MEMORANDUM

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

DATE: November 18, 1997

FROM: Greg Burkhart, Safety Team Leader
Neuropharmacological Drug Products, HFD-120

APPEARS THIS WAY
ON ORIGINAL

TO: NDA 20-764

SUBJECT: Serious Skin Rash During Use of Lamotrigine in the Lennox-Gastaut NDA.

In March 1997, a boxed warning was added to lamotrigine labeling to warn about serious rash occurrence (hospitalization for rash, Stevens Johnson Syndrome [SJS] or Toxic Epidermal Necrolysis [TEN]) with lamotrigine use. The possibility of a greater risk with pediatric use (<16 years of age) was discussed in the new warning, and in fact, had prompted the necessity for updating the warning and prominently placing it in a box.

The additional concern that risk may be greater with pediatric use resulted from a preliminary review of the Lennox-Gastaut NDA (NDA 20-764) by Dr. Feeney. In these data, the overall risk of serious rash was 1.3% (5/399; 3 reported as SJS), but in the RCT showing evidence of pediatric effectiveness, the risk was 3.8% (3/79; 2 reported as SJS). Adding additional concern was the published article by Dooley that observed a risk of 4.4% (3/68 with one SJS) with pediatric use. In the NDA that lead to the initial approval of lamotrigine for use in adults as adjunctive therapy, the risk for serious rash was 3 per 1000 patients while for SJS the risk was 1 per 1000 patients. Thus, at the time of the modification in labeling, we had concluded that pediatric users were substantially at more risk than adult users and that the risk for life-threatening rash could be as high as

GW has now submitted additional data and analyzes to the Lennon-Gastaut NDA expanding the pediatric experience to 1233 patients. While GW has made many submissions to the file on this issue, the sponsor's October 23, 1997 submission, intended as a draft briefing document for an anticipated advisory committee meeting to discuss the risk for rash with pediatric use, provides a good summary of the relevant data.

GW has also provided (1) a summary report from the UK PEM study of lamotrigine that included pediatric exposure; (2) a summary of the US and global post-marketing surveillance (PMS) experience; (3) literature reports describing additional lamotrigine experience with

pediatric use; (4) study reports from GW sponsored studies in US Medicaid and Saskatchewan that described hospitalized rash rates with phenytoin, phenobarbital and carbamazepine, and (5) literature reviews on Stevens-Johnson Syndrome and TEN that included studies of the risk of serious rash with drugs in general.

In addition to the material provided by GW, the division also has received completed consults from the Dermatology review division that evaluated the clinical characteristics of the serious rash cases, and from DPE that provided a review of US PMS for rash reported with pediatric use. Finally, Dr. Jim Knudsen, from the safety team, reviewed data from the pediatric experience in other AED NDAs for cases of serious rash.

My memorandum will review the risk for serious rash in the pediatric database of the Lennox-Gastaut NDA, compare the risks for rash during pediatric use of lamotrigine to that in adults, and then describe what we know about the risk for serious rash with other AEDs. Dr. Feeney reviews the overall safety experience with lamotrigine in the Lennox-Gastaut NDA in his memorandum.

Focus on Serious Rash and Its Definition

SJS and TEN are life-threatening mucocutaneous disorders that many experts consider to be related diseases with TEN more severe, and by definition, having more dermal involvement. While both can result in death or permanent sequelae, such outcomes are more likely with TEN.

In the general US population, SJS is reported to be more frequent occurring at a rate of about 1 per 100,000 per year while TEN is reported to occur in about 1 per million per year. In a case-control study of *adult* SJS/TEN in Europe, antibiotics and AEDs were strongly associated with SJS/TEN occurrence (NEJM 12/14/95 page 1600). For carbamazepine, phenobarbital, phenytoin the ORs were 90 (95% CI; 9, infinity), 45 (95% CI; 19,108) and 53 (95% CI; 11, infinity). Similar studies have not been conducted in children.

In the adult NDA, there were 4 possible cases of SJS and 1 TEN. However other rashes also occurred that were not so named, but which resulted in drug discontinuation and/or hospitalization, the hospitalization not because of epilepsy but reportedly because of the seriousness of the rash. Minor rash occurrence was also more frequent with lamotrigine than placebo. Thus, there was a wide range in clinical severity for lamotrigine-associated rash including medically serious rashes that are probably not classic cases of SJS or TEN.

Because we were concerned that focusing on SJS and TEN would underestimate the risk for medically serious rashes and because of the poor agreement among dermatological experts in naming rashes1, we focused on all serious rash occurrence in evaluating the pediatric data.

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1 The point referring to poor inter-rater agreement among experts in naming rashes, which has been described in the literature, was confirmed by the 3 experts reviewing the rash cases in the Lennox-Gastaut NDA. The two consulting dermatologists hired by GW to review the cases could

Serious rash was defined as reported cases of SJS or TEN, or hospitalization to manage a rash during which lamotrigine was discontinued.

There are two problems with our definition of serious rash that should be considered. First, children may have a higher background rate of serious rash for reasons not related to medication use. In fact, Erythema multiforme (EM) minor is considered to be of an infectious disease etiology, but the appearance of the skin eruption is similar to that with SJS, which is sometimes called EM major, but more likely to involve the extremities.2 A higher background rate of serious rash in children could make comparative data more important to evaluating any apparent increase in risk. In the adult NDA, there were no serious rashes observed with placebo. The second problem occurs because of the inclusion of dermatological events, such as angioedema, that may be distinct from the rash of interest.

Summary of the Adult Experience with Lamotrigine

Sponsor's table 5.1 shows the adult experience in the initial NDA leading to lamotrigine's approval in adults as an adjunctive treatment in epilepsy. The rate of serious rash was about 3 cases per 1000 patients with 4 cases of SJS and 1 TEN observed in the NDA development program. Further analyzes of the NDA data (shown in GW table 5.20) providing compelling evidence that the risk for serious rash was about 6 fold greater with concomitant VPA use. There was also some evidence that both the initial dose and the rate of dose escalation were associated with rash occurrence although the data were not as convincing and more difficult to interpret than with VPA.

The sponsor has also conducted a US post-marketing study of adult lamotrigine use (ALERT study) and observed 2 cases of serious rash in 767 patients with one case reported as SJS. In US PMS there have been cases of TENs reported with significant permanent sequelae and one rash-associated death. Similar cases and death have been reported from foreign PMS.

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not agree on which cases were SJS, and the FDA consulting dermatologist considered none of the rashes to represent confirmed cases of SJS or TEN.

2 Interestingly, clinicians discussing this in the literature frequently commit a tautology by arguing that EM minor is non-drug induced and hence so name those rashes as EM minor when they believe the etiology to not a drug.

Table 5.: Summary of Incidence of Cutaneous Reaction to LAMICTAL in Adult Clinical Trial Patients.

ADULT (≥ 16 YEARS)	TOTAL
N	3348
RASH	359 (10.7%)
RASH LEADING TO DC	118 (3.5%)
RASH ASSOCIATED HOSP	11 (0.3%)
POSSIBLE SJS	4 (0.1%)
SJS OR HOSP	11 (0.3%)

APPEARS THIS WAY ON ORIGINAL

GW Table 5.1 on page 15 of 10/23/97 submission

Rates of Serious Skin Rash in the Lennox-Gastaut NDA (20-764) APPEARS ON

When NDA 20-764 was initially submitted, it provided complete safety data for 399 patients exposed to lamotrigine and included data from study 123, an RCT conducted in Lennox-Gastaut patients. Of the 399 patients, 385 were less than 16 years of age. APPEARS ON ORIGI

Following Dr. Feeney's initial review of these data and after the boxed warning was added to labeling, GW submitted additional experience for 686 pediatric patients who participated in studies that had completed in the US and UK after the NDA filing, and from 162 pediatric patients in an ongoing Japanese RCT. The additional data only provided experience on rash-related AEs and did not expand the general safety database. Thus, the total pediatric database to evaluate the overall safely of lamotrigine was 385 while there was data on rash-related events in 1233 pediatric patients (385+162+686). APPEARS THIS ON ORIGI

There was significant variation in the risks for serious rash observed for different studies and groupings of studies in the pediatric database raising concern about the validity of combining data across the studies. APPEARS THIS ON ORIGI

In study 123, the risk for serious rash was 3.8% while in the original NDA database it was 1.3% (5/385). For the 686 patients added from the UK and US, which included 98 pediatric patients from an additional RCT, the risk for serious rash was 0.9% (6/686). In the ongoing Japanese study, the risk for serious rash was 1.8% (3/162). APPEARS THIS ON ORIGI

The majority of the 686 patients added from the completed UK and US studies were followed in a compassionate use protocol (study 26). We asked GW to explain the methods used to follow the patients participating in this study and how cases of serious rash were ascertained.

Quality of Data Collection in Protocol 26

In a July 29, 1997 submission, the sponsor explained the procedures for data collection in study 26 which contributed a substantial amount of the pediatric experience with lamotrigine. The protocol required patients to visit the investigator every 6 months and specifically discussed the capture of AEs, separately discussing rash occurrence. Clinically significant AEs were to be recorded and described on the CRF. The study was monitored by a CRO although there was no discussion of monitoring frequency or what was found during monitoring. Because of the interest in skin rash, GW retrospectively followed up all clinically significant rashes with the reporting sites to collect additional information on the clinical characteristics and outcome of the rash.

To my knowledge, a full study report for study 26 has not been submitted, and we do not know the lost to follow-up rate for the study. While I believe that the overall quality of data in study 26 is suspect, I also believe that serious rash occurrence, as we have defined it, could have been, and probably was ascertained by the investigator. If we had information that patients who did not keep their visits were followed up in a valid manor, we could be more assured about the data quality for study 26.

Somewhat reassuring is the observation that the risk for serious rash in these data is not materially different from that observed in the open experience included the original Lennox-Gastaut database. Of the 385 pediatric patients, 306 were followed in open studies with 2 cases of serious rash reported giving a risk 0.6%. So I would conclude that if there is a problem with ascertainment of rash in the pediatric database, it may extend to all open experience. However, in the other RCT completed in the US, there was one serious rash in 98 patients assigned lamotrigine while the Japanese RCT the risk was 1.8%. Therefore, it seems likely that the variation in risks that we have observed by study may be more a function of small sample size and not ascertainment.

Evidence that the Risk of Serious Rash is greater than Expected: Experience in RCTs

US study 123 was the only RCT conducted in Lennox-Gastaut patients and was included in the original NDA. The rate of serious rash was 3.8% (3/79) in patients assigned lamotrigine and 0% (0/90) for patients assigned placebo. Of the total 169 patients in study 123, 14 patients were > 15 years of age with none of these 14 having a serious rash.

US study 40 was a RCT conducted in pediatric patients for adjunctive treatment submitted after the NDA filing. There was 1 serious rash in 98 patients assigned lamotrigine and none in the 103 patients assigned placebo. Combining this RCT experience, gives 4 cases of serious rash in 177 patients assigned lamotrigine (some older than 15) compared to 0 of 190 (some older than 15).

In the ongoing Japanese RCT, there have been 3 serious rashes in the 162 assigned to lamotrigine and I presume that none have been reported for placebo (study still in progress and not sure of the denominator or actual placebo data, but none have been reported to the FDA for placebo).

Both study 40 and the Japanese study were submitted after the NDA and only included data on rash events.

Thus, in my opinion, the risk for serious rash in the pediatric database seems to be strongly associated with lamotrigine use.

Review of Serious Rash in the Pediatric Database

Of the 1233 pediatric patients with exposure to lamotrigine, there were 18 rashes classified as possibly serious. GW excluded 4 of these because of concurrent hanta virus infections was found on autopsy (1); lamotrigine was continued well after the event (1); patient was hospitalized because of seizure frequency not the rash (1) and, after further review, the patient was not actually hospitalized (1). After these exclusions the risk for serious rash in the pediatric database was 1.1% (14/1233).

Of these 14 serious rashes, 13 were hospitalized because of its severity and 7 were reported as SJS. There were no deaths, permanent sequelae or cases reported as TEN.

Three dermatologists reviewed the 14 cases to assign a diagnosis, one of whom is a clinical reviewer at the FDA. They agreed that there were no cases of TEN, but generally disagreed as to SJS occurrence. The two GW consultants did agreed that two of the cases reported as SJS were actually SJS, but the FDA reviewer did not consider any of the cases as confirmed SJS.

Risk for Serious Rash by Age, Correctness of Dose Regimen and Concomitant VPA

Since the Japanese study is still ongoing and assignment is blinded, GW does not have information about the 162 patients assigned lamotrigine or those assigned placebo except for the 3 patients with serious rash occurrence with lamotrigine. Thus, further description of the risks for serious rash will focus on the remaining 1071 patients in the pediatric database.

Sponsor's table 5.3 compares the experience in the adult NDA with that in the 1071 patients in pediatric database. As can be seen there is about a 3 fold increase in serious rash in children although the overall rate of rash is not that different.

e 5.3 Comparison of Rates of Rash between Adult and Pediatric Clinical Trial Patients

ADULT (≥ 16 YEARS)	TOTAL (%)
N	3348
RASH	359 (10.7%)
RASH LEADING TO DC	118 (3.5%)
RASH ASSOCIATED HOSP	11 (0.3%)
POSSIBLE SJS	4(0.1%)
SJS OR HOSP	11 (0.3%)
PEDIATRIC (< 16 YEARS)	
N	1071
RASH	138 (12.9%)
RASH DC	51 (4.8%)
RASH HOSP	10 (0.9%)
SJS	5 (0.5%)
SJS OR HOSP	11 (1.0%)

GW Table 5.3 on page 18 of 10/23/97 Submission

Sponsor's table 5.13 shows the risk by age group. All but one of the serious rashes occurred in children < 12 years of age.

Table 5.13 Rash Associated with Hospitalization or Reported as SJS in Pediatric Clinical Trial Patients by Age Groups

Age Group	N	SJS or Hosp	% SJS or Hosp	SJS	%SJS
Pediatric 0 - 5 years	340	3	0.9%	0	0%
Pediatric 6 - 11 years	530	7	1.3%	5	0.9%
Pediatric 12 - < 16 years	201	1	0.5%	0	0%

GW Table 5.13 on page 26 of 10/23/97 submission.

GW also developed a definition of "correct" dosing and applied it to the 1034 children with information on dosing. Sponsor's table 5.16 shows these findings. There was no difference in the serious rash risk by "correct" and "incorrect" dosing. However, all of the cases that were identified as SJS occurred with children incorrectly dosed.

Table 5.16 Summary of Incidence of Rash by "Correct" or "Incorrect" Dosing

Dosing	N	Rash	DC	Hosp	SJS	SJS or Hosp
"Correct"	294	40 (13.6%)	12 (4.1%)	4 (1.4%)	0 (0%)	4 (1.4%)
"Incorrect"	740	95 (12.8%)	38 (5.1%)	6 (0.8%)	5 (0.7%)	7 (0.9%)

GW Table 5.16 on page 30 of 10/23/97 submission.

Sponsor's table 5.20 shows the effects of concomitant VPA use on the risk for serious rash in adults and the pediatric database. In adults, serious rash was strongly associated with VPA use while in children there was little difference in risks. In both databases, VPA use with enzyme inducing AEDs, was associated with lower risk for serious rash.

Table 5.20 Summary of Rates of Rash with Various Concomitant AED Combinations with LAMICTAL

ADULT	VPA ONLY or VPA+NEI	VPA+EI	NO VPA
(≥ 16 YEARS)			
N	205	301	2842
RASH	40 (19.5%)	28 (9.3%)	291 (10.2%)
RASH DC	25 (12.2%)	10 (3.3%)	83 (2.9%)
RASH HOSP	3 (1.5%)	2 (0.7%)	5 (0.2%)
SJS	1 (0.5%)	0 (0%)	3 (0.1%)
SJS OR HOSP	3 (1.5%)	2 (0.7%)	5 (0.2%)
PEDIATRIC (< 16 YEARS)			
N	294	149	628
RASH	60 (20.4%)	7 (4.7%)	71 (11.3%)
RASH DC	28 (9.5%)	0 (0%)	23 (3.7%)
RASH HOSP	4 (1.4%)	0 (0%)	6 (1.0%)
SJS	4 (1.4%)	0 (0%)	1 (0.2%)
SJS OR HOSP	5 (1.7%)	0 (0%)	6 (1.0%)

GW Table 5.20 on page 33 of 10/23/97 submission

Risk of Serious Rash with Pediatric Use of Lamotrigine Based upon Post-Marketing Experience

Literature Reports

The GW 10/23/97 submission contains a good summary of the risks seen across many reported, and mostly small, studies of lamotrigine use in pediatric patients. In reviewing the reports, substantial details of the methods are frequently lacking so that it is hard to conclude much about the reports. Some of the reports do not even mention rash.

The highest risk observed was in the study reported Dooley where 3 of 68 developed a serious rash.

PEM Study Findings

GW submitted the full study report from a PEM study of lamotrigine in the UK. A summary and discussion of these findings was included in the 10/23/97 submission. Sponsor's table 5.6 shows the serious rash risks by age from the PEM study. Of the 1598 patients <= 12 years of age, there were 6 serious rashes, 5 of which were reported as SJS giving a risk of about 4 per 1000 patients. The risk for serious rash in patients <= 12 was 5.7 fold greater than patients > 12 years of age. There was no information on concomitant VPA use or "correct" dosing for pediatric patients overall, but of the 5 SJS cases, all were reported to be using VPA.

Table 5.6 *Number of Serious Rashes from the Adult and Pediatric Databases and PEM Study*

	N	SJS or Hosp	SJS or Hosp	Hosp	Hosp %	SJS	SJS %
Total Pediatric Exposure	1233	14	1.1%	13	1.1%	7	0.6%
Pediatric Database < 16	1071	11	1.0%	10	0.9%	5	0.5%
PEM (Age ≤ 12)	1598	6	0.4%	6	0.4%	5	0.3%
PEM (Age > 12	10741	7	0.07%	7	0.07%	7	0.07%
Adult Database ≥ 16	3348	11	0.3%	11	0.3%	4	0.1%

Serious Rash is defined as rash associated with hospitalization or rash reported as possible SJS.

GW Table 5.6 on page 20 of 10/23/97 submission

US PMS

Both Dr. Davis from DPE and GW have evaluated the US post-marketing experience for reports of serious skin rash in pediatric patients using lamotrigine off-label.

According to the DPE consult by Dr. Davis, there have been 35 reported cases of hospitalized rash in the US through the "first half" of 1997. GW found 37 US cases but extended the time through September 1997. DPE and GW agree that there have been no domestic deaths although

there have been 4 rash-associated pediatric deaths reported with foreign use.

Dr. Davis found that 27 of the 35 reports reported either EM or SJS while GW found that 23 of the 37 were consistent with SJS. According to GW, 1 of these cases was consistent with TEN. Of the 27 cases of EM or SJS reviewed by Dr. Davis, 82% were reported to be taking concomitant VPA.

Both GW and DPE estimated the reporting rates of serious rash using slightly different techniques and data sources. DPE used IMS's NPA and NDTI databases to estimate a range for the number of users less than 16 years of age in the US. Both databases were necessary because the NPA database, while collecting dispensing data from a significant number of US pharmacies, does not capture patient characteristics such as age. NDTI, a much smaller sample of office based physicians, records "mentioned" treatments as well as age and other characteristics of the patients. Thus, Dr. Davis used NDTI to estimate the age distribution for "mentioned" lamotrigine users in NDTI and applied that age distribution to the estimated number of prescriptions from NPA. He then used a range of estimates for the average duration of use to get a range for the number of users less than 16. Using this range for the denominator (users), he calculated a range of reporting rates. He then assumed varying degrees of under-reporting to generate a range of risk estimates.

GW used Scott Levin's database, which records the age of patients receiving the prescription as well as whether the prescription is new or a refill. To do this GW assumed that the number of new users less than 16 years of age was the total number new prescriptions ever dispensed. Since it is generally accepted that most the risk is early in treatment and since most cases spontaneously reported have been within 60 days, they just put the number of reported cases over this estimated dominator (they excluded the one patient reported with a rash occurring 90 days). Then, by assuming different degrees of under-reporting, they generating a range of risk estimates.

As it turns out, both sets of estimates by DPE and GW were fairly comparable. DPE estimated that as many as 23,900 patients less than 16 have taken lamotrigine whereas GW estimated that there have 36,300. Sponsor's table 5.8 shows the reporting rates for serious rash in the US as a function of under-reporting by age. Assuming an under-reporting rate of 10%, the risk for serious rash is about 1%. Dr. Davis arrived at a similar range of estimated risks.

Table 5.8 Estimated Rates of Serious Cutaneous Adverse Events (per 100 patients) at Three Putative Spontaneous Adverse Event Reporting Rates : 100%, 50% and 10%.

Age (yr)	Estimated No. of Patients Exposed	Hospitalized for Rash and/or Reported as SJS or TEN		
		100% *	50%	10%**
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
0-15	36,300	0.10	0.20	0.99

GW Table 5.8 on page 22 of 10/23/97 submission.

One interesting fact from NDTI was that in these data, VPA was mentioned concomitantly with lamotrigine 33.5% of the time. Since NDTI is supposed to record treatments mentioned at that time for the condition, most consider NDTI to always underestimate ongoing concomitant use. If true, then concomitant VPA use is probably higher than the 33.5% for patients captured by NDTI. How well NDTI generalized to US medical practice is unknown.

Discussion

Given the substantial difference in the risks of serious rash observed between lamotrigine and placebo in the RCT experience available with pediatric use, it seems compelling that lamotrigine is strongly associated with serious rash. The experience in the pediatric database and in the PEM data suggest that there probably is a substantial difference in the level of increased risk between adults and pediatric patients. Overall in the pediatric database, lamotrigine use was associated with about a 1% risk for serious rash. As in adults, the risk for serious rash appears to be mostly during the first 2 months of use although serious cases have been observed after 2 months.

There were no cases of TEN and no deaths were observed in the NDA. The majority of the cases were not as severe as classic cases of SJS/TEN. In an estimated US exposure of from 24,000 to 36,000 pediatric patients with off-label lamotrigine use, there have been no reported deaths and 1 reported case of TEN.

While it seems clear that lamotrigine has increased the risk for serious rash, one could ask whether the increase is any different from that with other AEDs used in pediatric patients. One study, referred to on page 26 of the GW submission, reports that of 335 pediatric Japanese patients newly treated with carbamazepine , 2 were reported to have SJS. Of course, in the adult case-control several AEDs were strongly associated with SJS/TEN occurrence.

GW also sponsored studies of US Medicaid (OHIO and Michigan) and Saskatchewan province to estimate the risk of severe rash in pediatric users of phenytoin, carbamazepine and

phenobarbital. However, despite a relatively wide net to find cases, few cases, judged to be severe, were observed. In Saskatchewan, there were 1967 new users of one the three drugs with 2 severe rashes. In Medicaid, again combining the data for all the drugs in both states, there were 7 severe rashes in about 6335 new users. Both studies, but particular the Medicaid study, may have underestimated the risk. The Medicaid study had limited record retrieval and by defining severity as to include ocular involvement for hospitalized cases may have significantly underestimated the number of cases. However, even if we assume that all possible cases found in Medicaid (broad net based upon claims and no review) are actual cases, the highest risk for any of the three drugs in the Medicaid study was still several fold less than the experience in the pediatric database.

Dr. Jim Knudsen of the division's safety team also reviewed other recent AED NDAs with pediatric experience. In the vigabatrin NDA, there were 159 pediatric patients in the primary NDA data with no cases of serious rash. For topiramate, there was 1 serious rash in 303 pediatric patients and this patient had started lamotrigine shortly before the onset of the rash. In the felbamate NDA, there was 1 SJS/TEN in 431 pediatric patients, but the data was not available and the clinical review did not specifically mention hospitalized rash. Since the sponsor refers to the carbamazepine NDA, which was approved in the 80's, we reviewed the narrative reports for 4 rash events sited in the 10/23/97 submission as medically serious. We could confirm that 1 of these had been hospitalized with a rash, but the quality of the information on the narrative was limited.

Thus, while there is really a paucity of data that even addresses the risk for serious rash in children in the general population, there is almost no data on risk for pediatric AED use. Most of what is available is of limited qualify, but seems to suggest that lamotrigine carries more risk. The only data suggesting that that another AED approaches the risk observed with lamotrigine is the reported Japanese experience with carbamazepine. Carbamazepine does carry labeling indicating an increased risk of SJS/TEN with some post-marketing cases described in its label.

In conclusion, while about 1% of pediatric users may have serious rash occurrence, as we have defined it, many of these rashes do not appear to be of the severity as classic SJS or TEN. However, life-threatening rashes certainly occur with lamotrigine during either pediatric or adult use and children appear to be at materially more at risk than adults. This level of concern seems to be accurately conveyed in labeling except that the absolute risk is probably 1% and not 2%. Use of VPA may potentate the risk for more severe rashes, but serious rashes occur even when it is not used. The role of the initial dose and rate of dose escalation requires more study.

/S/ 11/18/97

Greg Burkhart, M.D., M.S/
Safety Team Leader
Neuropharmacological Drug Products

cc:HFD-120\Burkhart\Leber\Katz\Feeney

ITEM 13

Patent Information Pursuant to 21 U.S.C. 355 for

LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets

NDA 20-764

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	LAMICTAL® CD Chewable Dispersible Tablets
Active Ingredient(s):	lamotrigine 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine
Strength(s):	5mg, 25mg and 100mg
Dosage Form:	Tablets
NDA Number:	20-764
Approval Date:	Pending

U.S. Patent 4,602,017

Expiration Date:	July 22, 2003
Type of Patent:	Drug Product Method of Using Drug Product
Name of Patent Owner:	Glaxo Wellcome Inc.
U.S. Agent:	David J. Levy, Ph.D. Patent Counsel, Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, North Carolina 27709 (919) 483-2723

The undersigned declares that U.S. Patent 4,602,017 covers the formulation, composition and/or method of use of LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets and should be included in Item 13 of NDA 20-764. This product is the subject of NDA 20-764.

September 13, 1996
Date

By: Robert T. Hrubiec
Robert T. Hrubiec, Ph.D.
Registered Patent Agent
Glaxo Wellcome Inc.

APPEARS THIS WAY
ON ORIGINAL

Time Sensitive Patent Information pursuant to 21 U.S.C. § 355 for

LAMICTAL® (lamotrigine) Oral Tablets

NDA 20-241

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name	LAMICTAL®
Active Ingredient(s):	Lamotrigine
Strength(s):	100mg, 150mg, 200mg and 250mg
Dosage Form:	Oral Tablets
NDA Number:	20-241
Approval Date:	12/27/94

U.S. Patent Number 4,602,017

Expiration Date:	July 22, 2003 (an extension of the patent term pursuant to 35 U.S.C. § 156 until July 22, 2008 has been applied for and is pending).
Type of Patent:	Drug, Drug Product and Method of Use
Name of Patent Owner:	Glaxo Wellcome, Inc.

U.S. Agent:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, North
Carolina 27709
(919) 248-2723

The undersigned declares that U.S. Patent Number 4, 602, 017 covers the composition, formulation and/or method of use of Lamictal® tablets. This product is the subject of this application for which approval is being sought.

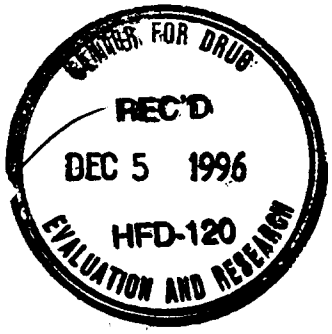
February 6, 1996
Date

David J. Levy, Ph.D.
Registered Patent Attorney
Registration No. 27,655

GlaxoWellcome

ORIGINAL
ORIG AMENDMENT
N(XR)

December 4, 1996



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9 Dec 96
Noted
/S/

Re: NDA 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets
Amendment to Pending Application: Patent Information

APPEARS THIS WAY ON ORIGINAL

Dear Dr. Leber:

In accordance with 21 U.S.C. § 355, Glaxo Wellcome Inc. is submitting additional patent information for LAMICTAL CD (lamotrigine) Chewable Dispersible Tablets. For the reviewer's convenience, we are also enclosing the patent information that was previously submitted on September 16, 1996 with the original NDA (Volume 1, page xvii).

If there are any questions or comments regarding this submission, please contact the undersigned at (919) 483-6466.

Sincerely,

Elizabeth McConnell

APPEARS THIS WAY
ON ORIGINAL

Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

cc: Jackie Ware, Pharm.D., Regulatory Management Officer, HFD-120

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone
919 248 2100

Patent Information

pursuant to 21 C.F.R. § 314.53
for
LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets

NDA 20-764

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	LAMICTAL® CD Chewable Dispersible Tablets
Active Ingredient(s):	lamotrigine
Strength(s):	5mg, 25mg and 100mg
Dosage Form:	Tablets
NDA Number:	20-764
Approval Date:	Pending

U.S. Patent 4,602,017

Expiration Date:	July 22, 2008 • The original expiration date of July 22, 2003 has been extended 5 years pursuant to 35 U.S.C. § 156.
Type of Patent:	Drug Product • Formulation / Composition Method of Use • Method of treating epilepsy
Name of Patent Owner:	Glaxo Wellcome Inc.

The undersigned declares that U.S. Patent 4,602,017 covers the formulation, composition and/or method of use of LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets. This product is the subject of this application for which approval is being sought. Please address all communications to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-7656

Respectfully submitted by:
Glaxo Wellcome Inc.

October 15, 1996
Date

Shah R. Makujina
Attorney for Applicant
Glaxo Wellcome Inc.

ITEM 13

Patent Information Pursuant to 21 U.S.C. 355 for

LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets

NDA 20-764

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	LAMICTAL® CD Chewable Dispersible Tablets
Active Ingredient(s):	lamotrigine 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine
Strength(s):	5mg, 25mg and 100mg
Dosage Form:	Tablets
NDA Number:	20-764
Approval Date:	Pending

U.S. Patent 4,602,017

Expiration Date:	July 22, 2003
Type of Patent:	Drug Product Method of Using Drug Product
Name of Patent Owner:	Glaxo Wellcome Inc.
U.S. Agent:	David J. Levy, Ph.D. Patent Counsel, Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, North Carolina 27709 (919) 483-2723

The undersigned declares that U.S. Patent 4,602,017 covers the formulation, composition and/or method of use of LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets and should be included in Item 13 of NDA 20-764. This product is the subject of NDA 20-764.

September 13, 1996
Date

By: Robert T. Hrubiec
Robert T. Hrubiec, Ph.D.
Registered Patent Agent
Glaxo Wellcome Inc.

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

DESK COPY

January 15, 1998

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, Woodmont II, Room 4037
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets
Amendment to Pending Application: Patent Information

Dear Dr. Leber:

In accordance with 21 U.S.C. § 355, and 21 CFR 314.53, Glaxo Wellcome Inc. is submitting additional patent information for LAMICTAL CD (lamotrigine) Chewable Dispersible Tablets. For the reviewer's convenience, we are also enclosing the patent information that was previously submitted on September 16, 1996 with the original NDA (Volume 1, page xvii) as well as additional inofmration submitted on December 4, 1996.

If there are any questions or comments regarding this submission, please contact the undersigned at (919) 483-6466.

Sincerely,

Elizabeth McConnell

Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

cc: Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120

Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

A Division of
Glaxo Wellcome Inc.

Patent Information

pursuant to 21 C.F.R. § 314.53
for
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

NDA 20-764

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	LAMICTAL® Chewable Dispersible Tablets
Active Ingredient(s):	lamotrigine
Strength(s):	5mg, 25mg and 100mg
Dosage Form:	Tablets
NDA Number:	20-764
Approval Date:	Pending

U.S. Patent 5,698,226

Expiration Date:	January 29, 2012 • 20 years from the filing of PCT/GB/00163 which issued as U.S. 5,556,639 of which U.S. 5,698,226 is a divisional of thereof.
Type of Patent:	Drug Product • Formulation / Composition
Name of Patent Owner:	Glaxo Wellcome Inc.

The undersigned declares that U.S. Patent 5,698,226 covers the formulation, composition and/or method of use of LAMICTAL® (lamotrigine) Chewable Dispersible Tablets. This product is the subject of this application for which approval is being sought. Please address all communications to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-7656

Respectfully submitted by:
Glaxo Wellcome Inc.

January 12, 1997
Date

Shah R. Makujina
Attorney for Applicant
Glaxo Wellcome Inc.

Patent Information

pursuant to 21 C.F.R. § 314.53
for
LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets

NDA 20-764

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	LAMICTAL® CD Chewable Dispersible Tablets
Active Ingredient(s):	lamotrigine
Strength(s):	5mg, 25mg and 100mg
Dosage Form:	Tablets
NDA Number:	20-764
Approval Date:	Pending

U.S. Patent 4,602,017

Expiration Date:	July 22, 2008 • The original expiration date of July 22, 2003 has been extended 5 years pursuant to 35 U.S.C. § 156.
Type of Patent:	Drug Product • Formulation / Composition Method of Use • Method of treating epilepsy
Name of Patent Owner:	Glaxo Wellcome Inc.

The undersigned declares that U.S. Patent 4,602,017 covers the formulation, composition and/or method of use of LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets. This product is the subject of this application for which approval is being sought. Please address all communications to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-7656

Respectfully submitted by:
Glaxo Wellcome Inc.

October 15, 1996
Date

Shah R. Makujina
Attorney for Applicant
Glaxo Wellcome Inc.

APPEARS THIS WAY
ON ORIGINAL

ITEM 13

Patent Information Pursuant to 21 U.S.C. 355 for

LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets

NDA 20-764

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	LAMICTAL® CD Chewable Dispersible Tablets
Active Ingredient(s):	lamotrigine 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine
Strength(s):	5mg, 25mg and 100mg
Dosage Form:	Tablets
NDA Number:	20-764
Approval Date:	Pending

U.S. Patent 4,602,017

Expiration Date:	July 22, 2003
Type of Patent:	Drug Product Method of Using Drug Product
Name of Patent Owner:	Glaxo Wellcome Inc.
U.S. Agent:	David J. Levy, Ph.D. Patent Counsel, Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, North Carolina 27709 (919) 483-2723

The undersigned declares that U.S. Patent 4,602,017 covers the formulation, composition and/or method of use of LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets and should be included in Item 13 of NDA 20-764. This product is the subject of NDA 20-764.

September 13, 1996
Date

By: Robert T. Hrubiec
Robert T. Hrubiec, Ph.D.
Registered Patent Agent
Glaxo Wellcome Inc.

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 20-764 SUPPL #_____

Trade Name: Lamictal CD (lamotrigine) Chewable Dispersible Tablets
Generic Name: lamotrigine

Applicant Name: Glaxo Wellcome **HFD#:** HFD-120

Approval Date If Known: 8/24/98

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. *An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.*

a) Is it an original NDA?

YES/_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

Form OGD-011347 Revised 8/27/97
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

The applicant has requested 3 years of exclusivity from the date of approval.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. *Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)*

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. *Is this drug product or indication a DESI upgrade?*

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-241; Lamictal (lamotrigine)Tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. *Does the application contain reports of clinical investigations?*
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) **If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a).** If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study UK 123

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. *In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.*

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /_ _/ NO /_X_/

Investigation #2 YES /__/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study UK 123_____ _____

_____ _____

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4. *To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.*

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /_X_/ NO /___/ Explain: _____

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ON ORIGINAL

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

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ON ORIGINAL

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

Signature: /S/ **Date:** 12/2/97

Title: Project Manager

Signature of Office/Division Director

Signature: /S/ **Date:** 12/3/97

cc: Original NDA Division File HFD-93 Mary Ann Holovac