

MEMORANDUM

COPY

DATE: February 10, 1998

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

TO: File, NDA 20-241

SUBJECT: Supervisory Review of NDA 20-241, for the use of Lamictal as Monotherapy in Adults with Partial Seizures

On 2/24/97, Glaxo Wellcome, Inc. submitted NDA 20-241 for the use of Lamictal (lamotrigine) as monotherapy for adults with partial seizures. Lamictal has been approved since 1994 for adjunctive treatment of partial seizures in adults.

The current submission contains reports of 5 controlled trials (1 US, 4 UK) in which Lamictal was evaluated as monotherapy. In addition, safety data in approximately 1900 patients enrolled in monotherapy studies with Lamictal has been submitted.

The 4 UK controlled trials were trials in which patients were randomized to treatment with either Lamictal or a standard AED (CBZ or PHT) and in which the goal was to demonstrate the equivalence of the applied treatments. The results of these studies are reported as having demonstrated no statistically significant between treatment differences. Because equivalence between treatments in such studies has no unambiguous interpretation, these studies do not contribute to a determination regarding the effectiveness of Lamictal as monotherapy, and will not be considered further in this memo. The sole study on which the decision about the effectiveness is based is the US study.

The clinical effectiveness data have been reviewed by Dr. Wang of Biometrics (reviews dated 12/2/97, 1/16/98, and 2/3/98) and Dr. Richard Tresley of the division (reviews dated 12/15/97 and 1/7/98). The safety data have been reviewed by Dr. Tresley. In addition, a Biopharmaceutics review has been completed by Dr. Vijay Tammara (9/15/97), and Dr.

Guzewska has reviewed CMC data (3/10/97).

In this memo, I will briefly review the effectiveness and safety data, and present my recommendation about the NDA.

EFFECTIVENESS

In April, 1994, the sponsor initiated two identical randomized controlled trials designed to demonstrate the effectiveness of Lamictal as monotherapy. However, due to slow enrollment, the sponsor proposed, in February, 1996, to combine the data from both studies and present the results as those of a single study. No data had been examined at that time, and the Division agreed with the proposal. The study was completed in August, 1996.

US 30/31

Patients receiving carbamazepine or phenytoin whose seizures were not adequately controlled were eligible for enrollment into the study.

Patients were entered into an 8 week baseline period, after which, if they had at least 4 simple partial, complex partial, and/or secondarily generalized seizures per 4 week period, they could be randomized to receive treatment with Lamictal or valproate in an 8 week Transition Phase.

During this 8 week Transition Phase, study medication was initiated during the first 4 weeks (Lamictal titrated to a maximum of 500 mg/day, valproate given as 500 mg BID), and concomitant CBZ or PHT was withdrawn over the second 4 weeks. Once monotherapy was achieved, a Monotherapy Phase was to last a maximum of 12 weeks.

A number of amendments were submitted during the course of the trial, several of which related to the analysis of the study. Ultimately, the primary outcome of the trial was to be the proportion of patients meeting escape criteria during weeks 13-28 (which encompassed the time starting at the withdrawal of concomitant CBZ or PHT and continuing through to the end of the Monotherapy Phase) compared to the proportion of patients

completing the Monotherapy Phase. The escape criteria were as follows, in which events on treatment are compared to baseline:

- 1) doubling of the average monthly seizure count
- 2) doubling of the highest consecutive 2 day seizure frequency
- 3) emergence of a new seizure type more severe than the current types
- 4) clinically significant prolongation of generalized tonic-clonic seizures

By protocol, patients who left the trial prior to the conclusion of the 12 week Monotherapy Phase **not** due to reaching one of the escape criteria were not to be included in the primary analysis. The primary analysis was to be a two tailed CMH test comparing the proportion of patients in each group who reached escape criteria during Weeks 13-28 (sample size was calculated on the basis of the proportion of patients completing the 12 week monotherapy phase).

