

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020241/S003 AND 020764/S001

MEDICAL REVIEW(S)

Ware

Memorandum

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

DATE: October 16, 1998

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

SUBJECT: Lamictal Monotherapy

TO: File NDA 20-241 / S-003
File NDA 20-764 / S-001

This memorandum explicates the basis for my decision to issue a second approvable action letter for two NDAs that will, when approved, allow two oral formulations of lamotrigine to be recommended for monotherapy use in the management of partial seizures in a subset of the population (patients being maintained on a single enzyme inducing anti-epileptic drug product [EIAED]) suffering from this seizure type.

My knowledge of issues affecting the application derives from the primary clinical reviews carried out by Dr. Tresley (6/25/98 and 7/21/98) and two supervisory memoranda issued (10/8/98 and 10/12/98) by Dr. Katz, the Deputy Director and Neurology Team Leader.

The initial approvable action letter issued on 2/24/98.

Of the two NDAs, NDA 20-241 has the earlier user fee goal date (October 17, 1998).

Issues/Questions relevant to the final approval of the two pending applications.

Is the totality of clinical experience so far gained with lamotrigine under conditions that approximate those likely to obtain when lamotrigine is administered at an effective monotherapy dose sufficient to support a conclusion that lamotrigine is safe for use when administered at that dose?

At the time (2/24/98) the approvable action letter issued, the critical question of Lamictal's safety for use as monotherapy could not be addressed definitively because the sponsor had yet to compile a complete accounting/analysis by dose/exposure of all clinical experience that had been gained with lamotrigine. Accordingly, it was not until after the review team began its evaluation of the firm's response (4/15/98) to the approvable action letter that the sparseness of the clinical experience with lamotrigine as monotherapy became fully apparent to the Division's staff.

It bears acknowledgement that clinical experience with lamotrigine, per se, cannot be said to be sparse. (After all, Lamictal is a marketed drug product). What is sparse is clinical experience gained under conditions wherein lamotrigine has been administered as monotherapy at doses that have been shown to be unequivocally effective.

As Dr. Katz recounts in his 10/8/98 memorandum, the precise number of individuals actually exposed to a 500 mg dose (the daily dose known to be effective) and the extent of time over which individuals were exposed to that dose were not provided by the firm in its initial response to the approvable action letter. In fact, it was not until early July of 1998, that the Division learned that at most 148 individuals had been exposed to a dose of 500mg a day, and that of these, only 75 had been at that dose for 6 months. Why this experience would be considered inadequate to support a conclusion that lamotrigine is safe for use at 500 mg a day seems self-evident, at least from the Division's perspective.

A disinterested observer might, nevertheless, be inclined to inquire as to why the sponsor was able to reach a contrary conclusion.

The explanation lies in the fact that the sponsor believes that Lamictal can be recommended for use in monotherapy at a much lower daily dose (100 to 200 mg), a dose at which there is considerable clinical experience, albeit not with monotherapy.

The Division finds the firm's arguments about the lower dose to be without merit. The firm's proposal is not based on evidence adduced in adequate and well controlled clinical investigations, but rests upon a series of "rational" arguments¹ that are advanced to explain why a daily dose of 100 to 200 mg ought to be effective in monotherapy. It bears acknowledgement, incidentally, that if, in fact, a dose of 100 mg a day were the effective monotherapy dose, the sponsor's position that lamotrigine is safe for use as monotherapy at that dose would not be an unreasonable one.

As a matter of long standing policy, however, determinations of drug safety are expected to derive from the evaluation of empirical evidence and not from arguments based on sanguine assumptions and hypothetical conjectures. Admittedly, a determination that a drug is safe for use is, to some degree, a matter of personal opinion. However, to be valid and persuasive it must be an opinion that derives from a carefully considered review of relevant clinical experience (i.e., a judgment) and not an opinion reflecting personal beliefs, sentiments, and conjectures.

To reiterate, insofar as determinations of drug safety are concerned, relevant experience from the Division's perspective is experience gained with appropriately well monitored patients taking a drug under conditions of use identical to and/or judged to be equivalent (vis a vis plasma level exposure) to those under which the drug has been shown to be effective in use.

