MEMORANDUM

DATE: August 19, 1998

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

TO: File, NDA 20-764

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

On 12/3/97, the division issued an Approvable letter to Glaxo Wellcome for NDA 20-764 (as well as to NDA 20-241/S-002) for the use of Lamictal CD Chewable Dispersible Tablets as adjunctive treatment for the generalized seizures of Lennox Gastaut syndrome in adults and pediatric patients. In that letter, the division requested a safety update, as well as revisions in the currently approved labeling. In addition, we requested the adoption of specific dissolution specifications, and transmitted the Nomenclature Committee's recommendation that the suffix "CD" not be included in the name of this product.

On 2/23/98, the sponsor submitted its response, consisting of a safety update and revised labeling. The sponsor's proposed labeling has been discussed in several telephone conversations with the review team and the sponsor, and we (the medical officer Dr. Feeney and myself) have agreed with the sponsor on final language. Dr. Feeney has reviewed the safety update (review dated 5/22/98), and in this memo, I will briefly comment on the safety update and highlight the important changes from the draft labeling that accompanied the Approvable letter to which we have agreed.

SAFETY UPDATE

The cut-off date for the safety update was 10/31/97, and includes a total of 1091 patients under the age of 16 years (an increase of 692 patients above the 399 total patients included in the original NDA and first safety update). These new patients were enrolled in prospective cohorts followed by the sponsor.

The update also includes information on deaths from 2 additional sources of data: 1) Non-US Compassionate plea patients, and 2) Post-marketing reports.

There were no additional deaths in the new cohort of 692 prospectively followed patients.

There were 4 additional deaths in the Non-US Compassionate Plea patients (3 SUDs, 1 multi-organ failure in a patient with status epilepticus). There were a total of 12 deaths from this database reported in the NDA.

There were (by Dr. Feeney's count) 12 new deaths in the Post-marketing experience. There were 13 deaths in the Post-Marketing experience reported in the original NDA. Of the new 12, 1 patient died form complications of TEN; as Dr. Feeney notes, of the total of 25 post-marketing pediatric deaths, 3 were directly or indirectly related to SJS/TEN.

Of the total 1091 pediatric patients, approximately 10% had serious adverse events, and approximately 9% of the 1091discontinued treatment for adverse events. A total of about 5% of pediatric patients discontinued due to rash of any kind.

Regarding rash, the sponsor had previously (submissions dated 7/22 and 10/21/97) submitted comprehensive reviews of these events in 1071 pediatric patients. The data in these submissions were previously reviewed and served as support for the extensive labeling changes previously made for the Lamictal label; the data in the additional 20 pediatric patients included in this update do not effect those sections of labeling previously written.

LABELING

We and the sponsor have agreed to the following changes.

1) **Box Warning**-In the Box Warning (as well as in several other sections in which language from the Box Warning is reproduced), in the sentence directing the prescriber to discontinue treatment at the onset of a rash, the sponsor has **removed** the clause "unless the patient's epilepsy is so severe that the risk of serious rash is considered acceptable". The sentence now reads that Lamictal should ordinarily be discontinued unless the rash is clearly not drug related.

Because the remaining sentence retains the word "ordinarily" when describing discontinuing treatment, this is acceptable (i.e., it allows for the possibility that treatment may be continued in the face of a rash under certain-unnamed-circumstances; this is consistent with the intention of the clause the sponsor removed).

2) **Warnings**-In the Adult Population portion of the Serious Rash sub-section, the sponsor has correctly changed the language in the first sentence. This sentence describes the incidence (0.3%) of patients who experienced a serious rash "associated" with hospitalization and discontinuation of treatment. We had originally written that this incidence applied to patients whose rash was the obvious cause of the hospitalization. In this same section, they have added a statement that rare deaths that are rash "related" have occurred in the post-marketing experience.

3) **Warnings**-The sponsor has drafted additional language in the Multiorgan Failure sub-section at our request that is acceptable.

4) **Adverse Reactions**-In the initial sub-section (Adverse Events in Adults), the sponsor quotes an incidence of discontinuations due to adverse events (11%) associated with a denominator of 4932. This differs from the 3923 described later in this section. The latter number represents the number of patients for whom the sponsor has complete ADR information; the former is the number for whom the sponsor has complete discontinuation data.

5) **Dosage and Administration**-This section has been changed substantially.

Our draft labeling presented dosing information first by concomitant AED usage (with or without VPA, essentially) then, within these categories, by age. The sponsor has restructured the section to present the data by age categories (2-12, over 12), and then within these age categories, by concomitant AEDs (carbamazepine, phenytoin, phenobarbital, and primidone, or VPA).