The sponsor also proposed performing an "intent to treat" worst case analysis, in which all lamotrigine dropouts were considered to have reached escape criteria, and in which all valproate dropouts (other than those who met escape criteria) were considered completers.

Time to reaching escape criteria was a planned secondary outcome.

RESULTS

A total of 169 patients at 36 sites were randomized (76 lamotrigine, 80 valproate). The table on page 6 of Dr. Tresley's 12/15/97 review describes the baseline demographics of the 2 treatment groups. The mean number of seizures (per 4 weeks) at baseline was 27 for the lamotrigine group and 19 for the valproate group, but the medians were essentially the same (9 and 10, respectively).

The following table, adapted from Dr. Wang's Table 1S (page 4 of her 12/2/97 review), describes patient flow as reported by the sponsor:

	Lamictal (N=76)	Valproate (N=80)
Transition Phase		
Dropouts (total)	20	9
Adverse events	11	4
Consent Withdrawn	3	0
Death	0	1
Inadequate Response (Wk 9-12)	3	1
Inadequate Response (Wk 13-16)	2	1
Protocol Violation	1	2
Number Meeting Escape Criteria	15 (19.7%)	30 (37.5%)
Total Completing Transition Phase	41 (53.9%)	41 (51.3%)
Monotherapy Phase		
(entering)	N=41	N=41
Dropouts (total)	6	7
Adverse events	4	2
Consent Withdrawn	1	2
Inadequate Response	0	1
Protocol Violation	1	2
Number Meeting Escape Criteria	7 (9.2%)	21 (26.3%)
Total Completing Monotherapy Phase		
(percent of total entering trial)	28 (36.8%)	13 (16.3%)
(percent of total entering Monotx)	(68.3%)	(31.7%)
Total Meeting Escape Criteria	22/76 (28.9%)	51/80 (63.8%)

Analysis of the proportion of patients entering the trial and completing monotherapy (ITT) yielded p-values of between 0.003 and 0.007, depending upon whether the analysis was adjusted for center or geographic region.

The per protocol analyses (examining the proportion of completers not including dropouts in the denominator) yielded p-values of between 0.000 and 0.001 (lamotrigine 28/50-56%; valproate 13/64-20%).

A worst case analysis of completers (as described by Dr. Wang) in which

all lamotrigine dropouts were considered failures, and in which all valproate dropouts were considered completers yielded p-values between 0.75 and 0.89 (lamotrigine 28/76-37%; valproate 29/80-36%).

Because the trial was originally planned as 2 individual trials, the results of "Trials" 30 and 31 were evaluated individually.

As can be seen in Dr. Wang's 12/2/97 review (page 8, Table 1R), the following results of analyses of completers (unadjusted for center or region) were seen:

	Study 30 (N=66)			Study 31 (N=90)		
	LTG	VPA	P-value	LTG	VPA	P-value
Per Protocol	50%	25%	0.068	61%	17%	0.001
ITT	35%	20%	0.159	38%	13%	0.008
Worst case	35%	40%	0.706	38%	33%	0.660

Dr. Wang performed an analysis of the combined study in which she stratified by trial. This analysis gave similar findings on all 3 analyses to those done previously.

Supplementary Analyses

As described in Dr. Wang's Addendum (1/26/98), additional analyses were performed based on a re-classification of patients' status as having met escape criteria. Specifically, for purposes of these analyses, Dr. Tresley examined CRFs and copies of patients' seizure diaries for all patients who were classified by the sponsor as having withdrawn from the study because of an adverse event. He examined these patients specifically because 1) a number of these adverse events were listed as being related to inadequate seizure control, and 2) these were the only patients for whom CRFs and seizure diaries were submitted. Dr. Wang performed what she termed "reasonable" worst case analyses of these data in which any patient withdrawn from the VPA arm and LTG patients withdrawn for AEs

(after patients were re-classified) were not considered as having met escape criteria, and all remaining LTG patients were considered escapers.

In these analyses (Table 3R, page 3 of the addendum), no between treatment statistical significance was achieved, although the results numerically favored lamotrigine.