Accordingly, because the substantial evidence supporting lamotrigine's effectiveness as monotherapy derives entirely from Study 30/31 in which

¹ These are enumerated on page 2 of Dr Katz's 10/8/98 review. The thrust of the sponsor's case is that a plasma concentration found to be associated with an anti-epileptic effect (whether obtained from work in an in vivo animal model or in clinical trials of adjunctive human use) is a plasma level that will be associated with an antiepileptic effect regardless of the clinical circumstances in which it is obtained. Accordingly, if a monotherapy dose regimen can be shown capable of producing lamotrigine plasma levels in the range known to be effective, that dosing regimen may be recommended for use. In further support of this argument, the firm notes that patients treated with precisely such a dose (100 to 200 mg a day) could not be distinguished in active controlled trials from patients receiving a standard AED.

subjects received almost 500 mg a day, the Division is willing to consider as relevant only that clinical experience gained at that daily dose or under conditions² of use that led to plasma levels of lamotrigine as high or higher than those obtained under the regimen employed in Study 30/31.

Following its recognition of the problem, the review team, under the direction of Dr. Katz, undertook additional discussions with the sponsor in the hope of gaining all potentially relevant exposure data. The amount of data the sponsor initially provided in response to these requests was quite limited. Indeed, it is noteworthy that as late as October 8, 1998, Dr. Katz found the clinical experience that had been submitted inadequate to justify the issuance of a second approvable action (see his memorandum of that date).

On October 9, 1998, however, additional reports of clinical experience gained under exposures to plasma levels of lamotrigine as high or higher than those likely to obtain when the product is administered at the recommended daily dose of 500 mg were submitted. Based on this experience, which doubles that previously available, Dr. Katz is able to recommend (see his memorandum of 10/12/98) that the application may be deemed approvable for Lamictal's use as monotherapy, but only in patients already on monotherapy with another enzyme inducing AED.

Lamictal's Use as initial monotherapy

My approvable memorandum (2/23/98) to the file of NDA 20-241 describes the evidence and findings that allowed me to conclude that lamotrigine had been shown to be effective in use as monotherapy for the management of partial onset seizures in adults.

My memo went to some lengths to explain why I have concluded that evidence necessary to support the approval of an anti-epileptic drug [AED] for marketing as monotherapy differs in kind and scope from the evidence that a fair minded and disinterested expert would ordinarily find

² The issue is complicated by the fact that the expected plasma level of lamotrigine is not only a function of dose, but also a function of whether or not the product is administered concomitantly with a drug that can modify its systemic clearance. Thus, for a given dose of Lamictal, the attained plasma level will be much higher when it is given with valproate (an inhibitor) than with an EIAED like phenytoin or carbamazepine.

sufficient to justify the approval of an AED for use as one component of a multi-AED regimen (i.e., in adjunctive use).

Specifically, for an AED to be deemed effective as monotherapy, there must not only be proof in principle that the AED has a capacity to beneficially effect a clinically valid measure of seizure activity, but there must be a robust showing that the drug product can, when administered under the conditions of use recommended in its approved labeling, maintain seizure activity at or below a level deemed clinically acceptable over a sufficiently meaningful interval of time (e.g., not days, but weeks or longer).

Evidence that Lamictal performs in the manner just described was adduced in but a single controlled trial (Study 30/31) that enrolled epileptic patients who were already being managed with a single EIAED. The nature of the patient sample and the conditions of drug treatment in Study 30/31 are of particular importance because the sponsor has proposed that Lamictal be approved for use as monotherapy not only under the conditions evaluated in Study 30/31, but also as initial monotherapy in epileptic patients not previously under treatment with an AED of any kind.

While it is theoretically possible that Lamictal might be effective in use and safe for use as "initial" monotherapy under the conditions of use proposed by the sponsor (i.e., a maximum daily dose of 200 mg), there is no evidence available from an adequate and well controlled clinical investigation to support that conclusion.

