**MEMORANDUM**

DATE: December 14, 1998

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

TO: File, NDA 20-241/SE1-003 and NDA 20-764 SE1-001

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

On 10/16/98, the Division issued an Approvable letter to GlaxoWellcome for the NDAs for Lamictal Tablets and Chewable Dispersible Tablets for the use of as monotherapy.

The sponsor responded with a resubmission dated 10/20/98. In this submission, they proposed changes in the Indications and Dosage and Administration Sections. These changes relate to the descriptions of the sub-populations of patients in whom the drug is not indicated as monotherapy (patients not receiving treatment from which they are to withdrawn and converted to monotherapy, patients receiving treatment with non-enzyme inducing drugs, and patients receiving treatment with 2 or more concomitant AEDs).

The sponsor's proposal includes several changes, including stating that safety and effectiveness have not been established for these groups (as opposed to our proposal which stated that it is not indicated for use in these groups) in both the Indications and Dosage and Administration Sections (in our D and A Section, we followed our statement with a statement that it is not indicated for these patients because safety and effectiveness had not been systematically evaluated). In addition, the sponsor has bolded their proposed statement in the D and A Section, and has slightly modified the language that describes the 3 sub-groups in both sections.

I find the sponsor's revisions appropriate and, therefore, recommend that the attached Approval letter be sent.

/S/

Russell Katz, M.D.

Cc:
NDA 20-241, 20-764
HFD-120
HFD-120/Katz/Ware

**MEMORANDUM**

COPY

DATE: October 12,1998

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

TO: File, NDA 20-241/S-003

SUBJECT: Additional Safety Data

As noted in my memo of 10/8/98, the sponsor had submitted well-documented safety experience in a cohort of 148 patients who achieved doses of Lamictal of 500 mg/day or greater as monotherapy. Of these 148, only 78 had received the dose for 6 months. I had concluded that this was insufficient to support a conclusion that this dose was acceptably safe, and I therefore recommended that the application not be Approved at this time.

As also noted in my earlier review, the sponsor apparently had additional data from patients receiving adjunctive therapy that was potentially relevant to the question.

Specifically, the sponsor referred to a previously submitted report of 2 studies (Studies 17 and 26) in which plasma level data were available for patients receiving Lamictal as adjunctive therapy. According to the sponsor, of the 633 patients enrolled into these 2 studies, 224 patients had plasma levels of greater than 8 mcg/ml, and 169 had levels greater than 9 mcg/ml. Because the mean plasma level from Study 30/31 was 8.7 mcg/ml (corresponding to a daily monotherapy dose of 500 mg), it was determined that experience gained in adjunctive therapy at plasma levels essentially equal to those expected to be achieved at the effective monotherapy dose would be relevant to the assessment of the safety of that dose. However, the sponsor had not presented duration data for this adjunctive cohort.

In a submission dated 10/9/98, the sponsor has now presented this duration data.

The sponsor now documents that 164 patients achieved plasma levels of at least 8 mcg/ml (as opposed to their original claim of 224). In Study 17, 79 patients had a mean concentration of about 12.8 mcg/ml for a mean duration of 34 months. In Study 26, 85 patients had a mean lamotrigine concentration of about 12.0 mcg/ml for a mean duration of about 5 months. More importantly, a total of 102 of these patients received doses that were associated with a final plasma level (recall that the plasma level was determined only once, at the end of the trial) of at least 8 mcg/ml for at least 6 months. While the plasma level was determined only once in this study, I find it reasonable to conclude that the exposure was likely relatively constant during the period in which a patient received a constant dose.

The total number of patients who were exposed to relevant plasma levels for 6 months now totals 180, more than a doubling of the previous number. This puts the maximum

excludable risk at 6 months at about 1.7%, a marked improvement over the 4% associated with the 78 patients at 6 months previously described. Although we do not have detailed titration data for these patients, it is reasonable to conclude that the rates of titration used in these studies to achieve these levels were within those to be described in labeling. Further, although we also do not have information about whether or not these are trough levels (I am told by Dr.Tamarra of the OCPB that the levels in Study 30/31 were trough levels), the majority of these patients had plasma levels substantially greater than 9 mcg/ml (the sponsor estimates that Cmax for a 70 kg person receiving Lamictal 250 mg BID as monotherapy is expected to be about 10 mcg/ml). For this reason, I find these data relevant.