However, as noted, these analyses were based on 1) a re-classification of only those patients originally classified as AE withdrawals, and 2) worst case assumptions (assigning certain dropouts as escapers for lamotrigine and the same category of dropouts as non-escapers for valproate).

I subsequently asked Drs. Tresley and Wang to perform analyses that were based on an examination of the primary records (CRFs and patient diaries) for **all** patients classified as dropouts with the goal of re-classifying them, and to utilize the re-classified data in additional analyses that did not rely on worst case assumptions. That is, patients' "escape status" was determined, and all patients classified as having met escape criteria were considered as failures assigned to their actual treatment group. The subsequent analyses were done as intent-to-treat analyses; that is, the denominators used were the entire cohorts randomized to each treatment.

These re-analyses are presented in Dr. Wang's Update review, and attachments, dated 2/3/98.

This review presents analyses based on re-classifications of patients' escape status performed by Dr. Tresley. This re-classification was based on a blinded examination of the CRFs and seizure diaries for **all** patients originally classified as dropouts for any reason. In this re-classification, any patient found to 1) have met escape criteria, 2) have had inadequate documentation of seizure activity for any significant duration, and 3) have originally been classified by the sponsor as having withdrawn due to Inadequate Response, was classified as having met escape criteria.

Dr. Wang's Table 2, page 1 of the Update displays Dr. Tresley's re-classification of patients. In brief, 10 additional Lamictal and 4 additional valproate patients were re-classified as having met escape criteria. Dr. Wang's Table 3, page 2 displays the results of the analyses of

these data.

The relevant analysis yielded the following results:

LTG % escapes	VPA % escapes	P-value
32/76 (42%)	55/80 (69%)	0.0012

Dr. Wang has performed additional analyses, in which the number of escapes in each treatment group varies, depending upon whether or not other categories of dropouts are considered as being escapers (e.g., those withdrawn due to AEs). These analyses all yield p-values below 0.05, including an analysis that considers all dropouts as escapers.

It should be noted that these analyses include in the numerators all patients who escaped (again, varying with the assumptions) after randomization. Analogous analyses were performed including as escapers only those patients who escaped after Week 13, which corresponds to the period declared primary in the protocol. The results of these analyses are presented in the Update as Table 4, page 3. These analyses all yield p-values below 0.05.

As can be seen, Dr. Wang also performed worst case analyses for this re-classified data, in which all patients who withdrew (not classified as escapers) in the LTG group were called escapers, and all such patients in the VPA group were called non-escapers. These analyses all yielded p-values greater than 0.05.

Secondary Outcome

Time to Escape

As seen in Dr. Wang's 12/2/97 review (page 6, Table 3S) the Median Time to Escape was >168 days for lamotrigine and 57 days for valproate, with p-values between 0.001 and 0.005 for the per protocol analysis. However, for the ITT analysis (in which all dropouts are considered to have reached escape criteria), the median time to Escape was 80 days for Lamotrigine and 58 days for valproate. This approach yielded p-values of between

0.060 and 0.027, depending upon whether the analysis was adjusted for geographical region (NE, SE, NW, SW US) or center, respectively. The worst case analyses yielded p-values greater than 0.24.

SAFETY

Safety experience in a total of 1920 patients enrolled in 27 studies of Lamictal monotherapy is included in the NDA.

Of these 1920, full safety reports are available for 9 of the studies, comprising 868 patients. These 9 studies include Study 30/31, as well as the 4 controlled UK trials and 4 additional uncontrolled studies. For these 9 studies, all adverse events are reported in the Integrated Safety Summary.

Most of the remaining 1052 patients were in various studies that were ongoing at the time of the NDA submission. For these patients, information about deaths and AEs leading to discontinuation are provided. One study was a monotherapy study in patients with migraine headaches, and for this study a full study report is submitted.

In many of these studies there were periods during which patients were on AEDs in conjunction with Lamictal (prior to achieving monotherapy). It is impossible for me, at this time, to know exactly how many of the patients in these studies actually achieved monotherapy, or how many were receiving monotherapy at the time that an AE occurred. My summary in this memo is based on Dr. Tresley's review.