Although the Division's approvable action letter did not address the distinction between initial monotherapy with Lamictal and monotherapy with Lamictal in patients being switched from monotherapy with an EIAED, the labeling attached to that letter did take note of the total lack of clinical experience available to support Lamictal's use under any condition as initial monotherapy. A note embedded within the draft labeling did ask the sponsor to develop and justify dosing recommendations for initial monotherapy, however.

I am mindful, therefore, that our request to develop such dosing instructions might have been taken by the sponsor as a sign that the Division was inclined to approve an initial use claim. Actually, that was

not my intent. In fact, although the letter clearly did not explicate my views on the matter, my determination that an effectiveness claim for monotherapy use must be supported by clinical trial data documenting that the AED is effective under the conditions of use recommended is fully articulated in my approvable action memo of 2/23/98 (see above).

Conclusions

The evidence and arguments put forth by the Division review team establish that Lamictal can be deemed safe for use and effective in use as monotherapy for the management of partial onset seizures in adults with epilepsy already on monotherapy with an enzyme inducing AED. I find the evidence inadequate to support a conclusion that Lamictal is either safe for use or effective in use as initial monotherapy.

Ordinarily, having reached such a "mixed" conclusion about an NDA's approvability, I would have preferred to enter into verbal negotiations with the firm and develop, during that review cycle, mutually acceptable product labeling. Given the closeness of the PDUFA promise date on the Tablet NDA and the press of competing regulatory work, however, the approach described is simply not feasible.

Accordingly, the Division's conclusions about these applications will be transmitted to the firm in the form of an approvable action letter. A version of Lamictal product labeling under which Lamictal can be deemed safe for use and effective in monotherapy use is attached.

Action:

Issuance of an approvable action letter with attached draft labeling

/s/

Paul Leber, M.D.
October 16, 1998

Memorandum

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

DATE: February 23, 1998

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

SUBJECT: NDA 20-241, S-003: Basis for approval as Monotherapy

TO: File NDA 20-241, Lamictal (lamotrigine) Tablets

This memorandum records for the administrative file the basis for my decision to declare Supplement-003 to Glaxo Wellcome's NDA for Lamictal Tablets approvable. This supplemental NDA expands Lamictal's claim to allow for the product's use as monotherapy in the management of partial onset seizures in adults.

Background information about Lamictal (lamotrigine)

Lamictal was first approved (1994) for marketing under labeling identifying it as an AED for adjunctive use in the management of partial onset seizures in adults. Evidence of effectiveness for this indication was established in three adequate and well controlled clinical investigations (US 05, US 06 and UK 35) of add-on design. In 1997, Lamictal was shown to be effective in the management of Lennox-Gastaut syndrome.

Generic issues affecting the assessment of monotherapy claims advanced for already marketed AEDs.

Most NCE AEDs are initially marketed under labeling that identifies them as "adjunctive treatments." This restricted claim is employed because the substantial evidence required for their approval derives entirely from clinical trials that evaluate their performance as a component of a multi-AED regimen.

In a typical add-on clinical trial of an investigational AED, subjects

(typically patients with partial onset epilepsy possessing attributes deemed to enhance their likelihood of responding to an active AED), after being observed for a number of weeks while on a stable AED regimen (one typically consisting of two, sometimes three, marketed AEDs) and found to qualify in regard to seizure type, severity and frequency, are randomized to receive one additional treatment (i.e., either placebo or the experimental AED), and followed forward in time (weeks to months).

A finding of a between treatment difference on some face valid measure of seizure frequency and/or severity over the period of follow-up favoring the group receiving the investigational drug (as compared to the group randomized to supplemental placebo) is taken as evidence of efficacy.

Once it is marketed, however, it is not uncommon for an AED carrying an adjunctive claim to be used as monotherapy. Given beliefs extant within the medical community, this usage is readily explained. Many practitioners, among their number prominent epileptologists, are simply confident (in their "clinical judgment") that an AED which is effective in adjunctive therapy will almost certainly be effective as monotherapy. A representative proponent of this view would argue that a drug shown to be effective as an adjunctive AED in a "difficult to treat" subset of patients suffering from a particular type of epilepsy is virtually certain to be effective when it is administered as monotherapy to less ill patients suffering from the same type of epileptic disorder. Many would undoubtedly add that the justification for making this extrapolation is strengthened when there is 1) evidence that the pharmacological effect of the investigational AED is expressed independently of other AEDs in in vivo and in vitro animal models of epilepsy, and 2) evidence from randomized clinical trials of an inability to find a difference in outcome among epileptic patients randomized to the investigational drug and a "known to be effective" dose of some approved standard AED.