Given this most recent submission, I can now conclude that there is sufficient data to recommend that the application can be Approved for the use of Lamictal as monotherapy in the setting of the conversion of a patient from an EIAED. I continue to conclude that the use of Lamictal as initial monotherapy should not be permitted in labeling.

/S/

APPEARS THIS WAY
ON ORIGINAL

Russell Katz, M.D.

Cc:
NDA 20-241/S-003
HFD-120
HFD-120/Katz/Leber/Ware/Tresley

APPEARS THIS WAY
ON ORIGINAL

COPY

**MEMORANDUM**

DATE: October 8, 1998

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

TO: File, NDA 20-241/S-003

SUBJECT: Supervisory Review of Sponsor's Response to Approvable Letter For the Use of Lamictal as Monotherapy

On February 24, 1998, the Division issued an Approvable letter to Glaxo Wellcome, Inc., for their supplementary NDA for the use of lamotrigine as monotherapy. In that letter, the sponsor was asked to address several safety concerns, as well as respond to requests included in draft labeling. Specifically, the following safety concerns were raised:

1) The sponsor was asked to calculate the incidence of Sudden Unexplained Deaths (SUDEP) for the monotherapy experience.

2) The sponsor was asked to include a comprehensive report of serious rash for the monotherapy experience.

3) The sponsor was asked to present all adverse event data for the monotherapy and transition therapy (that portion of the total experience in which patients were still receiving treatment with concomitant AEDs before being switched to monotherapy) experience separately.

In addition, a safety update was requested.

The sponsor responded to the Approvable letter with a submission dated 4/15/98. Because of various deficiencies in this submission, we requested additional information from the sponsor; they responded to these requests with submissions dated 6/10/98, 7/2/98, 9/9/98, 10/1/98, and 10/6/98. The first 2 of these submissions have been reviewed by Dr. Richard Tresley (reviews dated 6/25/98 and 7/21/98, respectively); the 9/9/98 submission consisted of draft final labeling. The latter 2 submissions contained data believed by the sponsor to be relevant to the question of the adequacy of the database and the sponsor's final proposed labeling.

The critical concern underlying most of our requests related to the issue of the adequacy of the safety experience at the effective dose. In their 4/15/98 response to the Approvable letter (and in their draft labeling accompanying the original NDA), the sponsor suggested that a daily dose of 100-200 mg/day could be effective as monotherapy, with the possibility of doses of up to 500 mg/day being necessary. In the 4/15/98 submission, they

included a rationale to support this dosing recommendation, despite the fact that in the one controlled trial on which a determination of effectiveness was based, the mean modal and mean doses in patients who achieved monotherapy were 493 and 491 mg/day, respectively (in this study, patients on either carbamazepine or phenytoin were switched to lamotrigine monotherapy at a target dose of 500 mg/day).

The sponsor's arguments are as follows:

1) *In vitro* and animal studies suggest that control of seizures is achieved at levels of exposure in humans associated with doses of 100-200 mg/day.

2) Plasma levels in humans who are receiving lamotrigine monotherapy are essentially the same as those in humans who are receiving concomitant VPA and Enzyme Inducing AEDs; the originally approved daily dose for these latter patients was 100-150 mg/day.

3) Active control trials (which demonstrated no difference between control and lamotrigine) used daily doses of up to 200 mg/day.

In summary, the sponsor argues that animal and *in vitro* studies demonstrate effectiveness at plasma levels that are achieved by humans who are receiving concomitant VPA and EIs (and in whom the drug has been shown to be effective). This establishes the "effectiveness" of these plasma levels in humans. Further, active control trials also "establish" this dose as effective.

These arguments do not establish these lower doses as being effective as monotherapy.

First, although we agree that the plasma levels achieved with monotherapy are likely to be similar to those achieved with concomitant VPA and EIs, no direct clinical evidence establishes the levels previously shown to be effective as adjunctive therapy as being effective in the **monotherapy** setting. Further, we can draw no useful conclusion about the effectiveness of lamotrigine as monotherapy from the active controlled trials (regardless of the dose studied), and the animal studies are also not helpful in this regard.