It is impossible to determine an accurate accounting of exposure by dose and duration for the entire database. For the 868 patients in the 9 studies for which full reports are available, 181 (21%) received treatment for at least 1 year. The mean daily dose in this cohort of 868 was 200 mg.

In the 4 UK controlled equivalence trials (in newly diagnosed patients), 78/447 (17%) received treatment for at least 1 year. The mean daily dose in this cohort was 134 mg.

DEATHS

In the entire cohort of 1920 patients, there were 17 deaths. Of these 17, 3 were considered to have been Sudden and Unexplained Deaths in Epilepsy (SUDEP).

WITHDRAWALS

In the cohort of 868 patients, a total of 353 (41%) withdrew, with 116 (13%) withdrawing for adverse events.

The most common AEs leading to discontinuation in this cohort were rash (6.1%), asthenia (1.5%), dizziness (1.4%), headache and diplopia (1.0%). Again, it is unclear how many of these occurred while the patients were actually on monotherapy with Lamictal (for example, in Study 30/31, most of the dropouts in the Lamictal treated patients that were attributed to AEs by the sponsor [11/15] occurred during the Transition phase, when patients were receiving a concomitant AED).

SERIOUS ADVERSE EVENTS

Most of the serious AEs reported fell in 2 categories; reaction aggravated, which is related to the underlying disease, and is discussed in the Effectiveness section, and rash. A total of 6/868 (0.7%) of patients were reported to have had a serious rash in the NDA submission.

The sponsor has made several submissions subsequent to the original submission, in response to requests by Dr. Tresley, to further clarify the data on rash. According to his review, in the total database of 1929 patients, there were 35 cases of rash (1.8%). There were a total of 8 patients with hospitalized rash, including cases of Stevens-Johnson and TENS (0.4%). Whether all cases of serious rash are accounted for in this analysis, whether all patients were on monotherapy at the time of onset of the rash, what the specific details of all the cases are (dose, duration, etc.), and what the ultimate status of the patients was, is unknown to me.

In Study 30/31, there was a 13% incidence of rash, and 1 case (1.3% incidence) of Stevens Johnson syndrome, and apparently 2 cases (2.6%) of

hospitalized rash.

DISCUSSION

EFFECTIVENESS

The sponsor has presented the results of a single randomized controlled trial designed to demonstrate the effectiveness of Lamictal as monotherapy in patients with partial seizures. This trial compared Lamictal 500 mg/day to low dose valproate.

The sponsor's analyses yield significant between treatment comparisons for the per protocol analyses (in which patients who withdrew for reasons other than meeting escape criteria were not considered), and for an intent-to-treat analysis, in which all patients randomized were considered in the denominator.

However, detailed inspection of the primary data by Dr. Tresley revealed that a number of patients classified as having withdrawn for adverse events, had, in fact, met the protocol established escape criteria. This motivated a search of the primary records for all patients who withdrew early from the trial, and resulted in a re-classification of several such patients as having met escape criteria. When the re-classified data were analyzed, analyses that assigned these patients to their randomized treatment group (so-called "reasonable" analyses by Dr. Wang) all yielded p-values below 0.05. When worst case assumptions were made, all analyses yielded p-values greater than 0.05. (It should be noted that, once re-assignment of all dropouts as either escapers or completers is made, analyses of percent of completers or escapers should yield identical results, since they are just complements of each other).

In deciding whether or not the NDA should be approved, 2 questions need to be addressed. The first is, is the study one in which a statistically significant between treatment difference has been shown; in other words, is the study positive?

If the answer to the first question is yes, we must decide whether or not

it supplies sufficiently robust evidence on which to conclude that the treatment is effective as monotherapy; that is, are the data sufficient to support approval.

Regarding the first question, the interpretation of the trial itself will depend upon how the dropouts are handled. In the Lamictal group, 16/76 (21%) patients were dropouts (did not meet escape criteria and did not complete monotherapy), compared to 12/80 (15%) valproate patients.