Although the reasons for such sanguine expectations are understandable, they are hardly the stuff upon which a sound regulatory decision can be based. Although add-on studies with a drug can contribute to the body of evidence supporting a conclusion that a drug has intrinsic activity as an AED, add-on studies cannot possibly establish that a drug will have any practical use as monotherapy. An add-on study, for example, is hardly an

appropriate setting in which to reliably ascertain the actual conditions of use (dose, dosing regimen, etc.) under which the AED would be both safe for use and effective in use when used as monotherapy.

The fact that a drug suppresses some surrogate measure of seizure activity when applied by itself in some animal model of epilepsy in no way speaks to whether or not that preclinical model is an apt and valid model of human epilepsy, let alone whether that model reliably predicts how humans with epilepsy will respond to treatment with the drug. Accordingly, such preclinical findings carry little, if any, weight in regulatory decisions about drug efficacy.

Finally, as is well known, claims of effectiveness based on active control trials that fail to find a difference carry very little force in any clinical setting in which there is any degree of variability in the severity and course of the disease being treated. The reason is that a finding of no difference in such circumstances can be readily explained by factors other than the equivalent pharmacological activities of the treatments being compared.

Accordingly, the Division has concluded that before a marketed AED can be granted a monotherapy claim, there must be evidence from controlled clinical investigations¹ that directly evaluate the performance of the drug under conditions of use that are reasonably representative of those under which the drug will be recommended for use if the monotherapy claim is approved. The demand that clinical testing occur under "conditions [of testing]... reasonably representative.. .of those [that will be] ... recommended" is fundamental. Merely proving in a clinical study that an AED has some measurable effect on seizure frequency in an atypical setting (e.g., among patients recently withdrawn from AED treatment in anticipation of a neurosurgical procedure) will not suffice, and for compelling reasons. Grave harm may befall the AED responsive epileptic patient who, unknowingly, takes an AED labeled as effective in monotherapy that is actually ineffective in such use. Accordingly, it is a matter of safety for use, not merely efficacy in use, that motivates the

¹Whether there must be more than one such study is not so certain as it once may have appeared to be (see later discussion).

Division's demand that clinical investigations intended to demonstrate the efficacy of an AED's use in monotherapy provide more than proof in principle of that capacity. In sum, the Division holds that it is vital to the public health that AEDs marketed as effective in monotherapy be reliably shown to work as claimed.

The Division is mindful, however, that it is difficult to develop evidence of the kind and quality just described. Moreover, it must be acknowledged that a sponsor seeking to develop the necessary evidence to support a monotherapy claim is to some degree disadvantaged by the fact that the agency has yet to offer formal guidance regarding design and interpretation of clinical trials that can be relied upon. This is not a reflection, incidentally, of the agency's lack of interest in the area; the practical problem is that several of the epistemologically preferred clinical trial designs widely employed with success in other areas of therapeutics are, at least according to some experts in epileptology, very difficult, if not impossible, to carry out with epileptic patients. For example, controlled trials that directly compare placebo and an investigational AED are said to be difficult to conduct because of the widely held belief within the community of epileptologists that patients with active epilepsy, even those who are controlled with a single AED, cannot responsibly be randomized to placebo, even for a relatively short period of time.

Although some clinical investigators (and IRBs) find placebo controlled trials in newly diagnosed epileptics², or in patients who have had a single seizure and are at risk of being diagnosed as epileptic acceptable, studies of this design are not common. As noted earlier, some use has been made of very short term studies that evaluate the effects of an AED given as monotherapy as compared to placebo in patients recently withdrawn from treatment in preparation for neurosurgical procedures intended to correct their epilepsy. Unfortunately, such 'pre-surgical' studies are "off point," providing evidence that speaks primarily to the intrinsic activity of the AED as monotherapy rather than to the AED's practical value as a

² Presumably, the need for sustained active treatment in such patients is less urgent, and, therefore, there is a greater willingness to accept the risk of exposure to placebo.

treatment for the patients likely to receive the drug if it were approved for such use.