In addition, the sponsor suggests that the standard of care for dosing patients (at least as initial monotherapy, a setting not studied in adequate controlled trials) with an AED relies on titration to an initial dose that could reasonably be expected to be effective. As stated above, however, there is no direct evidence that these low doses can reasonably be expected to be effective. This is especially important in the setting of initial monotherapy. In this setting, patients are not expected to have frequent seizures initially after the decision is made to treat (given that the natural history of seizures in most patients with newly diagnosed epilepsy is that a next seizure is unlikely in the immediate period after diagnosis). In such a setting, a prescriber could easily conclude, erroneously, that a low dose of an AED is effective, and therefore stop any further titration when, in fact, the

absence of seizures during this period is simply a reflection of the natural history. For this reason, it is quite possible that titration to the known effective dose may not occur in this setting, leaving these patients potentially dangerously underdosed.

For these reasons, I must conclude that the recommended dose should be that which was shown to be effective in the one adequate controlled trial presented, and that is 500 mg/day.

Given this conclusion, we have asked the sponsor on numerous occasions to present the total experience at this dose (500 mg/day) or greater in the true monotherapy setting; that is, in patients who were receiving no concomitant AEDs.

On 7/2/98, the sponsor submitted this information.

A total of 148 separate individuals have received at least one day of lamotrigine at a dose of 500 mg/day or greater as true monotherapy. Of these, 103 patients received this dose for at least 12 weeks, 75 received this dose for at least 6 months, and 55 received this dose for at least one year. A total of 42 have received this dose for at least 2 years, and 26 have received this dose for at least 3 years.

In a submission dated 10/1/98, the sponsor refers to a previously submitted report of data from 2 open studies (Studies 17 and 26) in which plasma levels of lamotrigine were obtained. In this cohort, plasma concentrations were obtained in 633 patients receiving Lamictal as adjunctive therapy; some patients received Lamictal at daily doses of greater than 700 mg. The sponsor notes that 224 patients (I counted 223) had plasma levels of at least 8 mcg/ml; 169 had plasma levels of at least 9 mcg/ml. The average plasma level in Study 30/31 was 8.7 mcg/ml. In the open data, the plasma levels were drawn once, and the sponsor has not yet told us whether or not these levels are trough levels, whether the levels in Study 30/31 were trough levels, and, critically, what the duration of exposure to these levels was in the open data (the mean duration of total treatment with Lamictal was about 5 years in Study 17 and 0.9 years in Study 26). If the sponsor can provide information supporting the conclusion that many patients (beyond the 148 for whom we have reliable dose/duration data) achieved appropriate plasma levels for appropriate durations, this would certainly contribute to the relevant database; however, at this time, we do not have answers to the questions that would help us assess the appropriateness of this open experience.

In addition, the sponsor has several monotherapy studies on-going in various psychiatric conditions (see below). Although the maximum dose in some of these studies may be up to 500 mg/day, the sponsor has no data from these studies as of this date.

It is critical to point out that, should the application be approved, a dose of 500 mg/day as monotherapy would yield levels of exposure to lamotrigine greater than those expected to be achieved with current dosing in any population. Currently, the maximum recommended dose is 500 mg/day, in patients also receiving EIAEDs (without VPA). For patients

receiving EIAEDs with VPA (the same patients in whom the sponsor suggested the plasma levels should be the same for any given dose as in those patients receiving lamotrigine monotherapy), the maximum daily dose is 400 mg/day (the maximum recommended daily dose in patients receiving only VPA is 200 mg). In these populations, the plasma levels of lamotrigine achieved would be expected to be less than those achieved by patients receiving lamotrigine 500 mg/day as monotherapy.

**SUDEP**

As Dr. Tresley reports, the incidence of SUDEP in the monotherapy cohort ranges from 0.0030-0.0034/patient-year, an incidence that is perfectly consistent with the rate (0.0035/patient-year) described in current labeling.