While this number is not an extraordinarily large number, as we have seen, the results of the trial will depend upon the assumptions one makes regarding what the rate of escape would have been in these patients.

In a recently approved application for the use of Depakene as monotherapy, an attempt to assess the effects of the large number of dropouts on the outcome was made by performing an analysis that evaluated the difference between treatments in median seizure frequency (the primary outcome in that trial) in the dropouts, compared to the between treatment difference in median seizure frequency in the completers. The estimated between treatment difference in median seizure frequency in the dropouts was essentially identical to that in the completers. This lent support to the conclusion that there was no material difference between the dropouts in either treatment group.

It is difficult to perform an analogous analysis of the dropouts in the Lamictal study, because information about the primary outcome does not exist for the dropouts. In the Depakene study, seizure frequency data were available for the dropouts. However, in the Lamictal study, by definition, patients classified as dropouts are those that did not reach escape criteria, nor did they complete; therefore, we cannot compute the proportion of dropouts who met escape criteria.

One could assign varying rates of escape to the dropouts in each group, based on various assumptions. For example, an analysis that attributes a rate of escape to both groups of dropouts equal to that of the control rate could be performed. Such an analysis would add 11 patients to the Lamictal escapers ($55/80 \times 16=11$) and 8 patients to the valproate escapers. This analysis could be considered conservative, and yields a p-value of less than 0.05. Dr. Wang has performed numerous other analyses

beyond those described in her reviews. They all essentially follow the pattern of the results reported; only in those analyses in which "worst case" type of assumptions are made (in which dropouts of various categories are all assigned as escapers in the Lamictal group and non-escapers in the valproate group) are the p-values greater than 0.05.

In my view, the study can be considered to be one in which a statistically significant between treatment difference has been demonstrated.

Although, as noted, a number of analyses (worst case) have yielded p-values for the between treatment contrasts that are greater than 0.05, essentially all other analyses are strongly positive, including a number that are quite conservative. While the positive analyses are based on assumptions about the rates of escape among the patients that dropped out early, the analyses that yield large p-values are based on assumptions that, in my view, are considerably more unreasonable.

Having answered the first question affirmatively, we must now turn to the second question; is this study sufficient to support approval of the proposed claim?

In answering this question, it is important to note that the data on which a claim for monotherapy is granted should be clearly convincing, because the risks of approving an ineffective treatment as monotherapy are great (patients have no alternate protection against seizures, as distinct from the case in adjunctive therapy). In other words, a trial (or trials) of a treatment for monotherapy study should provide evidence not only of statistical significance, but of clinical significance.

Given these considerations, a closer look at the results of such a study is warranted. For example, it is useful to examine the actual number of patients who complete a specific duration of treatment with monotherapy, as well as the number of patients who actually achieve monotherapy. In this regard, it is useful to examine the data on which a recent approval for monotherapy was based.

As noted above, Depakene was recently approved for monotherapy of complex partial seizures on the basis of one trial. This trial compared high dose valproate to low dose valproate. Although the trial used a

different design than the Lamictal trial, both trials included an initial period of approximately equal length (8 weeks) in which patients were switched to monotherapy from therapy with 1 standard AED.

In the Depakene study, approximately 80-90% of patients in the trial achieved monotherapy (received at least 1 dose of monotherapy). In addition, approximately 50% of all randomized patients and 57% of the high dose group who entered the monotherapy phase completed that phase, which was 16 weeks long.

In contrast, about 53% of all randomized patients entered the monotherapy phase in the Lamictal study. Approximately 37% of all patients randomized to Lamictal and 68% of Lamictal patients who entered the monotherapy phase completed this phase.

The question of clinical significance is a difficult one. Ordinarily, approval of an NDA is based solely on a reliably documented finding of statistical significance between drug and control in trials (or, in certain cases, in one trial) that are (is) adequately designed. The decision to approve an application on the basis of trials that yield statistical significance is predicated on the (usually unstated) assumption that the trial is designed so that statistical significance **implies** clinical significance. That is, the designs of the trials usually are such that the Agency can conclude that the drug is "worth" being available on the market because the statistical significance seen implies some worthwhile benefit (however minimal in however small a subset of patients with the particular condition) compared to the risks.

Any other approach to determining the clinical significance of a between treatment difference in the outcomes chosen in drug trials will rely upon an arbitrary choice of effect size that will be difficult to justify, and will almost always reflect a personal judgement with which others may very well disagree.

In epilepsy studies, in particular, outcomes have been utilized in the past that have been criticized as being arbitrary. For example, the use of the outcome Proportion of Patients Seizure Free for some duration, perhaps 3 months. Such an outcome would classify a patient with a 90% reduction in

seizures as a failure, an outcome that most people would consider highly beneficial. Similarly, the use of an outcome like Percent of Responders, where a Responder is a patient with a 50% decrease in seizures, is subject to the same criticism. For these reasons, most studies of AEDs simply examine mean (or median) seizure frequency, with a statistically significant difference between treatment, however small, accepted as clinically meaningful.

In addition to the arbitrary nature of the choice of a particular size of a treatment effect as a way of defining success, it is generally agreed that the "size" of a treatment effect determined in a clinical trial cannot be considered to reflect the "true" estimate of the treatment effect in any reasonable way. The size of the difference in the outcome chosen between the treatment and control as well as the absolute "size" of the effect in the treatment group represent one realization of the treatment effect that is highly dependent upon the conditions of the study, including, and especially, the specific sample of patients enrolled. This "treatment effect size" cannot then, for many reasons, be considered to represent the "real" treatment effect. In fact, in reality, the adequate and well controlled trials which ordinarily provide the substantial evidence of effectiveness required for approval really only demonstrate activity of the drug that is presumed to be beneficial (so-called proof of principle), but they are incapable of providing the "true" treatment effect in the wider population for which the drug will be indicated. Indeed, it may make no sense to speak of a single such treatment effect.

In an attempt to insure that the benefit of treatment has some clinical meaning, one may consider the potential benefit in relation to the benefit to be received by other available treatments. Of course, in the overwhelming majority of the cases, a direct comparison to other available treatments is unavailable and deemed unnecessary. (It should be noted that the current trial does not address this issue. The dose of valproate chosen as the control was deliberately low to permit a difference to be detected between it and Lamictal, and so make the trial interpretable. If the dose of valproate had been greater, it is likely that the difference seen between the 2 treatments would have been considerably smaller, at least.) Certainly, the Act does not speak to the question of comparative efficacy, and ordinarily, no such comparison is

required by the Agency. However, the Agency can require, when the risks of the treatment seem unusually great, that a sponsor demonstrate superiority of the drug to other standard treatments. In such a case, the risks may be seen to be acceptable if there is evidence that some patients will receive a benefit from it that cannot be provided by other available treatments. In other cases, of course, the risks are considered so great that no evidence of effectiveness, either in degree or otherwise, can justify approval.

It is in this context that we must consider the case of monotherapy for the treatment of seizures. The sine qua non for approving such a claim is the demonstration of a reliable statistically significant between treatment difference. In this case, only one study is available. As I have noted above, I believe that this single trial has demonstrated such a difference. Against the background of evidence of Lamictal's effectiveness as adjunctive therapy, I believe that the data from a single study could be considered to be sufficient to grant a claim for monotherapy. Indeed, the recently approved FDA Modernization Act, and the Agency's draft document, **Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products**, both suggest that this would be a setting in which one adequate and well controlled trial would suffice to grant such an additional claim. Further, as noted, we have recently based such a claim on the results of an single study.

However, as I have also said, before granting such a claim, one would like some reassurance that, in some absolute sense, a reasonable proportion of patients can be adequately controlled by Lamictal when given as monotherapy. Although, as we have seen, any choice for exactly what the definition should be for "reasonable" will inevitably be arbitrary and arguable, the risks of inadequate treatment with monotherapy strike me as being so great as to at least consider the notion that the usually acceptable standard of proof of activity may be inadequate in this case.

