. As we have seen earlier, the doses patients actually received did not always correspond to the doses they were intended to receive (this was particularly true for the higher doses when given as adjunctive treatment). The sponsor has been asked to provide dose response data for the doses actually administered.

Other Studies

As described earlier, the sponsor has submitted complete adverse event data for 1446 patients with epilepsy. In general, the adverse events seen in this cohort mirror those (in kind and relative frequency) seen in the controlled trials. The following table lists those adverse events in this cohort which occurred with an incidence of at least 10% in decreasing frequency (entries represent the number of patients reporting the given event at least once):

Event	N	(%)
Somnolence	464	32%
Headache	431	30%
Fatigue	419	29%
Dizziness	418	29%
Abnormal Thinking	344	24%
Paresthesia	309	21%
Injury	295	20%
Nervousness	288	20%
Anorexia	277	19%
Confusion	264	18%
Ataxia	246	17%
Nausea	232	16%
Depression	225	16%
Diarrhea	218	15%
Impaired Concentration	184	13%
Pain	174	12%
Aphasia	171	12%
Abnormal Vision	171	12%
Emotional Lability	163	11%
Diplopia	157	11%
Tremor	156	11%
Speech Disorder	155	11%
Nystagmus	156	10%
Insomnia	150	10%

LABORATORY ABNORMALITIES

There were few differences noted between the incidence of significant laboratory abnormalities between topiramate and placebo treated patients in placebo controlled trials. Specifically, only elevated Alkaline Phosphatase (3% vs 1%) and SGOT (1.4% vs 0.5%) and decreased Phosphorous (6% vs 2%) occurred at least 2 times as frequently on topiramate compared to placebo.

However, in the entire NDA database, a number of patients were reported to have discontinued, died, or experienced a serious adverse even. in the setting of a laboratory abnormality.

Approximately 11 patients were reported as having serious adverse events associated with elevated liver enzymes. The exact number of such patients is unclear, as is the number who discontinued treatment because of the elevations. At least 5-6 of these patients continued on treatment, with, presumably, resolution of the abnormalities, and at least 2 patients were ultimately diagnosed as having had hepatitis A. As far as I can determine at this time, the greatest elevation of SGOT was approximately 625 in an asymptomatic patient in whom treatment was apparently continued. In a number of these patients, discontinuation of a concomitant AED resulted in resolution of the elevation. Data addressing outcome, other potential etiologies, treatment, and follow-up, were missing for many of these patients; requests for additional information are pending.

Other laboratory abnormalities were noted rarely, and the most frequent lab abnormalities in the 1446 patient cohort being low phosphorous (at least once in 14% of patients), low bicarbonate (10%), and low glucose (6%). The low bicarbonate is consistent with the fact that topiramate is a carbonic anhydrase inhibitor, but the low phosphorous and glucose are unexplained.

Hematology

The only hematologic abnormality seen consistently at a greater incidence in topiramate treated patients compared to placebo treated patients in the controlled trials was low WBC (defined as < 2800 WBC/mm). The incidence was 6% in topiramate patients compared to 3% in placebo patients.

However, of the 1446 topiramate treated patients with epilepsy, a number of patients were noted to have had abnormalities considered serious.

A single patient, receiving treatment for 88 days at a dose of 600 mg/day, sustained decreases in Hemoglobin (15.3 baseline, 10.8 treatment),

platelets (normal baseline, 71,000 treatment), and WBC (normal baseline, 3400 treatment). The patient was also receiving valproate and carbamazepine. No additional follow-up information is available.

A total of 8/1446 (0.6%) were reported to have had thrombocytopenia (< 75,000/mm). Of these 8, 7 were receiving concomitant valproate and/or carbamazepine. In at least one case, the thrombocytopenia (nadir of 28,000) resolved with withdrawal of the valproate.

In the total epilepsy population of 1446, 22 patients (1.5%) were reported to have had persistent or recurrent low WBCs (< 2800 cells/mm). Of these 22, only 2 patients had values <2000; neither of these 2 were discontinued from treatment.

One patient discontinued due to anemia (Hgb 9.5 gm), and 5 others had low values for Hgb, Hct, of RBC counts, but none of these 5 discontinued treatment.

Cardiac Findings

One patient, a 59 year old woman with no prior history of arrhythmias, experienced atrial flutter after 9 days of topiramate 400 mg/day. The topiramate was discontinued, she was treated, and the flutter resolved.

Two (2) other patients withdrew because of EKG abnormalities (one RBBB), but the NDA contains only sketchy information about these events.

CONCLUSIONS

Adjunctive Therapy

The sponsor has submitted the results of 5 adequate and well controlled trials that demonstrate the effectiveness of topiramate as adjunctive

treatment for patients with partial seizures. These studies have examined single doses vs placebo, as well as multiple doses vs placebo.

Certain conclusions about the effects of different doses can be made. First, the one study that examined the effects of 200 mg/day of topiramate (Study YD) did not demonstrate a statistically significant effect of the treatment, although there were quantitative changes in the direction of improved seizure control. Nonetheless, the data do not support the conclusion that topiramate 200 mg/day is an effective dose.

The data support the conclusion that 400 mg/day is the minimally effective dose. The comparison between this dose and placebo was clearly statistically significant in Study YD, and was essentially so in Study Y1 (p=0.065). In the latter study, the number of patients enrolled was half that in Study YD, the absolute Change from Baseline in Median Seizure Frequency and Responder Rate in this group were comparable in the 2 studies, and the Differences between placebo and 400 mg/day on these 2 outcomes were also comparable.

Dose response beyond 400 mg/day, however, has not been well established. Two studies examined the effects of 3 doses. Study YD examined the effects of topiramate 200, 400, and 600 mg/day vs placebo, and Study YE examined the effects of topiramate 600, 800, and 1000 mg/day. In these studies, all doses of 400 mg/day and greater were shown to be statistically superior to placebo, **but there was no evidence of dose response within either study**. This lack of dose response was supported by the results of the 3 additional controlled trials (Y1, Y2, Y3) which examined the effectiveness of 400, 600, and 800 mg/day vs placebo, respectively. That is, the absolute responses are similar for these individual dose level studies when compared across these 3 studies (doses) and when compared to the results of Studies YD and YE. However, hints of apparent dose response are suggested somewhat if one examines the **differences** between drug and placebo in Change From Baseline Median Seizure Frequency and Responder Rate across the studies. The following table describes these differences (the entries for placebo are the Change from Baseline; the entries for topiramate are the **differences** between that dose and the placebo change from baseline):

DIFFERENCES BETWEEN PLACEBO AND DRUG ON MEDIAN PERCENT CHANGE IN SEIZURE FREQUENCY FROM BASELINE AND RESPONDER RATE

Study/Dose Group	Difference in Change From Baseline	Difference in Responder Rate
YD		
Pla	12	18
200	15	9
400	36	29
600	33	28
YE		
Pla	2	9
600	39	35
800	39	31
1000	34	29
Y1		
Pla	1	8
400	40	27
Y2		
Pla	-12	10
600	58	37
Y3		
Pla	-21	0
800	45	43

For example, the difference between drug and placebo on Median Seizure Frequency for 600 mg/day vs placebo in Study Y2 is 58%, compared to a difference of 35% for 400 mg/day vs placebo in Study YD. However, across study comparisons can be misleading; for example, as can be seen from the table, differences between drug and placebo responses are often the result of different placebo responses, which suggest that the populations in different studies are not necessarily comparable. It bears repeating that no dose response is seen in the 2 studies that examined more than one dose of topiramate, and hints of dose response based on isolated comparisons across studies cannot be considered to establish a dose response.

There are a number of explanations for this apparent lack of dose response above 400 mg/day, including the possibility that these doses are already on the plateau of the dose response curve, the power to detect differences between these doses was low, and/or patients in general did not achieve the actual doses to which they were randomized, resulting in studies that in reality did not adequately examine the question of dose response. In any event, in my view, the data do not establish that doses greater than 400 mg/day afford any greater protection against partial seizures than that afforded by 400 mg/day.

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SAFETY

The sponsor has submitted safety data for at least 1400 patients with epilepsy, with presumably an additional cohort of approximately 400 for whom information about deaths and serious adverse events is available. As best as I can determine at this point, approximately 600 patients have been treated with at least 400 mg/day for at least 6 months. The size of the safety database, therefore, is sufficient to support approval.

Although there are a number of deficiencies in the submission that have made it difficult, if not impossible, to have as detailed and complete an understanding of the safety profile of topiramate as we would like (see below), I believe that we do have sufficient information at this time to conclude that there no safety issues that would preclude approval. I believe that the numbers and types of adverse events seen, including deaths, serious adverse events, and discontinuations, are acceptable given the benefit afforded by this treatment for the serious disease of refractory seizures. However, having said this, I should hasten to add that the application contains significant inadequacies in the presentation of adverse event data that may require considerable work on the part of the sponsor before the application can be approved.

In the first place, the sponsor has not accounted for the discrepancies between the dose to which a patient was randomized and the actual dose received in its presentation of the dose response data for adverse events. While I believe that we can be reasonably confident that patients alleged to have received 400 mg/day generally actually reached that dose (examination of the mean doses achieved in patients randomized to 400 mg/day in the controlled trials suggests that this is so), we have less confidence that this correspondence between actual and randomized dose persisted for patients slated to receive higher doses. In truth, of course, if one accepts that the dose to be recommended in labelling should be the lone dose of 400 mg/day, the lack of specific exposure data to doses greater than 400 mg/day becomes, in some sense, less critical; that is, as long as the safety experience has been accrued at doses at least as great as 400 mg/day (the recommended dose), the cohort is acceptable. Nonetheless, in order for labelling to contain accurate statements about

the safety of doses greater than those recommended, we will need the safety experience to be described in terms of numbers of patients who actually received specific (mean daily) doses for given intervals of time.