**RASH**

As Dr. Tresley notes, the sponsor has performed an analysis of serious rash (as previously defined) in the 868 patients in completed monotherapy studies. Further, the sponsor has analyzed the incidence of rash (both serious and non-serious) by study type (initial monotherapy vs studies in which patients were switched to monotherapy) and dosing ("correct" vs "incorrect" dosing).

There were no serious rashes in 453 patients in Initial Monotherapy studies (active controlled trials). There was an incidence of serious rash of 1% (3/302) in studies in which patients were switched from an EIAED to lamotrigine monotherapy, and of 0% (0/112) in patients switched from VPA to monotherapy. The overall rates of any rash in these 3 cohorts were 14%, 8%, and 22%, respectively.

When analyzed by dosing ("correct" vs "incorrect"), the incidence of serious rash is, of course, 0% for the Initial Monotherapy and VPA switched patients in each of these categories. The incidence of serious rash in the EIAED switched patients was approximately equal in the 2 dosing groups. The overall rate of any rash was 18% (93/517) and 6% (21/351) in the "incorrect" and "correct" dosing groups, respectively (patients in all 3 types of studies had higher incidences of any rash in the "incorrect" vs the "correct" dosing groups). In each of these dosing groups, the incidence of all rash was greatest in the VPA switched patients (29% [21/72] in the "incorrect", 10% [4/40] in the "correct" group).

There were no serious rashes in the 148 patients who received at least one day of at least 500 mg/day of monotherapy.

**OTHER ADVERSE EVENTS**

As noted by Dr. Tresley, several serious psychiatric events were reported that had not been previously reported (i.e., mania, suicide attempts). This is likely due to the additional experience in patients with depression and bipolar disorder, in which conditions the

sponsor is performing several clinical trials (at the time of the 7/2/98 submission, there were 9 completed and one on-going trials in these conditions). In these trials, the maximum dose of lamotrigine monotherapy was, by protocol, 500 mg/day.

In the 148 patients receiving at least one day of at least 500 mg/day monotherapy, no serious adverse events other than what had previously been seen were noted.

**COMMENTS**

The sponsor proposes that Lamictal be approved for use as monotherapy. In draft labeling, they propose dosing recommendations for 2 separate patient populations: those for whom Lamictal will be their initial treatment, and those who will be switched from other AEDs to Lamictal monotherapy.

The sponsor's draft labeling recommends a maximum daily dose of 500 mgs, but suggests that lower doses may also be effective.

We have seen above that the sponsor actually claims that doses of 200 mg/day of Lamictal would be expected to be effective as monotherapy. As I have described, the arguments presented do not support this contention, and, therefore, if the NDA were to be approved, this section of labeling would have to recommend 500 mg/day as the dose known to be effective.

For this reason, the sponsor must submit sufficient experience at this dose (or greater) for us to adequately assess the safety of the product given as monotherapy.

As noted above, they have submitted the experience at these doses in 148 patients, 75 of whom have received these doses for at least 6 months, and 55 of whom have received these doses for at least 1 year. Also, as noted earlier, a daily dose of 500 mg/day of Lamictal is expected to result in plasma levels of lamotrigine greater than those for which we have adequate safety data from previous experience. Specifically, current labeling recommends a daily dose of 100-200 mg/day for those patients also receiving VPA alone, up to 400 mg/day for those receiving VPA plus EIAED, and 300-500 mg/day for those patients receiving EIAEDs without VPA. In these cases, the level of exposure is less than what will be achieved at 500 mg/day given as monotherapy. For example, healthy volunteers receiving no other medications at steady state had a t1/2 of lamotringine of 5 hours and a clearance of 0.58 ml/min/kg, patients taking VPA plus EIAEDs had similar values and healthy volunteers receiving just VPA had a t1/2 of 70 hours and a clearance of 0.18. Patients taking only EIAEDs had a t1/2 of almost 13 hours, with a clearance of about 1.2 ml/min/kg.