Unfortunately, there is no immediately obvious way to address this concern. One could argue that, if a claim for monotherapy is to be granted, evidence should be submitted that demonstrates that the treatment proposed is not worse than available treatments as monotherapy. The

rationale underlying such an approach would be that practitioners should be confident that, when they are prescribing the new treatment, they are not doing so in the face of a better alternative.

There are several potential problems with this approach. First, it can be seen as close to encroaching on the practice of medicine, over which the Agency has no authority. Beyond that, however, such an approach presupposes that currently used treatments for monotherapy can be considered, a priori, appropriate choices against which to measure any proposed treatment.

While, of course, currently available AEDs are used as monotherapy, few are approved explicitly for such use, and I am unaware of scientifically valid evidence that demonstrates their utility as such. Further, even if they had been demonstrated to have been effective as monotherapy in controlled trials, my earlier comments suggest that this fact could not be used to support a conclusion that they were effective to any specific degree. In this case, perhaps a trial that directly compared the proposed treatment to an appropriate control as well as to a "standard" drug (e.g., perhaps the treatment patients had been on prior to their conversion to monotherapy) would be useful. However, the appropriate design of a trial to demonstrate that a proposed treatment and a "standard" treatment are equivalent, or at least that the proposed treatment is not significantly worse than the standard, has not been determined, but might itself raise a number of questions.

The outcome of Study 30/31 (approximately 40% completion rate) is best interpreted, then, against the backdrop of the difficulties inherent in interpreting the meaning of the various estimates of the treatment effect size adduced in a clinical trial (including the absolute rate of response in the drug group), as well as the uncertainties about the design of a trial that would have the capacity to "definitively" detect a "clinically meaningful" effect of a monotherapy treatment. In my view, these considerations make it difficult, if not impossible, to attach a meaning (*vis a vis* clinical utility) to the estimate of the treatment effect seen. The drug is "active" as monotherapy; with labeling that accurately describes the results of the trial, prescribers should have the opportunity to use it as such.

In sum, therefore, I can conclude the following: 1) in the context of an approved indication for adjunctive therapy, a single adequate and well controlled trial may serve as the basis for approval of a claim for monotherapy for an AED, 2) Study US 30/31 is an adequate and well controlled trial that demonstrates a statistically significant between treatment difference in favor of Lamictal, and 3) Study 30/31 is sufficient to support a claim for the use of Lamictal as monotherapy.

SAFETY

The sponsor has submitted what, on face, is certainly sufficient experience from monotherapy trials to support approval, especially since we expect that the safety profile will be of less concern here than compared when Lamictal is given as adjunctive therapy.

However, the sponsor's presentation of the safety data leaves a number of unanswered questions. For example, it is unclear if the ADRs (including serious ADRs) presented occurred during monotherapy or during treatment with concomitant AEDs. Further, the sponsor has not provided information on SUEs with appropriate patient-time exposure data.

Importantly, there is no one comprehensive report addressing the issue of the occurrence of serious rash. For example, it is still not clear to me how many cases of hospitalized rash there were in Study 30/31. The sponsor should be requested to submit a detailed such report, including information about whether the events occurred during true monotherapy, and whether the events occurred in controlled trials.

CONCLUSIONS

The sponsor has submitted sufficient information to judge the application approvable with appropriate labeling. The additional safety information discussed above will be necessary before a final decision regarding approval can be made.

RECOMMENDATION

The attached Approvable letter, with attached draft labeling, should be sent to the sponsor.

APPEARS THIS WAY
ON ORIGINAL

[^]
/S/

Russell Katz, M.D.

Cc:
NDA 20-241
HFD-120
HFD-120/Katz/Leber/Tresley/Ware
HFD-710/Sahlroot/Wang

APPEARS THIS WAY
ON ORIGINAL