A design strategy that has found increasingly wide acceptance, a variant of which is presented in the present application, is one that evaluates an AED's effectiveness as monotherapy in the subpopulation of epileptic patients who, by virtue of their clinical history and prior response to treatment, are deemed appropriate candidates for conversion from combination AED (presumably patients doing well) to monotherapy with an AED or from one monotherapy treatment (presumably patients not doing as well as hoped) to another drug given as monotherapy. Trials of this design assign such patients to one or more regimens that, if followed as planned, bring them to monotherapy with either the investigational or active control treatment. Such studies can be persuasive from a regulatory perspective because 1) they test the drug under conditions that are reasonably representative of the conditions under which the drug will actually be recommended if approved, and 2) given an appropriate choice of control, can generate a between treatment difference (i.e., an outcome with an unambiguous interpretation).

An important drawback of the design just described is that it may result in an outcome that achieves nominal statistical significance and yet not be substantively meaningful. This can occur when there is extensive censoring over the course of the study. For example, if only a minority of patients randomized in a study employing such a design tolerate conversion to the assigned monotherapy, and the proportion randomized that do make it to monotherapy subsequently discontinue early on after conversion to their newly assigned monotherapy, the result of the study, even if it finds a statistically significant between group difference by test of protocol rule, may only arguably speak to the effectiveness of the drug under the intended condition of use. In his thoughtful memorandum of February 10, 1998, Dr. Katz discusses a number of other problems associated with the interpretation of monotherapy AED trials, illustrating many of his points with reference to considerations that affected the Division's interpretation of a single clinical trial that assessed valproate's efficacy for use as monotherapy.

In sum, judgments about monotherapy AED use claims are vexing,

especially so when they turn on the interpretation of clinical studies in which extensive censoring has occurred.

Yet another issue complicating the regulatory assessment of monotherapy trials is the extent of independent substantiation of clinical trial results required to justify a particular choice of regulatory action. In general, as a matter of scientific and epistemological principle, the value of following what is tantamount to the carpenter's rule of measuring twice and cutting once is self-evident. Not surprisingly, therefore, the Division's clinical review staff and its statistical consultants generally prefer to base their conclusions about the effectiveness of drug products on corroborated results derived from more than one adequate and well controlled clinical AED study.

At present, however, it is arguable whether current agency policy allows the Division to demand this level of evidence.

The "evidence document³" suggests it may not. In a discussion of examples of settings in which one trial might suffice, the document states (i.e., in section d. Studies in combination or as monotherapy):

"... known effectiveness of a drug as part of a combination (*i.e.*, its contribution to the effect of the combination is known) would allow a single study to support its use as monotherapy, or as part of a new combination, for the same use...."

Although I have personal reservations about the wisdom of applying this "dicta" to agency determinations that lead to the use of AEDs in monotherapy, my evaluation of the evidence advanced in this Lamictal application must take this dicta into account, especially because it now seems entirely consonant with the revisions to the standard of substantial evidence that appear in the FDA modernization Act of 1997.

³ Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, March 1997

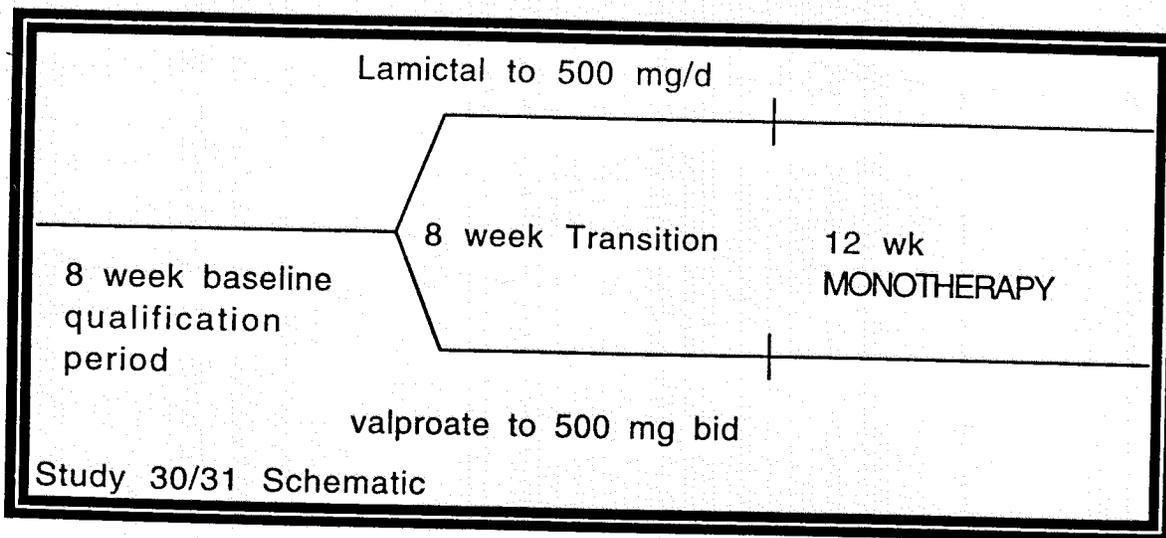
Findings of the Division's Review of the Application.

The Review team's views of the findings provided in the supplemental NDA are comprehensively summarized in Dr. Katz's February 10, 1998 memorandum to the NDA file. In Dr. Katz's judgment, the combined results of Studies US 30/31, when analyzed as a single source of clinical evidence, are sufficient to justify approval of a claim that Lamictal is effective as an AED as monotherapy. I am mindful that the primary clinical reviewer, Dr. Tresley, does not share this judgment.

Study 30/31

The study is a synthetic composite of the results of two identically designed, initially independent, clinical trials, that were begun in 1994. In 1996, because of slower than expected recruitment, the sponsor proposed to treat the studies as components of a single multi-clinic investigation, and analyze their results accordingly. Presumably, this decision was taken in the absence of knowledge of the interim outcome of either trial.

Design



The schematic immediately above outlines the 3 phases of the study.

Subjects on monotherapy with either carbamazepine or phenytoin who were presumably not doing as well as hoped, were assessed over an 8 week long baseline qualification period during which the clinical features of their seizure disorder were characterized and quantitated.

At the end of that period, subjects who met entry criteria were to be randomized to a regimen intended, over the course of an 8 week transition period, to bring them into treatment with either Lamictal or valproate. During the first 4 weeks of the transition period, the original monotherapy was to be maintained, while the experimental treatments were added. During the second 4 weeks of the transition phase, each patient's original drug (phenytoin or carbamazepine) was withdrawn.

Conduct

Over the baseline period, the median seizure frequency for 156 patients qualifying for randomization at 36 distinct sites was in the range of 8 to 9 seizures per 4 week interval. The conduct of the study, as expected, was marred by a high rate of censoring: 26/76 randomized to lamotrigine and 16/80 randomized to valproate withdrew during either the transition or monotherapy phases of the trial. It is noteworthy that the classification of subjects as withdrawals rather than "escapes" was in many cases arguable.

Outcome

The final amended protocol called for a comparison of treatments based on the numbers of treatment failures⁴ ("escapes") among all patients who did not "withdraw" from the study.

⁴ What constituted an escape was defined by protocol and include: a doubling of the monthly seizure count, a doubling of the highest 2 consecutive day seizure count, the emergence of a new more severe seizure type, or prolongation of generalized tonic-clonic seizures.

The sponsor's primary analysis is highly favorable to lamotrigine⁵, but may be deemed potentially misleading because it fails to account for the experiences of all subjects randomized. A number of alternative analyses have been conducted, each employing a slightly different means to impute (account for) outcomes of censored patients. Although a very conservative imputation scheme which counts lamotrigine withdrawals as "escapes" and valproate "withdrawals" as successful completions fails to attain statistical significance, more reasonable imputation schemes do not fundamentally undercut the study's positive statistical results. Why they do not is discussed at length by Dr. Katz in his 2/10/98 supervisory review.