Beyond the issue of the accurate description of doses received in the trials, the submission has, according to Dr. McCormick, considerable deficiencies in the presentation of the safety data. The deficiencies can be considered to fall into 3 categories.

1) **Inaccurate translation of primary data**-based on her review of Case Report Forms of several patients, Dr. McCormick has identified a number of instances in which the sponsor has inaccurately translated primary terms. For example, several events reported as "aphasia" by the sponsor in the NDA safety database actually represented patients who were so somnolent and/or confused that they could not speak normally. Only upon review of the CRFs could it be determined that the sponsor's translation of the primary report was wrong. These miscodings were primarily seen for events listed as Cognitive/Psychiatric, and the sponsor will need to go back, re-review the primary data in these cases, re-translate these events, and re-calculate incidences of these events based on their re-review. They should also provide us with a detailed description of the process they utilized in performing this re-review.

2) **Unclear reporting of Cognitive/Psychiatric Adverse Events**-it has not been possible to gain a comprehensive understanding of topiramate's capacity to effect cognition, mental state, and/or behavior because the sponsor has not submitted a comprehensive synthesis of these events. Specific terms (e.g., thinking abnormal, concentration impaired, psychosis, confusion, amnesia, aphasia, etc.) are not only poorly defined, but do not convey, as submitted by the firm, either the true proportion of patients experiencing one or several of these events, or paint a meaningful picture of patients' clinical status. We do not know, for example how many patients exhibited a constellation of these signs and symptoms, or how many reported only a single term (unlikely as that is). In short, the absence of a well thought out, detailed synthesis of this toxicity precludes us from writing adequate labelling that describes this aspect of topiramate's toxicity.

3) **Inadequate enumeration and follow-up of laboratory abnormalities**-in addition to inadequate descriptions of adverse clinical events, an accurate accounting of patients with important laboratory abnormalities has also been difficult to locate. Specifically, there have been 1) uncertainties in numbers of patients with specific abnormalities (e.g., the actual number of patients with serious elevations of liver enzymes is not clear), as well as 2) sketchy information about other laboratory findings (e.g., descriptions of at least 2 patients with EKG abnormalities are inadequate). In general, follow-up information about patients with events of interest has also been poor. The sponsor should be required to present complete and accurate data on all patients considered to have had serious laboratory abnormalities, including those who discontinued with and/or because of laboratory abnormalities, and accurate follow-up information where available (if such follow-up information is not available for a given patient, the sponsor should include an explicit statement to that effect).

In sum, the data submitted establish that topiramate is an effective anti-seizure medication when administered as adjunctive therapy. However, the sponsor has not performed an analysis of the ability of topiramate to specifically prevent partial seizures, and must do so to support their proposed labelling claim. The sponsor has not established the effectiveness of topiramate when given a
must perform an additional appropriate analysis to establish that topiramate is effective in preventing

The sponsor has established that the risks of topiramate are acceptable, but must do additional work to better characterize the incidence and character of some of the adverse events seen as noted above.

RECOMMENDATIONS

An approvable letter should be issued asking the sponsor to provide the additional data, information, and analyses described in the Comments section above.

Russell Katz. M.D.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: DEC 29 1995

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Topiramate, NDA 20-505

TO: Dr. Paul Leber

The sponsor's analysis of the topiramate clinical data, especially the safety data, is clearly not complete, for the reasons described by you and Drs. McCormick and Katz. Nonetheless, I believe the results in hand already show a drug that is quite effective as add on therapy in suppressing partial seizures in a drug-resistant population and that also shows at least some evidence of effectiveness as monotherapy. The dose response relationship has been particularly well studied.

Topiramate is also a drug that has a high rate of, and wide array of, important and troublesome (considered serious and/or causing drop-outs), but probably not dangerous, adverse effects that are almost certainly acceptable in an AED, even if they limit the use of the drug. There is also considerable exposure to doses well above the apparent maximum effective dose, which is somewhat reassuring. Defining the adverse effects, who is at risk of them, and their ultimate outcome will be a substantial task, as you and all reviewers have concluded, but it seems very likely that this can be done successfully. All this persuades me that topiramate is approvable, albeit with considerable further effort to define and describe the adverse effects of the drug. Nothing in an approvable action, however, implies that new data or analysis could not lead to a different conclusion. A few specific points:

What is a problem though, is the very small data base and the lack of significant safety data at an actual (as opposed to intended) 1000 mg dose.

2. Effectiveness vs Seizure types

Since the reviews were written, Dr. Sahlroot has looked at the types of seizures seen in the 5 add-on studies and has concluded that virtually all were partial seizures, both before and after treatment. The issue, therefore, of whether there is a shift of seizure type, is no longer of concern. Dr. Sahlroot may need to document his analysis further. It still remains to be shown whether, given a seizure, there is an altered (decreased) likelihood of

3. Safety

There is a great deal still to do here to characterize the actual nature of the adverse effects of topiramate. I have modified the letter somewhat but it is unchanged in essence.

Robert Temple

Robert J. Temple, M.D.