Further, they have included statements, at our request, regarding the lack of information about Lamictal's use with AEDs other than those for which data is available (the ones listed above). The labeling now states for these other drugs, a slow titration (akin to that proposed for use with VPA) might be useful, and that the maintenance dose for Lamictal in conjunction with these other drugs may be somewhere between that described for use with VPA and that for use without VPA, but with an enzyme-inducer (one of the 4 listed above).

In addition, for the pediatric population, the sponsor has proposed that the initial dose and titration scheme be lower than those actually used in the study, based on a population pharmacokinetic analysis that demonstrated that children have higher plasma levels than adults during titration for a given dose. Given the concerns about the incidence of rash being related to initial dose and/or rapidity of titration, the sponsor has proposed these lower regimens (the maintenance doses are unchanged). Concomitant with these recommendations, the sponsor has added language alerting the prescriber to the fact that these were not the doses used in the trials, and consequently it may take weeks to months to achieve therapeutic doses.

Based on a recent phone call with Dr. Kathy Peterson, of the Canadian Health Protection Branch, we have become aware that, depending upon a given child's weight, the initial dose, as well as doses to be achieved during titration, are impossible to deliver given the current tablet sizes (lowest strength is 5 mg chewable tablet, not scored). Because of this, we phoned the sponsor on 8/13/98 and asked them to re-propose language for the Warnings and Dosage and Administration sections that highlights this fact and that instructs the prescriber how to act in those cases when the calculated doses are not achievable. They have proposed the following changes in labeling that alert the prescriber to this fact, and that permit safe dosing.

1) At the end of the Warnings Section, language has been added that instructs the prescriber that children are under 17 kg should not receive Lamictal because of the inability to initiate treatment according to the recommended dosing regimens due to the unavailability of a tablet smaller than 5 mg.

2) In the Dosage and Administration Section, prescribers are now instructed to round down various calculated doses (initial dose, dosing increments) in order to 1) actually achieve the various doses, given the lack of availability of doses less than 5 mg, and 2) maintain a titration rate that is consistent with a rate felt to be safe.

6) A number of changes have been made in the **Patient Information** section.

The sponsor has agreed to the proposed dissolution specifications, and has removed the suffix CD from the name as we had requested.

Further, the sponsor has made a commitment to 1) emphasize the specific dosing recommendations, including the restriction on treatment of low weight children, in all promotional material about the use of Lamictal in patients with Lennox-Gastaut syndrome, and 2) develop additional dosage forms (e.g., lower tablet strength) to facilitate dosing in children.

RECOMMENDATIONS

The attached Approval letter should be issued.

/S/

Russell Katz, M.D.

cc:
NDA 20-764
NDA 20-241/S-002
HFD-120
HFD-120/Katz/Leber/Feeney/Ware

MEMORANDUM

DATE: November 17, 1997

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

TO: File, 20-764

SUBJECT: Supervisory Review of NDA 20-764, for the use of Lamictal Chewable Tablets in patients with Lennox-Gastaut Syndrome

Glaxo Wellcome submitted NDA 20-764 for the use of Lamictal Chewable Tablets in patients with Lennox-Gastaut syndrome and in adults with secondarily generalized seizures on 9/17/96. In support of these 2 claims, the sponsor submitted the results of 3 controlled trials; one in the former indication, and 2 for the latter. In May, 1997, however, the division was informed by the sponsor that a recent internal audit they performed of the 2 studies in support of the generalized seizure claim revealed significant deficiencies they felt precluded their use to support that claim, and they withdrew that portion of the NDA. As a result, the sponsor now proposes only the single study, UK 123 in patients with Lennox Gastaut syndrome, as support for a single additional claim.

The effectiveness data have been reviewed by Dr. Tresley of the division (review dated 5/13/97) and Dr. Wang, of Biometrics (review dated 6/27/97). The safety data have been reviewed by Dr. Feeney of the division (reviews dated 10/10/96, 3/7/97, and 11/13/97) and Dr. Burkhart, Team leader of the division's safety group. In addition, the application was reviewed by Dr. Tammara of the Division of Pharmacokinetic Evaluation I (review dated 5/17/97), by Dr. Guzewska, chemist (reviews dated 1/6/97 and 9/15/97), and by Ms. Sager, of the Office of Environmental Assessment (review dated 1/14/97).

In this memo, I will briefly review the effectiveness and safety data, and offer my recommendations for action on the NDA.

EFFECTIVENESS

STUDY 123

This was a placebo controlled, double blind, parallel group study performed in 43 centers in Europe, Australia, and the U.S.

Patients age 3-25 with more than one predominant seizure type, including drop attacks (atonic, tonic, major myoclonic) and/or tonic-clonic seizures for at least 1 year, with observable seizures occurring at least on average every other day, and abnormal EEG and intellectual impairment and on a stable regimen of AEDs were entered into a 4 week placebo baseline period. Subsequent to this period, patients entered into a 16 week treatment period, the first 6 weeks of which were a dose escalation phase. Patients were randomized to receive 1 of 4 dosing regimens, determined by weight and concomitant valproate. After the 6 week dose escalation phase, patients were to be on a stable dose of study medication, after which the dose could be increased during the last 8 weeks if seizures were not well controlled.

The doses of concomitant AEDs were to be held constant, save for a decrease in dose due to adverse events.

The primary outcome measure (by protocol amendment submitted 4/26/95, while the trial was on-going) was to be the percent change from baseline in the frequency of major seizures (drop attacks and tonic-clonic seizures). Secondary measures included the percent reduction in the frequency of specific seizure types, the percent reduction in the frequency of atypical absence seizures, Quality of Life measurements, and Global assessments.

The primary method of analysis was to be the extended Mantel-Haenszel chi square test stratified by center, utilizing a specific within-center ranking methodology. A sample size of 160 was calculated to detect a 32% reduction from baseline in seizure frequency at 80% power.

RESULTS

A total of 179 patients entered the study, but only 169 were ultimately randomized (79 lamotrigine, 90 placebo).

The following table displays patient flow.

	Lamictal	Placebo
Patients enrolled	79	100
Patients randomized	79	90
Patients completing	72 (91%)	76 (84%)
Patients in ITT analysis	78	89

In this study, 1 center enrolled 9 patients; the next greatest number of patients in a center was 7 (5 centers). At 10 centers, patients were randomized to only 1 of the 2 treatments.

The median percent change from baseline in the frequency of major seizures for weeks 1-16 for the Lamictal and placebo groups was 32% and 9%, respectively. The sponsor did not present the results of the protocol specified primary analysis. Dr. Wang has performed this analysis, which yielded a p-value of 0.069.

However, the protocol specified analysis relied on a very specific within center ranking methodology which is very sensitive (loses power) to the situation in which many centers have small numbers of patients, (as was the case here) and, especially, to a situation in which centers have only one treatment represented (as was the case here in 10 centers).

For this reason, a number of other analyses of this variable were performed, which attempt, in varying ways, to adequately deal with this problem. Some of the analyses ignore center, others consider regions as "center" equivalents (based on aggregating data from all the centers in a given country). Dr. Wang's Table 5R, page 14 of her review, summarizes the results of these 5 additional analyses, all of which yield p-values from 0.001-0.04. (Interestingly, the 2 analyses performed in which center is included in the model yield p-values that are significantly greater than

analyses which do not). In addition, multiple analyses of the individual seizure types (drop attacks and tonic-clonic seizures) all yield p-values below 0.05.

Finally, a cumulative distribution plot of the ratio of on-treatment seizures to baseline seizures (page 15 of Dr. Wang's review) reveals a consistent difference in favor of drug. However, it should be noted that the parameter graphed (ratio of seizures) is not the primary variable in the study (change from baseline in seizure frequency).

SAFETY

Complete prospective safety experience in a total of 399 children is presented in the NDA. Of this cohort, 244 have been exposed for at least 6 months, and 188 had been exposed for at least 1 year.

In addition to the cohort of 399 patients for whom essentially complete follow-up was available, there were additional sources of data (compassionate use-type studies, post-marketing reports) in the US and Europe, for which accurate patient accounting is not available.

DEATHS

In the cohort of 399 pediatric patients, there have been 3 deaths, 2 of which have been termed Sudden Unexplained Death in Epilepsy (SUDEP); one in a 13 year old girl who had been receiving Lamictal for 138 weeks, and one in a 3 year old boy who had been receiving treatment for 200 days.

A third child, an 8 year old boy, had been on Lamictal for 830 days when he was found dead after a seizure. An autopsy revealed aspirated gastric contents.

There were an additional 15 patients who died in the wider database. In addition, there are 9 post-marketing reports of death.

Of the 15 deaths in the larger database, presumably 6 were related to the underlying epilepsy, 2 died of pneumonia, 1 was found dead in bed, 1

drowned, 1 died after cardiac surgery, and 1 died after 2 severe bouts of status epilepticus, and for 2 deaths, no details are known.

The remaining case was a 7 year old girl who died 22 days after initiation of Lamictal. Twelve days after starting treatment (she was also receiving valproate) she developed fever, rash, and hair loss, with elevated white count and liver function tests. Lamictal was continued, and she developed a diffuse rash, mouth ulcers, and conjunctivitis, which were attributed to Coxsackie virus. She went on to have vomiting, dehydration, and worsening seizures. The Lamictal was discontinued, but she progressed to bilateral pleural effusions and respiratory distress. She subsequently died and autopsy revealed hanta virus and chlamydia.

Of the 9 post-marketing deaths, information was available for 8. The one case of interest was an 8 year old boy admitted to the hospital with SJS and acute renal failure. Although he recovered, he died unexpectedly 2 weeks after his recovery; an autopsy revealed a granuloma in the myocardium.

In the safety update (1/17/97) 4 additional deaths are reported.

One was a 12 year old girl with the onset of TEN 27 days after initiation of treatment. Although the rash apparently responded to steroids, she died of adult respiratory distress syndrome. Another case of importance was a 7 year old boy who developed liver failure post status epilepticus. He subsequently developed multiple organ failure and died. The treating physician concluded that this series of events might have been related to treatment with Lamictal.

DISCONTINUATIONS

In the database of 399 patients, 46 (11.5%) discontinued due to an adverse event. The most common AE resulting in discontinuation of treatment was rash (24/399 or 6%). Other AEs resulting in discontinuation of 1% or more patients were worsening seizures (2%) and ataxia (1%).

ADVERSE EVENTS

Other adverse events seen in the database of 399 patients are tabulated on pages 12-16 of Dr. Feeney's review of 3/7/97 (sponsor's Table 5.29), and the adverse events in the controlled trial (UK123) are tabulated in Dr. Feeney's review as pages 17-21 (sponsor's tables 5.32 and 5.38).

Multi-Organ Failure

Current labeling describes a rare syndrome of multi-organ failure with varying degrees of liver failure resulting in death in 5/7000 patients exposed to Lamictal in pre-marketing development. Labeling states that these cases are often seen in association with other serious medical events (e.g., status, sepsis), making the cause of the multi-organ failure impossible to reliably identify.

In the pediatric experience, there were a total of 49 cases of "multi-organ failure"; 38 associated with a rash and 11 cases not associated with a rash. The sponsor makes a distinction between the 2 types of cases, the former presumably more consistent with a drug hypersensitivity reaction which responds to withdrawal of treatment, and the latter more often related to status epilepticus and more frequently fatal.

Of the 38 rash associated cases, 26 were post-marketing cases, and none of the remaining 12 were in the cohort of 399. Of the 38 cases, there were 2 deaths. One of these deaths was the previously described case in which hanta virus was detected; the other was the previously described case of SJS with apparent recovery and subsequent cardiac arrest, with myocardial granuloma.

It should be noted that while a few of the cases involved serious medical events, a number of cases involved relatively mild involvement of several systems that included, for example, fever, somewhat elevated LFTs, "leukocytosis", etc. Although these cases have all been termed "multi-organ failure", this does not, in my view, accurately describe the nature of a number of the events seen.

Of the non-rash associated cases, 8 were post-marketing reports, and the remaining 3 were not in the cohort of 399. Of these 11 cases, 9 died. According to Dr. Feeney's review, all 9 suffered status epilepticus as initiating events.

Disseminated Intravascular Coagulation (DIC)

In the sponsor's tabulation of the rash associated multi-organ failure cases, there are 5 cases with DIC. Dr. Feeney suggests, in his 3/7/97 review, that in all of these cases, other associated serious medical events (as opposed to treatment with Lamictal) are more likely to be the cause of the DIC.

As Dr. Feeney notes, however, the sponsor also references a publication which describes 2 children (who were also receiving concomitant valproate) who presented with rashes within 2 weeks of starting treatment with Lamictal and who developed DIC and multi-organ failure. In these cases, there was apparently no antecedent medical event that could explain the occurrence of DIC.

RASH

In January, 1996, Dooley et al published a report in Neurology that described the experience in what was presumably the entire cohort of children treated with Lamictal in Nova Scotia between 1990 and 1994. In this cohort, 5/68 children developed a rash. One patient had either Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN), and a total of 3/68 were hospitalized with rash. Because of these cases and other cases being reported to the Agency's post-marketing reporting system, the Division of Epidemiology was consulted. Their review (8/21/96), by Harold Davis, M.D., identified 21 cases of hospitalized rash in children 14 years of age or younger. Given various assumptions about (under) reporting, reporting rates of hospitalized rash were between 2-20/1000 patients in the pediatric population, compared to rates of 0.7-5.6/1000 adult patients.

Because the data suggested that the rate of serious, potentially life threatening rash in children was not only greater than in adults but

significantly greater than the background rate in children, as well as greater than the rate in children on other AEDs, the sponsor issued a Dear Dr. letter in March, 1997. Further, the labeling was changed to incorporate a Black Box Warning describing the risk in children (recall that at that time, as is currently the case, the drug had not been approved for any pediatric indication).

While data on only 399 patients was included in the original NDA, subsequent to the submission several additional studies were completed. Based on this additional experience, the sponsor has presented data on a total of 1071[1] children under the age of 16 years for purposes of evaluating the capacity of Lamictal to cause rash, including serious rash. These patients have been followed prospectively, though with slightly different methodology (e.g., several hundred patients have been assessed by telephone follow-up, which the sponsor has convinced us was capable of detecting serious reactions).

In order to investigate the relationship between Lamictal use and the occurrence of rash, the sponsor and Agency have given particular attention to those rashes considered serious, the definition of which is a rash leading to hospitalization for which Lamictal was discontinued, or a rash characterized as possible Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) either by the investigator or the sponsor if the description of the rash included mucous membrane involvement or the presence of "blistering skin lesions". Cases of otherwise serious rash for which a reasonable alternative cause (other than drug) was established were not considered in these analysis. Cases of hospitalized rash for which drug was not discontinued were not considered serious in these analyses.

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[1]Actually, the sponsor has presented rash data for an additional 162 pediatric patients in Japan. In this cohort, there were 3 cases of serious rash. They are not included in further discussion in this memo largely because the sponsor does not have reliable dose and concomitant medication information for these patients. If they **are** included in the calculation of the crude rate of serious rash, they do not appreciably change the rate obtained when the total experience is limited to the 1071 patients discussed.

Of the 1071 children in this database, 11 (1%) had a rash that met the above definition of serious. Of these 11, 5 were considered by the sponsor to be SJS, and a total of 10/11 were hospitalized (one of the SJS cases was not hospitalized). The sponsor had 2 expert consultant dermatologists evaluate all cases of serious rash; we also consulted with an Agency dermatologist who reviewed these cases. The number of cases diagnosed by these experts as SJS ranged from 0-5.

Of these 11 rashes, 10 occurred within 60 days of initiation of treatment with Lamictal. In one other case, the rash occurred approximately 200 days after the initiation of treatment with Lamictal, but 6 weeks after the addition of phenytoin. This patient was admitted to the hospital for rash and increased seizures, and, despite the temporal relationship of the rash to the initiation of phenytoin, the Lamictal was discontinued. These series of events resulted in this case being considered a serious Lamictal related rash. Of the 14 cases (including the 3 Japanese cases), 12 were receiving other AEDs (I cannot tell, from the sponsor's submission, whether the 2 who were not receiving concomitant AEDs were in the cohort of 1071).

Of the 1071 children considered here, a total of 138 (13%) developed a rash. Of these 138, a total of 51/138 (37%, or 5% of the total) had treatment with Lamictal discontinued.

For purposes of comparison, the sponsor has submitted data on 3348 adults who have been treated with Lamictal. In this cohort, a total of 359 (10.7%) had a rash, with 118/3348 (3.5%) leading to discontinuation of Lamictal. Of this cohort, 11/3348 (0.3%) had a rash that met the above definition of serious.

In the controlled trial (UK 123), a total of 2/79 (2.5%) of Lamictal patients had a serious rash, compared to 0/90 placebo patients.

There were no deaths related to rash in this cohort, and all rashes resolved with treatment discontinuation.

In addition to the data from the prospective cohort of 1071 presented by

the sponsor, they have presented data on rash in children from several epidemiologic sources.

1) Prescription Event Monitoring (PEM)

This was an observational study conducted by the Drug Safety Research Unit in the United Kingdom. In this study, all first prescriptions for Lamictal written by general practitioners between 12/91 and 2/95 were identified. Six months after the prescription, a form was sent to the GP's, on which they were to record any adverse event (independent of cause) that had occurred since the first prescription for Lamictal. Additional follow-up was obtained for any important medical event.

A total of 19,448 follow-up forms were sent (corresponding to this number of first prescriptions for Lamictal). Of this total, 1,598 forms for children equal to or less than 12 years old and 10,741 forms for patients greater than 12 years of age were collected. In this pediatric cohort, there were 5 cases of SJS (one not hospitalized) and one additional case of erythema multiforme with hospitalization. This yielded an estimated incidence of serious rash of 6/1598 (0.38%). As noted, data were presented for children of 12 years and younger (not 16 as in the prospective data). Although data were collected for all patients (children and adults), the data for children between the ages of 13 and 16 were not presented. However, the estimated incidence of serious rash in the cohort greater than 12 years of age was 7/10741 (0.065%), making the estimated incidence in children more than 5 times greater than that in this older cohort.

2) U. S. Post Marketing Spontaneous Reporting System (SRS)

Although Lamictal is not approved for use in children in the US, such use is not uncommon. The sponsor commissioned a study of this experience by , which surveyed retail pharmacies (said to capture 75% of all prescriptions of 64% of retail pharmacies in the US).

This study examined prescriptions written between 1/1/95 (approximately the initiation of marketing) and 9/30/97. For this period of time, an estimated 330,00 new and 819,000 refill prescriptions for

Lamictal were dispensed. This study used the data on new prescriptions to calculate incidence of serious rash, since the data suggest that these rashes invariably occur soon (within 60 days) after initiation of treatment.

The survey revealed that 11% of these 330,000 prescriptions (36,300) were dispensed to patients under the age of 16.

During this period, a total of 173 adverse event reports in patients under the age of 16 were received by Glaxo Wellcome. The exact age was indicated on 92% of these reports; in the other 8, the patient was referred to as a "child" and was assumed to be under the age of 16. A total of 37/173 (21%) of these reports were of patients hospitalized due to rash and/or reported to have either SJS or TEN. One of these occurred about 90 days after the initiation of treatment, and is not included in the further discussion. Of the remaining 36 patients, the onset of the rash was reported, and was within 8 weeks of initiation of Lamictal treatment. Based on various estimates of reporting rates, the following estimated rates of serious rash can be generated (based on the sponsor's table 5.8, submission dated 10/23/97).

		Rates of Serious Rash Reporting Rates		
Age Group	#Patients Exposed	100%	50%	10%
0-15	36,300	0.1	0.2	1.0
0-5	9,075	0.04	0.09	0.44
6-10	14,520	0.11	0.23	1.17
11-15	12,705	0.12	0.24	1.18

3) Registry of SJS/TEN in Germany

This is a registry of drug related rashes (in effect since 1990) that regularly contacts over 1500 academic departments of pediatrics, dermatology and all burn units and internal medicine departments in hospitals that have ICUs or more than 200 beds. The sponsor asserts that "...in Germany, almost all hospitalized cases of SJS/TEN are detected.".

In 1993, the first year of marketing of Lamictal, a total of 5 cases of SJS/TEN were reported, in a cohort of 1,270 patients newly exposed to Lamictal (it is unclear how the estimate of Lamictal exposure was obtained), yielding an estimated incidence of 0.4%. We have no information about the age of the patients in this registry.

In an attempt to put the occurrence of serious rash with Lamictal in context, the sponsor has presented data that speak to the background incidence of serious rash in the general pediatric population, and, in particular, the rate in children receiving other AEDs.

In evaluating the rates of serious rash with other AEDs, the sponsor has submitted data from two sources: the Saskatchewan Health and MEDICAID databases. In both of these studies, cohorts of new users of the drugs evaluated were "...retrospectively identified in prescription files from large insurance plans.". In these studies, a new user was defined as a patient who had been in the insurance plan for at least 2 years at the time they were given the first prescription for the drug in question. All hospitalizations for cutaneous conditions that occurred within the first 60 days of initiation (dispensing of the prescription) of treatment. Medical records of these cases were evaluated by expert dermatologists.

1) Saskatchewan Study

This study utilized data from the Saskatchewan Health Plan, which is a government insurance plan covering over 95% of the population. Cases of hospitalization for any rash were screened and reviewed by experts, and confirmed cases of SJS, TEN, hypersensitivity syndrome, erythema multiforme, angioedema, or exfoliative dermatitis were identified. The following data were obtained for children under the age of 16*:

	New Users	Cases	Cases/1000 patients
Phenytoin:	734	1	1.4/1000
Carbamazepine	712	1	1.4/1000
Valproate	521	0	0/1000

*based on sponsor's table 5.10, submission dated 10/23/97.

The following data were obtained for patients 16 years and older*:

	New Users	Cases	Cases/1000 patients
Phenytoin	8154	7	0.9/1000
Carbamazepine	9026	5	0.6/1000
Valproate	983	0	0/1000

*based on sponsor's table 5.10, submission dated 10/23/97.

2) MEDICAID Study

No details about the methodology of this study are given, except that hospital records were searched for any hospitalized rash, and then the following factors were used to classify the cases (based on review of charts by Dr. Allan Halpern of the University of Pennsylvania) as serious:

1) SJS
2) TEN
3) erythema multiforme
4) symptom complex of dehydration, ocular involvement, fever>102°F.

The study was performed using data from 2 states.

Given these definitions, the following data are obtained for children under the age of 16*:

State 1

	New Users	Cases	Cases/1000 patients
Phenytoin	1143	4	3.5/1000
Carbamazepine	1770	0	0/1000
Valproate	1050	0	0/1000

State 2

	New Users	Cases	Cases/1000 patients
Phenytoin	1431	1	0.7/1000
Carbamazepine	1285	2	1.6/1000
Valproate	799	0	0/1000

*based on Sponsor's Table 5.11, submission dated 10/23/97.

Potential Risk Factors

The sponsor has presented evidence that they believe suggests that dose and concomitant valproate use (beyond age) are risk factors that increase the probability of experiencing a serious rash while taking Lamictal. Following is the data supporting this view.

1) Dose

The sponsor acknowledges that it is difficult to detect an effect of dose on the incidence of serious rash because there are only a few such cases. However, they have attempted to demonstrate that there is a dose relationship for the occurrence of all rash in adults.

Toward this end, they present data from monotherapy trials in adults with epilepsy (initial doses 25, 50, 100 mg/day) and a study in migraine patients (initial dose of 200 mg/day). They show (their Figure 5.3) a clear dose response in the percentage of patients who discontinue Lamictal due to rash which increases monotonically with initial dose (about 2% in the 25 mg/day initial dose group to about 37% in the group that initiated treatment with 200 mg/day).

In addition, they demonstrate a clear dose response in the monotherapy epilepsy studies when examining the mean daily dose over the first 5 weeks of these studies and dropouts due to rash, ranging from a

discontinuation rate of close to 2% in the low dose (mean dose 62.5 mg/day) to a discontinuation rate of close to 13% for the high dose group (mean dose 375 mg/day).

The sponsor has proposed specific dosing recommendations for children that vary depending upon the type of concomitant AEDs that are being given.

Specifically, because lamictal clearance is inhibited in the presence of valproate, concomitant valproate results in an increase in lamictal plasma levels. Consequently, the sponsor proposes lower starting doses of lamictal in patients taking concomitant valproate. Indeed, the sponsor proposes 3 dosing regimens: 1) for patients receiving any valproate, with or without enzyme inducing AEDs, 2) for patients taking EIAEDs without valproate, and 3) for patients taking Lamictal monotherapy.

In the various studies included in this submission, pediatric patients have been dosed with many different regimens, some of which were "incorrect" (inconsistent with the sponsor's current recommendations), and some of which were "correct" (consistent with the sponsor's current recommendations).

The sponsor has examined the 14 cases of serious rash (including the Japanese cases), and found that 10 cases occurred in patients who were receiving the "incorrect" dose, which exceeded the "correct" dose (it is impossible to determine, given the data presented, how many of these cases were US cases, and therefore correspond to the total of 1071).

However, when the sponsor calculates the rate of rash, either any rash or serious rash, the rates are similar whether patients received the "correct" or "incorrect" dose. Specifically, the following data, adapted from the sponsor's Table 5.16, displays the relevant data for the portion of the cohort of 1071 for whom dosing data were available :

Dosing Regimen	Any Rash	Serious Rash
"Correct"	40/294 (13.6%)	4/294 (1.4%)
"Incorrect"	95/740 (12.8%)	7/740 (0.9%)

The sponsor also evaluated the relationship between dose and serious rash in the German registry.

In the German registry, as noted earlier, 5 cases of SJS/TEN in 1270 new exposures were reported in 1993, the first year of Lamictal marketing. In the third quarter of 1993, the company changed the dosing regimen, and informed physicians of the need for altered dosing depending upon concomitant medications (i.e., valproate). In each of the next 2 years, 2 cases of SJS/TEN were reported, with increasing use of Lamictal (about 15,500 in 1994 and 34,700 in 1995). In 1996, presumably with further increased Lamictal use, no cases were reported.

2) Concomitant Valproate

Examination of the 14 cases of serious rash reveals that 8 of these cases (57%) were in patients receiving concomitant valproate. The sponsor states the rate of valproate usage in this population is about 41% (although the sponsor confirms that accurate dosing and concomitant medication information is not available for the Japanese experience, they have included the 3 Japanese cases in this analysis).

An examination of the data in the cohort of 1071 pediatric patients reveals that the incidence of serious rash in patients taking any concomitant valproate, 1.1% (5/443) was similar to the rate in patients taking no valproate, 1.0% (6/628). However, the rate of serious rash in patients taking valproate as the only concomitant AED or taking valproate with non-EIAEDs was 1.7% (5/294), compared to a rate of 0% (0/149) in patients taking valproate with EIAEDs as concomitant therapy, a finding which is consistent with the sponsor's belief that the risk of serious rash increases with increasing Lamictal dose (at least one of the presumed mechanisms by which valproate presumably increases the risk of rash). Interestingly, the rate of serious rash in adults not taking valproate was 0.2% (5/2842), compared to a rate of 1.2% (6/506) in adults taking any

valproate.

In the German registry, 8/9 cases of SJS/TEN reported between 1993-96 were receiving concomitant valproate. Because data on the use of valproate in the epilepsy population is not available, these data cannot speak to the question of whether these cases were related to valproate use.

In the PEM database, all 5 of the SJS cases in children, and 4/5 hospitalized rashes in children, were receiving concomitant valproate. Although pediatric use of valproate is unavailable from the PEM database, a separate source of use data in the pediatric population suggests that the background rate of concomitant valproate use is 41%. Using this as an estimate of exposure, the sponsor calculates that the estimated rate of serious rash (SJS or hospitalized rash) in patients receiving concomitant valproate is 0.8% (5/655) compared to a rate of 0.1% (1/942) in patients not taking valproate.

Biopharmaceutics

The sponsor has asked for a waiver of the requirement to perform a bioequivalence study for the 25 mg CD tablet, based on dissolution data and the fact that it is compositionally proportional to the 100 mg CD tablet. Dr. Tammara has recommended that the waiver be granted. Further, he has recommended that specific dissolution specifications be adopted.

Nomenclature Concerns

The division sent a routine consultation to the Labeling and Nomenclature Committee on 9/23/96. Their response, dated 11/18/96, objected to the use of the expression "CD", because it is generally accepted that this means Controlled Dose (i.e., a controlled release product). Further, they objected to the use of the term "dispersible" (not recognized by USP).

These concerns were conveyed to the sponsor by Dr. Ware in a phone call dated 11/22/96. Glaxo responded to these comments in a submission

dated 8/27/97. This submission was sent to the Nomenclature Committee on 9/18/97. Although we have not yet received an official response from the Committee, Dan Boring, chair of the Committee, sent an E-mail to Dr. Ware on 11/12/97. In this e-mail, he reiterates his objections to the use of the CD term, but agrees that Chewable Dispersible is an acceptable expression, although he states that the USP will remove the word "chewable" from all monograph titles very soon. He recommends that either of the following names are currently acceptable:

(lamotrigine tablets) chewable or (lamotrigine tablets) chewable dispersible. In labelling, it could look like this:

Lamictal
(lamotrigine tablets)
Chewable Dispersible Tablets.

CONCLUSIONS

The sponsor has presented a single adequate and well controlled trial in patients with Lennox Gastaut syndrome, as well as complete safety experience in almost 400 pediatric patients and detailed safety data pertaining to the occurrence of rash in 1071 pediatric patients.

The one controlled trial submitted demonstrated a statistically significant difference between Lamictal and placebo on decreasing the frequency of major seizures (drop attacks and tonic-clonic seizures) in patients with Lennox Gastaut syndrome when given as adjunctive therapy. Although the p-value resulting from the specific analysis specified in the protocol failed to achieve the traditional level of significance ($p=0.069$), this analysis was very sensitive to the relatively large number of centers with few patients, and especially to the presence of a large number of centers (10) in which only 1 of the treatments was represented. The Agency's statistical consultant performed 5 additional analyses, all of which yielded p-values below 0.05. Nominally significant results on the individual seizure types of interest contributed to the confidence in the result as well.

Although only one study was submitted, this is sufficient to support the proposed claim because 1) there is no evidence to suggest that the results of this trial are questionable (that is, this is the only controlled trial performed in this population, and, therefore, there are no controlled trials that provide contradictory evidence) and 2) Lamictal has already definitively been shown to be effective as an anticonvulsant (against partial seizures). There is precedent for permitting the addition of seizure types/syndromes to approved labeling for AEDs in these circumstances.

For this reason, I conclude that there is substantial evidence of effectiveness for the proposed claim.

I believe the drug can be judged safe in use with appropriate labeling. In particular, potentially serious rash is the adverse event of greatest concern. Although the rate of serious rash appears to be 1) greater than that in adults and 2) greater than that in children receiving other commonly prescribed AEDs, most (although not all) of the rashes do resolve with rapid recognition and drug withdrawal. I am not convinced that the sponsor's belief that the rate of serious rash is related to dose (or dose titration) and/or the presence of concomitant valproate has been proven (although there are certainly hints that this may be true). Nonetheless, I believe that labeling can be written that adequately describes the data that are available, and that lets the prescriber 1) decide whether the use of Lamictal is warranted in any particular patient, and 2) use the drug reasonably safely if the decision is made to use it.

Of concern also are the cases described as multi-organ failure and DIC. Although there appear to be a large number of these, many are from spontaneous reports, and for many it is difficult, if not impossible, to adequately assess the causality (treatment with Lamictal as opposed to other primary precipitating events). Indeed, it is not currently clear to me what the actual description of some of the cases are, although it does appear that for a significant number of these cases, the designation of multi-organ failure is somewhat misleading. These cases do involve dysfunction of several body systems, but often do not lead to "failure" of these systems, as that term is ordinarily understood. Nonetheless, I believe that labeling should contain language that describes these cases,

including our uncertainty about their description and relationship to treatment.

Finally, the comments of Dr. Tammara and those incorporated in the most recent e-mail of Dan Boring of the Nomenclature Committee should be conveyed to the sponsor.

RECOMMENDATIONS

The Division should issue the attached Approvable letter.

/S/

Russell Katz, M.D.

Cc:
NDA 20-764
HFD-120
HFD-120/Katz/Leber/Feeney/Burkhart/Ware/Tresley
HFD-710/Wang