These kinetic parameters all suggest that patients receiving VPA and EIAEDs will have plasma levels approximately equal to those achieved by patients receiving Lamictal monotherapy. As noted, the maximum recommended dose for these patients is 400 mg/day. The recommended maximum daily dose for patients receiving VPA alone is 200

mg; it is the firm's contention that the plasma levels of lamotrigine achieved when a given dose of Lamictal is added to VPA are about twice those achieved when that same dose of Lamictal is given alone (a view with which we generally agree). The recommended maximum dose for patients receiving only EIAEDs is 500 mg/day, but in these patients the plasma level expected to be achieved would be about ½ to 1/3 of that achieved in patients given the same dose as monotherapy.

Therefore, the experience gained in other settings cannot be relied upon to support the safety of the effective monotherapy dose (500 mg/day). Given this, we must ask, then, if the total experience at this dose is sufficient to permit a conclusion that Lamictal can be given safely at this dose.

If we look at the total experience at 6 months (75 patients), we can be 95% confident that, if Lamictal causes a serious adverse event within 6 months (recall none were seen), the true incidence of such an event would be no more than 4%. If we examine the total experience at 2 months (125 patients) the true incidence of any unseen adverse event within this period of time after initiation of treatment is likely to be no more than about 2%. Is this cause for concern?

Beyond any generic concerns raised by this relative paucity of safety experience, with Lamictal we are, of course, concerned about the rate of serious rash associated with its use. Current labeling states that there are 3 factors that are at least potential risk factors for the occurrence of serious rash: 1) concomitant use of VPA, 2) high starting dose, and 3) rate of titration. The latter 2 factors are, at least theoretically, controllable with appropriate labeling. That is, labeling could recommend as low a starting dose and as slow a titration as is thought to protect against the occurrence of a serious rash (although in my view this has important consequences for the kinds of patients for whom Lamictal could be recommended-see below).

However, the first "risk factor", co-administration of VPA, is thought to be related to VPA's inhibition of Lamictal clearance; in other words, this is actually believed to be directly related to the increased plasma levels of Lamictal that result from its co-administration with VPA. Simply stated, then, there is concern that the rate of serious rash is related to elevated plasma levels of Lamictal.

For example, in the original NDA database in adults, the rate of serious rash in patients receiving VPA alone or VPA and non-EIAEDs as concomitant therapy (1.5%) was about [redacted] higher in patients taking either VPA and EIAEDs or no VPA (0.7 and 0.2%, respectively). This relationship to concomitant VPA use was not as striking in children, where the analogous rates of serious rash were 1.7%, 0%, and 1.0%, respectively. The overall rate of serious rash in children was about 1%, compared to about 0.3% in adults.

In addition, the sponsor estimates, based on the PEM database in the UK, that the rate of serious rash in children receiving concomitant VPA was about 8 times greater than in children not receiving VPA (0.8% vs 0.1%, respectively; see my review of 11/17/97,

pages 16-17). Further, the data generally suggest that the overall rate of any rash is greater in patients taking VPA compared to patients not taking VPA.

It should be pointed out here that most, although not all, serious rashes have occurred within 2 months of initiating treatment with Lamictal. In children, at least one case was reported about 200 days after the initiation of treatment (I have been unable to easily obtain the distribution in time of the cases in adults, although there were few such cases).

The data do not definitively establish that the rate of serious rash in adults is greater when patients are receiving concomitant VPA compared to when they are not, and, even if they were, there is no definitive evidence that such an increase is related to the resulting increased levels of Lamictal. However, the data do raise these specters, and, in the absence of evidence suggesting otherwise, it is prudent to consider these factors as at least reasonable hypotheses.

The decision to approve the NDA, then, in my view revolves around the estimate of the maximum incidence of any serious adverse event associated with Lamictal use. As we have seen, the maximum incidence of any such event (in particular, serious rash), can be expected to be 4% at 6 months after initiation of treatment, and 2% at 2 months after initiation of treatment.

As we have also seen, the levels of exposure to lamotrigine at the proposed dose will be greater than those achieved at the currently recommended maximum doses. Further, as we have also seen, there is at least some reason to believe that the risk of serious rash is potentially related to increased doses of Lamictal. Given these concerns, we must ask if the possible rate of serious rash (or other serious event; e.g., multi-organ failure) of 4% within 6 months of initiating treatment would be acceptable; that is, if the rate were known to actually be 4%, would the NDA be approvable (with appropriate labeling). If it would, then the application could reasonably be approved now, in the absence of affirmative evidence that this was, in fact, the true rate. If, on the other hand, a rate of serious rash of 4% is considered too high to support approval (that is, that no labeling could be written to mitigate this risk), then the NDA should not be approved at this time. (We could, of course, consider the maximum risk to be 2%, based on considerations described above; namely that most of the serious rashes have occurred within 2 months of initiating treatment. However, serious rashes have occurred later, some much later, and I see no reason to make the most sanguine assumptions about the period of potential risk).

My view is that a risk of serious rash of 4% would simply be unacceptable. I believe that labeling will not be able to mitigate the risk posed to the public health by this incidence of a potentially life threatening event for several reasons. While ultimately, of course, the judgment that a particular risk is too great to permit approval is a personal one, my view is based, in part, on the following.

First, there is no good evidence that these serious rashes are predictable or are associated with premonitory signs that make them preventable in any given patient (indeed, of course, the ultimate risk of serious rash may be much greater than currently described in labeling, given that some percentage of patients in whom the drug was discontinued because of any rash might have gone on to develop a serious rash had treatment not been withdrawn). The absence of any maneuver known to reliably decrease the risk of these serious events makes the absolute rate more of a concern.

Second, under the best of circumstances (see below), the time it would take to achieve the effective dose as monotherapy would be at least 11-13 weeks (based on a regimen in which Lamictal is added to an EIAED over 8 weeks while the dose of the AED is kept stable, followed by the gradual withdrawal of the AED over time; switching patients from regimens including VPA-patients who were not studied in the trial-would take longer). Although a similar regimen was employed in the controlled trial (actually the titration was performed more rapidly), in my view it is likely that practitioners will consider this too long, and will be tempted to decrease the time to reach the effective dose as monotherapy, thereby potentially increasing the risk of rash. While, of course, labeling would warn against this, experience suggests that there is still a real potential for practitioners to disregard such labeling.

Finally, of course, other AEDs are available as monotherapy; there is no evidence that Lamictal offers any advantage to these.

For these reasons, I do not believe that the application should be approved until sufficient experience can be accrued to establish the safety profile as being acceptable. Of course, the current ICH guidelines describe the amount of safety data ordinarily required prior to approval of a new chemical entity: 300 patients exposed to a relevant dose for at least 6 months, and 100 for a year. While one could make the case that these numbers should not be required for an amended indication for an already approved drug (the case here), I still believe that the amount of chronic safety data is inadequate to support approval, given our concerns about the safety of Lamictal at higher doses (plasma levels) than those recommended in current labeling. Although in this memo I have concentrated on the potential of Lamictal to cause serious rash, the additional data I recommend be collected prior to approval will also, of course, help further define the risk of other unknown serious adverse events, if any, associated with these higher levels.

Beyond considerations related to the relative lack of experience at a maintenance (chronic) dose of 500 mg/day, additional difficulties arise from the fact that there is a paucity of relevant data supporting safe titration recommendations. This is because, while current labeling provides a template for titrating (under various different scenarios) up to a daily dose equivalent to 400 mg/day of Lamictal, there is little well documented evidence about reaching a dose of 500 mg/day. While the sponsor acknowledges that there is a relative paucity of empirical evidence to establish the safety of this increment from 400 to 500

mg/day, they maintain that the rate of titration they propose to recommend to achieve this final dose is well within rates of titration already included in current labeling.

In a submission dated 10/6/98, the sponsor makes the above claim, and also submits revised dosing recommendations. In this most recent submission, they provide dosing recommendations (and justifications) for 1) withdrawal from EIAEDs, and 2) initial monotherapy. They have additionally revised labeling to note that they can give no recommendations about conversion from VPA and there are no recomendations for conversion from more than one AED.

In thinking about appropriate dosing recommendations for conversion to monotherapy, there are 3 potentially relevant scenarios: 1) conversion from EIAEDs, 2) conversion from VPA alone, and 3) conversion from a regimen of EIAEDs and VPA.

In the first scenario, the sponsor proposes recommending that Lamictal be titrated to a dose of 500 mg (while keeping the dose of the EIAED stable) using currently approved labeling for the addition of Lamictal to an EIAED; according to this scheme, the effective dose will be achieved in, at a minimum, 8 weeks. At that point, the concomitant AED is to be withdrawn over time. Here, the question of how rapidly this is to be achieved must be raised.

The sponsor proposes to achieve the complete withdrawal of the AED over 4 weeks (as was done in the controlled trial). While recommending a withdrawal used successfully in the trial appears reasonable, it should be noted that the number of patients in whom this regimen was employed was quite small (about 40). For this reason, the safety of the regimen has not been adequately documented and established. Therefore, an alternate view would be to use an appropriate regimen that is already approved.

In this scenario, a dose of 500 mg Lamictal plus an EIAED is equivalent to a dose of Lamictal of about 250 mg/day ***as monotherapy***. Now, we must determine how quickly current labeling suggests that we can go from this dose to 500 mg as monotherapy.

If we go to the algorithm in current labeling describing the addition of Lamictal to a regimen of EIAEDs plus VPA (recall that this is the situation most closely resembling that of monotherapy), this increment of 250 mg/day should take about 5 weeks. If we rely on the assumption that a daily dose of Lamictal as monotherapy is equivalent to about ½ that dose given with VPA alone, and follow current dosing guidelines, this increment of 250 mg/day would be achieved in about an additional 3 weeks. This is calculated, using the current recommendations, as follows:

At the end of Week 4, patients are at a total daily dose of 25 mg. Using the most rapid titration (50 mg/day every week), we reach a daily dose of Lamictal of 125 mg at the end of Week 6 (which is about equivalent to the dose of 250 mg of Lamictal as monotherapy that the proposed labeling recommends be achieved by week 8). In any event, by the end of Week 9, the daily dose of Lamictal is 275 mg, which is about equivalent to a total daily

dose of Lamictal of 500 mg as monotherapy. Therefore, we have reached the final dose, using this method of calculation, 3 weeks after we reached a dose equivalent to 250 mg/day as monotherapy.

This calculation highlights a recurrent difficulty in determing safe titration rates from currently approved dosing regimens. Because current dosing recommendations (as far as titration rates) are the same for the addition of Lamictal to regimens of EIAEDs plus VPA as for the addition of Lamictal to a regimen of VPA alone, the time calculated to reach a given dose of Lamictal as monotherapy will depend upon whether we consider a given dose of Lamictal monotherapy as being equivalent to half that dose when given in combination with VPA alone, or twice that dose when given with an EIAED alone.

Regardless of which assumption we make about the equivalence of a Lamictal monotherapy dose to the same dose given in conjunction with a given concomitant AED, if we are willing to make such an assumption, we can choose a time to reach the effective monotherapy dose that will result in a rate of titration consistent with that described in current labeling. **However, no approved dosing regimen accounts for exposures greater than those to be achieved by a daily dose of Lamictal of 500 mg.** That is, we can write labeling that would permit a monotherapy dose of 500 mg/day to be achieved with a ***rate of titration*** consistent with current labeling, but we cannot rely upon the fact that these rates are approved to support the safety ***of this rate*** **to achieve doses above 400 mg/day**.

I recognize that the concerns I have raised relate to changes that can be viewed as relatively minimal, in terms of the increment in absolute dose (related to both chronic use and the safety of any proposed rate to reach this dose). Nonetheless, given our great concerns over time about the potential risks associated with elevated levels of this drug in particular, I believe it is reasonable to ask the sponsor to accrue additional experience at these higher doses.

As noted above, the sponsor has decided to not include specific dosing recommendations for the situation in which patients receiving VPA alone are converted to Lamictal monotherapy. Such a situation would give rise to particularly complicated dosing recommendations. Briefly, current labeling recommends that when Lamictal is added to VPA alone, the maximum dose should be 200 mg/day. Doses of Lamictal greater than this added to a regimen of VPA alone will give rise to very high plasma levels of lamotrigine very quickly, and therefore greater doses could not be added without also lowering the dose of the concomitant VPA. Because of the complex kinetics of this interaction, it is not at all clear how rapidly either should be done (increasing the Lamictal and decreasing the VPA) to maintain an effective rate of increase in Lamictal exposure consistent with current labeling.

The sponsor has also chosen to offer no guidelines for converting patients on several drugs to Lamictal monotherapy. This specifically includes regimens of an EIAED plus VPA. I believe such guidelines could be given (based on similar assumptions and

calculations as described above), but the same fundamental flaw exists; no such regimen can rely on the approved **rates** to support the safety of that rate when doses above 400 mg/day as monotherapy are achieved.

As stated earlier, the sponsor has proposed that Lamictal be recommended as initial monotherapy, as well as monotherapy for patients currently receiving AEDs. I would argue that it should not be approved as initial monotherapy.

First, of course, it was not studied in this setting, although its utility in these patients could possibly be reasonably inferred from its demonstrated effectiveness in patients switched to monotherapy from other AEDs.

My main objection to its use as initial monotherapy, however, arises from the fact that achieving the effective dose in this setting will take an inordinately long period of time.

Again, given that monotherapy is expected to result in plasma levels akin to those achieved in patients receiving VPA plus EIAEDs, dosing recommendations for initial monotherapy should mirror currently approved recommendations for these patients (remember that there is no empirical clinical data to otherwise guide dosing recommendations in this setting).

In this setting, then, the effective dose of 500 mg/day will be achieved in approximately 13 weeks, at a minimum (given a dose of 25 mg every day at the end of week 4, and increasing the dose 50 mg/day at weekly intervals). The maximum time to achieve this dose, given current labeling, is 52 weeks.

If, on the other hand, we employ the "VPA alone" assumption (that is, a given dose of Lamictal given as monotherapy is equivalent to ½ that dose when given to VPA alone), then the effective dose of Lamictal could be reached in about 9 weeks according to current labeling recommendations (this is the sponsor's proposal). Again, it should be noted that, while such a recommendation would result in a rate of titration consistent with current labeling, it does not guarantee the safety of this rate when achieving doses greater than those recommended in current labeling.

In my view, a titration period of 9-13 weeks (at a minimum) in a patient in whom the decision to treat with an AED has been made, and who is unprotected during this period of time, is potentially dangerously long. Further, I believe that if such a dosing recommendation were permitted in labeling, practitioners would also find this interval unacceptably long, and would tend to shorten it, probably by employing a combination of an increased starting dose and/or a more rapid titration. In the absence of evidence that such maneuvers are not unacceptably dangerous, it is my view that such recommendations should not be permitted in labeling, and therefore that initial monotherapy is unacceptable.

## RECOMMENDATIONS

I recommend that the application not be approved at this time, because the sponsor has not presented sufficient long term safety experience at the effective dose. Further, given our concerns about the relationship between the rate of titration and the risk of serious rash, the data presented is insufficient to establish that the rate of titration proposed by the sponsor (although consistent with currently approved rates of titration) is safe above doses of 400 mg/day of Lamictal. The sponsor should be sent a second Approvable letter, in which the Division should explain the reasons we have concluded that 500 mg/day is the effective dose, and that there is currently insufficient experience at that dose to justify approval at this time.

If a decision is made to issue an Approval letter at this time, I further recommend that the labeling not include dosing recommendations for initial monotherapy, for the reasons described above.



/S/

Russell Katz, M.D.

cc:
NDA 20-241/S-003
HFD-120
HFD-120/Katz/Leber/Ware/Tresley

COPY

**MEMORANDUM**

**DATE:** February 23, 1998

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

**TO:** File, NDA 20-241/S-003

**SUBJECT:** Biopharmaceutics Comments for Labeling

Dr. Tammara, in his biopharmaceutics review of 9/15/97, recommends that several comments related to the kinetics/interactions of Lamictal be included in labeling. I have discussed these proposed changes with him. We agree that most of the relevant information embodied in his proposals is already in current labeling, and, for this reason, most of his recommendations need not be included in the draft labeling that will accompany the Approvable letter.

The one proposal that should be included is the request to add a description of the kinetics of Lamictal given as monotherapy in patients in the Table in the PK section.



/S/

Russell Katz, M.D.

Cc:
NDA 20-241
HFD-120
HFD-120/Katz/Ware