Interpretation

Because only 28/76 lamotrigine randomized, as compared to 13/80 valproate randomized subjects completed the full 12 weeks of the study's monotherapy comparison phase), the interpretation of Study 30/31 rests to a greater extent than I would prefer on each analyst's personal judgment/opinion about the impact of this censoring. I must acknowledge that I am disconcerted by the fact that only 82 of the 156 patients randomized entered the 12 week monotherapy phase, especially since these patients were on monotherapy at the time they were recruited for the trial. On the other hand, the fact that of the subset of those randomized who did enter the monotherapy phase, 68 % of those on lamotrigine as compared to only 32% of those on low dose valproate, completed it may be reasonably and responsibly interpreted as showing that lamotrigine, in this study at least, was effective when administered as monotherapy in at least some patients. Thus, Study 30/31 can be counted as a source of positive evidence that speaks to the efficacy of lamotrigine when administered as monotherapy

⁵ The sponsor's analysis which compared the numbers of completers among the subset of those randomized who did not withdraw produced highly significant 'p' values (i.e., below $p = 0.001$). If an analysis is conducted that counts withdrawals on lamotrigine as failures and those on valproate as completers, the results are, not surprisingly, not significant.

Are the results of Study 30/31 sufficient to support a regulatory action

The pivotal question in my view is, therefore, not whether Study 30/31 is a source of positive support for Lamictal's efficacy when given as the sole anti-epileptic treatment (it is), but whether it, as a single positive study, is sufficient to justify approval of an AED monotherapy claim.

My hesitation here does not arise out of a concern about a lack of legal justification for taking an action based on such limited evidence. To the contrary, as noted previously, not just the recently promulgated evidence document, but the Act's recently revised (1997) section on the nature of substantial evidence make clear that an agency official can conclude there is substantial evidence of efficacy even if that evidence derives from the results of but a single adequate and well controlled clinical trial.

My hesitation stems from a contemplation of the risk associated with being wrong if Lamictal, the positive findings of Study 30/31 notwithstanding, proves to be ineffective when used as monotherapy. As noted previously, an approval in such circumstances has the potential to cause considerable harm including both irreversible injury and even death. It seems critical, therefore, when considering the approval of an AED as monotherapy on the basis of the uncorroborated results of a single controlled clinical trial to make sure that there are no other sources of clinical evidence extant that would undermine the basis for the approval.

One potential source of such information, not fully described in the sponsor's ISE, are 3 (perhaps 4, depending on the way one counts) randomized active controlled trials that were described in the NDA as failing to find a between treatment difference. These studies (UK 74, UK 106 and UK 48/49) involve comparisons of groups of patients randomized to lamotrigine and other "active" AED. Although these studies cannot contribute to the body of evidence supporting Lamictal's efficacy, they could, if they revealed a consistent trend favoring the AEDs employed as active controls over Lamictal, be taken as a reason not to approve the supplement.

Accordingly, I asked (2/20/98) Dr. Tresley to amend his clinical review to

include a more detailed examination of the results of the 3 studies.

Upon examination of Dr. Tresley's draft review (2/20/98), I am persuaded that the reported results of these 3 trials provide no basis for a concern that Lamictal might be less effective in monotherapy than the AEDs used as controls in these studies.

In conclusion, although the evidence is not as strong as I would prefer, I am persuaded it is sufficient under current regulatory policy to justify a conclusion that Lamictal is effective in use as monotherapy.

Safety for use and product labeling

Although there is no finding that signals a basis for a concern that Lamictal will be unsafe for use in monotherapy, a number of analyses remain that are necessary to provide a complete characterization of the risks associated with its use. Until this information is received, final product labeling cannot be agreed upon. Accordingly, the approvable action letter that I will issue not only makes a number of requests for additional information, but conditions final approval of the supplement upon the firm's willingness to adopt labeling that conforms in all substantive detail to the draft attached to the approvable action letter.

Action taken

Issuance of an approvable action letter.

/s/

Paul Leber, M.D.

2/23/98

cc: