

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-253 & 22-254

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	
From	Norman Hershkowitz
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-253, 22254, _____ b(4)
Supplement#	(0)
Applicant	Schwarz Biosciences Inc. (UCB)
Date of Submission	9/28/07
PDUFA Goal Date	
Proprietary Name / Established (USAN) names	TBD/ Lacosamide
Dosage forms / Strength	Tablets 50, 100 150, 200, 250 and 300 mg (22253) iv solution (22254) b(4)
Proposed Indication(s)	Adjunctive Treatment of Partial Onset Seizures in Adults
Recommended:	Approval for tablets and iv solution. _____ b(4)

Cross Discipline Team Leader Review Template

1. Introduction

Lacosamide has been developed for two separate indications, partial onset seizures and pain associated with diabetic peripheral neuropathy (DPN). This CDTL Division of Neurology Products (DNP) review will concentrate on efficacy results in partial onset seizures. That for DPN will be reviewed by Division of Anesthesia, Analgesia and Rheumatologic Products (DAARP). Safety data in this application has been reviewed by both division, and while this review will concentrate on safety in epilepsy, all data will be discussed. Because of specific interest in a potential cardiac signal the Division of Cardiovascular and Renal Products (DCRP) was asked to comment not only on the formal QT study but issues of PR prolongation and general cardiac safety.

2. Background

According to the Sponsor Lacosamide, (R)-2-acetamido-N-benzyl-3-methoxypropionamide, is a member of a series of functional amino acids. From a mechanistic perspective lacosamide appears to act as a sodium channel blocker, an action shared by a number other anticonvulsants including phenytoin, carbamazepine, oxcarbazepine and lamictal. The Sponsor also notes that lacosamide's anticonvulsant activity may also be related to its ability to bind to collapsin

response mediator protein-2 (CRMP-2), a phosphoprotein which is mainly expressed in the nervous system and is involved in neuronal differentiation and control of axonal outgrowth. This reviewer believes that this latter mechanism is highly speculative.

3. CMC/Device

In CMC review of tablets (22253) submitted to DFS, performed by Drs. Shiromani and Sood, a recommendation of "approvable" was made pending responses to a letter containing questions (3/20/08) and the final Compliance and Environmental Assessment recommendations. No phase 4 commitments were made. A later memo (7/16/08) submitted to DFS recommended approval based upon acceptable responses to question and an acceptable Compliance report. The environmental Assessment found no concerns. Off note the Sponsor agreed to the following (although these do not appear to be phase 4 commitments):

[Redacted]

No issues CMC issues regarding the iv solution (22254) were identified. Inspections and microbiology were also found adequate. Approval was recommended by the CMC reviewer.

[Redacted]

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4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review found no nonclinical issues and is recommending approval. They are, however recommending, the following phase 4 commitment:

"Further assessment of lacosamide's effect on brain development is needed and that this assessment may be conducted postapproval. Such an assessment should certainly involve dosing in rat throughout the critical periods that correspond to the entire period of human fetal

development with, perhaps, direct dosing of the neonate, and, as Dr. Fisher notes, the use of sensitive methods for assessing neurobehavioral function and expanded histopathological examination of the brain. “

Early animal studies indicated potential cardiac effects involving slowing of atrio-ventricular and ventricular conductivity as evidence by the lacosamide-induced increase in PR interval and QRS duration. However, obvious hERG channel effects or QTc changes were not apparent. For this reason clinical cardiac adverse events were closely monitored. A formal QTc study was, off course also performed.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Fadiran and Zhang, clinical pharmacologists, performed the general clinical pharmacology review, while Dr Tandon reviewed the _____ iv solution formulations. b(4)

General PK Properties:

Lacosamide is a Biopharmaceutics Classification System (BCS) class 1 drug. Lacosamide tablets bioavailability was approximated to be about 100%. It is absorbed with a Tmax of 0.4 to 4 hours and a T1/2 of approximately 13 hours. This drug experiences <15% protein binding. The drug is eliminated by the kidneys. Most of the drug in the urine is in the form of lacosamide (40%) or its metabolites with the major metabolite (SPM12809) making up 30% of that which is recovered. Its major metabolite is believed to be inactive. The relative contribution of P450 isoforms in the oxidative metabolism of lacosamide is not clear. But, the Sponsor determined that formation of the major metabolite, SPM 12809, is through the CYP2C19 pathway. The clinical pharmacology reviewer, however, notes that the relative role of P450 isoforms in the oxidative metabolism of lacosamide is not clear.

Drug-Drug Interactions:

In vitro studies indicate that lacosamide is not a significant inhibitor (1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4, 3A5), although it inhibits CYP2C19 to some extent. In vitro studies also indicated some induction of CYP 2C9 and 2C19, but only a small effect was noted in interaction studies with omeprazole (see below).

No interactions because of protein bindings was anticipated. Lacosamide was not a substrate for p-glycoprotein.

Definitive studies, in vivo, studies were performed on a number of potential concomitant drugs (anticonvulsants, oral birth control agents, hypoglycemic and cardio – active agents). The table below summarizes the conclusion, based upon CI of Cmax and AUC, drawn from these studies.

Effect of lacosamide on pharmacokinetics of other drugs:

Drug	Effect
Carbamazepine	None
Valproic acid	None
Digoxin	None
Oral Contraceptive	↑ Cmax of ethinylestradiol (~20%)
Omeprazole	None
Metformin	effect controversial, one group showed increase and the other group showed decrease in exposure of metformin. PD not studies. Clinical relevance not clear

Effect of other drugs on lacosamide pharmacokinetics:

Drug	Effect
Carbamazepine	None
Valproic acid	None
Omeprazole	No effect on LCM, but ↓ SPM12809 by 60%
Metformin	None

Population PK drug-drug interactions were also examined, which indicated that LCM exposure is reduced by 15-20% when lacosamide is co-administered with carbamazepine, phenobarbital, or phenytoin. The finding on carbamazepine contradicts the above noted findings and according the clinical pharmacology reviewer is difficult to interpret because of this disparity, lack of statistical significance of this effect and confounding covariates.

Special Populations:

The clinical pharmacology reviewer note that studies indicate that while no dose adjustments would be necessary for patients with mild to moderate renal impairment, patients with severe renal failure will require dose reductions. Studies indicate that similar adjustments would be necessary for patients with moderate hepatic impairment. Elderly patients experienced a 20-25% greater exposure when weight was taken into consideration. The clinical pharmacology reviewer felt that although this would not warrant dose adjustment on its own, because of increased incidence of impaired hepatic and renal function in this class of patients, some caution should be noted in this population. Although females experienced greater exposure, when weight was factored in this difference disappeared. This led the clinical pharmacology reviewer to conclude that no adjustment is necessary. There were no racial differences in exposure when adjusted for body weight. Poor CYP2C19 metabolizers were examined in a small study. No substantial difference was noted in the plasma concentrations of the parent drug with extensive metabolizers. However, there was a significant differences (75 to 85%) observed in the SPM 12809 metabolite. Because of this metabolites low level, in comparison to the parent, this was not thought to be significant enough for a dose adjustment

iv Solution formulations

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As all efficacy studies were performed using a tablet formulation it was necessary to establish equivalent bioavailability between this formulation and the iv solution.

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The sponsor conducted two bioequivalent studies in healthy subjects evaluating the bioequivalence of solution for infusion at different infusion rates versus the oral tablets (Study SP645 and SP658). Dr Tandon, the clinical pharmacology reviewer notes that such studies demonstrated:

- 15 minute IV infusion of 200 mg versus tablets (2x100 mg):
BE with respect to AUC(0-t)
Not BE with respect to Cmax
- 30 minute IV infusion of 200 mg versus tablets (2x100 mg):
BE with respect to both AUC(0-t) and Cmax
- 60 minute IV infusion of 200 mg versus tablets (2x100 mg):
BE with respect to both AUC(0-t) and Cmax

In addition to the above definitive bioequivalence studies the sponsor performed two studies in epilepsy patients already on a presumed therapeutic dose of lacosamide tablets. The intravenous formulation was substituted for tablets for a period of up to 5 days. The intravenous formulation infused over various times (10, 15 and 30 minutes). Minimal differences in the Ctrough and Cmax values for the 10, 15 and 30 minute infusion were observed. Dr Tandon concluded that it could be concluded, "the 10, 15, 30 and 60 minute infusions at a given dose give comparable plasma concentrations of LCM."

OCP Recommendations:

- OCP found the application acceptable "provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert."
- A phase IV commitment is recommended to "determine which enzymes may be involved in the metabolism of lacosamide in addition to CYP2C19."

6. Clinical Microbiology

No issues were identified (see CMC).

7. Clinical/Statistical- Efficacy

The clinical efficacy review was performed by this CDTL, Dr. Norman Hershkowitz.

The Sponsor submitted 3 adequate and well controlled trials for review. Supportive studies were also included. The adequate well controlled trial consists of a phase 2b, dose finding study (SP667) and two phase 3 trials (SP754 and SP755). All three trials were of similar design (see below). The table below presents a summary of dose, time and numbers of patients studied in these protocols.

Trial number/Clinical development phase/Trial design	Number of subjects randomized to receive LCM ^a	Number of subjects randomized to receive placebo ^a	Maximum duration of treatment ^b
SP667/Phase 2/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200, 400, and 600mg/day)	200mg/day: 107 400mg/day: 108 600mg/day: 106	97	21 weeks
SP754/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (400 and 600mg/day)	400mg/day: 204 600mg/day: 97	104	21 weeks
SP755/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200 and 400mg/day)	200mg/day: 163 400mg/day: 159	163	18 weeks
Total	200mg/day: 270 400mg/day: 471 600mg/day: 203 Total: 944	364	

LCM=lacosamide

^a Because of audit findings suggesting noncompliance with the SP667 protocol, all 3 randomized and treated subjects at Site 12 were removed from the Safety Set (SS). As a result, 418 subjects were included in the SS.

^b All 3 trials had a 12-week Maintenance Phase.

The Sponsor describes 4 additional trials as supportive for the claim of efficacy. All supportive trials were uncontrolled and open-label studies whose data principally contributed to the safety database.

As noted above all three studies were of a similar design. They were all multi-institutional, double-blind, placebo-control, parallel cohort, adjunctive treatment studies in adults (>16 years old) with partial epilepsy (simple partial, complex partial and partial secondarily generalized). Trials were rather similar in design. The schedule of evaluations was similar across studies. Initial screening was performed on the first day of the baseline period. Seizure diaries were provided at this time and patients were instructed in their use. Patients then entered an 8 week baseline phase. They were randomized following this period if they continued to fulfill inclusion/exclusion criteria (there was a requirement for a minimal seizure frequency during this period). Inclusion/exclusion criteria were relatively routine for this class of study. Patients entered the treatment phase following randomization which consisted of a titration and a maintenance period. The titration period in SP 667 and SP754 were of 6 weeks duration and that of SP 755 were of 4 weeks in duration. All titrations proceeded at the rate of 100 mg qD (in a BID divided dose) every week. All doses were administered in an evenly divided BID regimen. Subjects who could not tolerate their final dose were permitted one back step of 100 mg/day during the titration period. The titration period was followed by a 12 week maintenance period in all studies. No back titration was permitted during this period. After the study was completed the patients were given a choice to continue on lacosamide in an open label study at a dose of 200 mg/day. If they so decided, they would undergo a blind transition period where they were titrated to a dose of 200 mg/day. If they declined they would undergo a down-titration that would proceed at a rate of 200 mg/day every week.

The primary endpoint required by the FDA and EMEA were different, but were based upon the standards typically used for those agencies. These different primary endpoints were agreed upon by the FDA in an end of phase 2 meeting. The FDA assigned endpoint was the change in partial seizure frequency per 28 days from baseline to the maintenance period. Seizure frequency (SF) was calculated by the formula: $SF = (\text{Number of Seizures}) \times (28 / D)$, where, D is the number of days. The manner that baseline seizure frequency was calculated was different between the initial dose ranging study, SP667 and the two phase 3 studies, SP754 and SP755. These differences were protocol driven. Thus, for SP667 baseline values were based upon the complete 8 week baseline period, but for SP754 and SP755 baseline value was based upon the last 56 days of the baseline period. For patients who discontinued during maintenance phase an LOCF frequency value was calculated. If the patient dropped out prior to entering the maintenance period an LOCF value for the titration period was calculated.

Statistical analysis of the seizure frequency change was performed on the log-transformed seizure frequency¹ based on an ANCOVA model with terms for treatment and pooled site. Log-transformed average seizure frequency during the Baseline Phase was used as the covariate. This maneuver is rather commonly used in these studies to normalize such data. The seizure frequency between treatment and placebo was compared using LS means. Percentage reduction over placebo was calculated by: $100 \times (1 - \exp[\text{LSM Treatment} - \text{LSM Placebo}])$, where LSM is the least squares mean from the analysis. This analysis was previously described in the Sponsor's statistical analysis plans. The log transformation allows a normalization of data. Criteria for statistical significance were $P \leq 0.05$.

¹ Log transformation was based upon the formula $\ln(x+1)$, where x is equal to the seizure frequency.

The primary outcome described above and its method of analysis is similar to those used for the approval of a number of drugs. The single difference is the fact that only the maintenance period as opposed to the full treatment (titration plus maintenance period) was used to calculate post-treatment seizures. More commonly the titration and maintenance are included in this calculation. Off note, this analysis was performed as a secondary endpoint analysis.

A number of secondary analyses were performed including, but not limited to: 50 percent responder to Maintenance Phases (the EMEA primary endpoint), change in partial seizure frequency per 28 days from Baseline to the Treatment Phase (ie, Titration + Maintenance Phases: a more typical for the primary endpoint as noted above), other responder rates ($\geq 75\%$, $\geq 50\%$ and $\geq 25\%$), Proportion of seizure-free days during the Maintenance Phase for subjects who entered the Maintenance Phase, proportion of subjects who achieved "seizure-free status" during the Maintenance Phase for subjects who completed the Maintenance Phase, Response to treatment by seizure type, Clinical Global Impression of Change, Quality of Life in Epilepsy-31.

All 3 studies underwent changes in sample size during their implementation. One had a decrease in sample size because of unexpectedly fewer dropouts and 2 had an increase in sample size because a repeat calculation indicated that the original determination of standard deviation and effect size, based upon another anticonvulsant study, was incorrect. These changes were made without unblinding and, according to the statistics reviewer, Dr. Massie, are justified.

Drop out rate during the trial differed slightly between placebo and the 200 mg/day dose, with the ranges in trials being 11% to 14% and 17 to 21% for placebo and lacosamide (200 mg/day), respectively. That for the 400 mg dose showed a larger difference with 11% to 14% versus 21 to 26% for placebo versus drug, respectively. High drop out rates were observed for the 600 mg/day with a range of 11 to 13% versus 33% to 42% for placebo and drug, respectively. Most drop outs in the drug treatment groups resulted from adverse events (see safety).

Subject demographics were comparable across treatment groups. The mean age amongst all studies was approximately 40 years old. Most patients were categorized as Caucasian with "black" making up only 2 to 6 percent of the studied population. Seizure types were also well distributed across treatment groups in all studies. Complex partial and partial secondary generalized were more common than simple partial seizures. The most common concomitant AED were carbamazepine (35.2% subjects), followed by lamotrigine (31.2%) and levetiracetam (29.0% subjects). The majority of patients were on 2 concomitant medications.

The results of the primary endpoint (percent change from baseline to maintenance) over placebo is presented for all three trials in the table below. The percent reduction from placebo is based upon logarithmically transformed data, but is actually very close to arithmetic percent changes. From these data it is apparent that both the 400 and 600 mg daily dose resulted in a significant reduction in seizures from placebo. This was also the conclusion of the Pharmacometrics reviewer, by Dr. Zhu, who noted that in a nonlinear regression least squares modeling response curve started to flatten out beyond the median exposure of 400 mg dose. From the data below, and as per Dr Zhu's analysis, there is no obvious additional therapeutic benefit

observed for the 600 mg/day as compared to 400 mg/day. In the 2 studies that examined the 200 mg/day dose a therapeutic trend was noted. This effect, however, was statistically significant for only one study. This reviewer believes that the 200 mg dose is therapeutic in some patients but may on average have a smaller effect resulting in an inconsistent statistical finding between both studies.

Trial/Comparison of LCM to placebo	% reduction over placebo	P-value	95% CI for % reduction over placebo
SP667			
LCM 200mg/day (N=107)	14.6%	0.1010	(-3.2, 29.4)
LCM 400mg/day (N=107)	28.4%	0.0023**	(11.3, 42.2)
LCM 600mg/day (N=105)	21.3%	0.0084**	(6.0, 34.1)
SP754			
LCM 400mg/day (N=201)	21.6%	0.0078**	(6.3, 34.5)
LCM 600mg/day (N=97)	24.6%	0.0061**	(7.8, 38.3)
SP755			
LCM 200mg/day (N=160)	14.4%	0.0223*	(2.2, 25.1)
LCM 400mg/day (N=158)	15.0%	0.0325*	(1.4, 26.8)

As noted above, the change in frequency from baseline to maintenance phase is not a typical endpoint. The more conventional endpoint of change from baseline to the experimental period (titration + maintenance) was examined as a secondary endpoint. Data from this analysis is presented below, and differs little from the primary endpoint. This serves as an excellent sensitivity analysis to the Sponsor's endpoint.

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Trial/Comparison of LCM to placebo	% reduction over placebo	P-value	95% CI for % reduction over placebo
SP667			
LCM 200mg/day (N=107)	10.8%	0.1650	(-4.9, 24.2)
LCM 400mg/day (N=107)	20.3%	0.0100*	(5.3, 32.9)
LCM 600mg/day (N=105)	21.3%	0.0033**	(7.8, 32.8)
SP754			
LCM 400mg/day (N=201)	19.0%	0.0043**	(6.4, 29.9)
LCM 600mg/day (N=97)	19.9%	0.0086**	(5.5, 32.1)
SP755			
LCM 200mg/day (N=160)	12.3%	0.0294*	(1.3, 22.1)
LCM 400mg/day (N=158)	15.1%	0.0164*	(3.0, 25.7)

The statistical significance of secondary endpoint, 50% responder rate (the EMEA primary analysis), exhibited results identical, in terms of which doses were statically significant from placebo, to the primary endpoints in the FDA analysis. Other secondary endpoints, dealing with numerical alterations is seizure rates exhibited statistical significant effects as compared to placebo or trended in the correct direction. The Global evaluations trended toward improvement in the 400 and 600mg doses. Effects of quality of life measures were small and inconsistent.

Another secondary endpoint was the reduction in seizures by seizure type (i.e. simple partial, complex partial and partial secondarily generalized). These data were only presented using descriptive statistics. There was likely insufficient power to draw definitive conclusions. In general both complex partial seizures and partial secondarily generalized all trended in a direction that suggested a therapeutic effect. The effect on simple partial was more inconsistent. No definitive trend was observed, with some studies showing decreases and others increases in seizure activity of drug over placebo. Nothing can be definitively drawn from these data as these seizures were the least frequently observed and the data would be prone to a sampling error.

Dr Massie, the statistical reviewer, confirmed the Sponsor's analysis for all performed studies. Dr Massie also noted that "overall, there was no compelling evidence that the treatment effect varied by gender." He also determined that there was no obvious age dependency for the age range studied (16 to 71 years of age). Considering the limitation of the small size of the non-Caucasian sample size, it was concluded that no obvious racial differences in effect was observed.

This reviewer concludes that both the 200, 400 mg/day dose (divided bid) impart a therapeutic effect in adjunctive treatment of partial seizures. The 600mg/day dose does not appear, on average, to be superior to the 400 mg dose. The 200 mg dose may, on average, appears to

have a smaller therapeutic benefit. However, on an individual basis, dosing will have to be adjusted not only based upon therapeutic benefit but also on tolerability. As will be discussed in the safety section, the 600 mg dose was poorly tolerated.

The Sponsor intends to market _____ formulations of lacosamide: tablets, intravenous solution _____ All pivotal studies were performed using a tablet formulation. Conclusions for efficacy for other formulations are based upon studies demonstrating equivalent bioavailability between those formulations and the tablet formulation. _____

_____ Bioequivalence was also demonstrated with the iv infusion solution when such infusions were performed over 30 and 60 minutes. Shorter infusions resulted in higher Cmax values in the formal bioequivalence studies (see Pharmacokinetic section above).

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8. Safety

Two separate major safety reviews were performed because of the two independent proposed indications: one by Dr. Villalba, for its anticonvulsant indication, and the other by Dr Pokrovnichka, for the neuropathic pain indication. In addition cardiology was consulted, not to only comment on QT studies, but also on other cardiac issues described below. A CSS review is also included with scheduling recommendations (see below). Although the Sponsor has simultaneously submitted an application to the European Union for approval, there is no foreign marketing experience.

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Dr Villalba principally reviewed phase 1 to phase 3 studies relevant for the epilepsy indication. Dr Vilalba also reviewed safety data from the studies using the _____ iv as well as the tablet formualtions. Dr Pokrovnichka's review concentrated on the tablet as it applied to the indication for diabetic neuropathic pain (DNP). The application includes a total of 4012 unique adult subjects exposed to LCM (including all routes of administration, all indications and healthy volunteers). Of these, 1338 subjects were in the partial-onset seizure studies (1327 subjects from studies with the oral tablet) and 2001 subjects in the neuropathic pain studies. The exposures in the epilepsy studies where of sufficient dosage and duration and met ICH guidelines. The database included both double-blinded placebo-controlled and open label studies. Of the subjects with partial-onset seizures exposed to oral LCM, 199 subjects also received IV LCM in Phase 2/3 trials. Intravenous studies were generally shorter in duration and either open label or were designed for comparison to the tablet formulation. Assuming similar PK and no obvious local issues of irritation, while these studies use a much smaller database, they should be considered sufficient for a determination of additional risks over the oral formulations.

In her review, Dr. Villalba distinguishes two phase 2/3 safety pools: EP S1 which includes patients from *all 3 placebo-controlled, double-blinded* studies and EP S2 which included all

patients receiving drug product in *all* phase 2/3 studies. These will be referred to below.

Deaths

No deaths were observed in phase 1 trials. A total of 9 deaths were observed in the epilepsy phase 2/3 studies. Eight of these nine occurred during open label studies. No deaths were observed in the placebo group. This leaves a comparison of 1 in drug Vs 0 in placebo in the EP S1 population. It should be remembered that the placebo population was third the size of those who received drug in the EP S1 population. These numbers are insufficient to draw any conclusions regarding an excess of drug-induced deaths. Four deaths were believed to be result of Sudden Unexpected Death in Epilepsy (SUDEP). Calculations by Dr. Villalba revealed no excess over that which would be expected in the studied population. On death, in a patient with a history of depression, was attributed to a completed suicide. None of the other deaths followed a particular pattern that can be easily attributed to a common cause.

There were a total of 15 deaths in patients on lacosamide in the DNP population. Four of these (4/1023) were in the controlled studies with none (0/291) in the placebo group. Of the 15 total deaths a majority (8) were cardiac-related (ventricular fibrillation, myocardial infarction, heart failure (n=2), myocarditis, cardiac arrest (n=2) and sudden death). Such a number is not unexpected for a patient population with diabetes and with many patients also having a history of hypertension, coronary artery disease, cerebrovascular disease, and/or peripheral vascular disease. One of the cardiac deaths was noted to include myocarditis/toxic hepatitis which occurred following completion of LCM treatment. This case may represent a suspected case of multiorgan hypersensitivity and will be discussed below. Three of the cardiac deaths however were observed in the placebo control studies, which may be suggestive of a potential cardiac related signal. However, the numbers of patients exposed in the placebo population is substantially lower than that in the drug population. These data however must be viewed against the background of other cardiac events, which will be discussed below. All but two of the remainder of deaths (5) was from a variety of cancers. No one type stood out. One case of a completed suicide was observed. Suicide and suicide ideation will be discussed below.

Other Serious Adverse Events

Comparison by Dr Villalba of rates of serious adverse events in the EP S1 epilepsy population revealed a higher rate amongst patients on drug then on placebo: :i.e. 6.5% and 3.8%, respectively. No obvious dose response was observed for these grouped rates. The most frequent reported serious adverse events, classified by system organ class (SOC), were Nervous Systems Disorders (1.6% in placebo and 2.1% in lacosamide in the EP S1 pool). The most frequent single preferred term was "convulsions" with 0.8 in placebo and 0.8 in the lacosamide group. While it may be unexpected that these rates are the same, when you lump all other epilepsy preferred terms (e.g. epilepsy, complex partial seizures, etc) you observe a comparison of 1.7% Vs 1.3%, in placebo and drug. Other, non-convulsive serious CNS adverse events observed which were more common in drug as compared to placebo groups, were dizziness, nystagmus, coordination abnormal, loss of consciousness and tremor. No

placebo patients exhibited these vents. Except for dizziness and nystagmus which were observed in 0.3% and 0.2% of patients, respectively, all events occurred in only 0.1% of patients (1 patients). Although the numbers of some of these events are low, many of these events are common with other anticonvulsants, with CNS adverse events limiting the dose that can be used. These are very common adverse events reactions associated with this class of anticonvulsants.

The next most frequent SAEs in the EP S1 population for patients with epilepsy were in the Psychiatric disorders SOC (0.7% for LCM and 0 for placebo-treated patients). Psychiatric events included preferred terms such as hallucinations, epileptic psychosis, psychotic disorders, completed suicide (see above), suicide attempt and insomnia. As Dr Villalba points out, the risk of such events are commonly seen in patients with epilepsy and although occurred in small numbers were only observed in patients receiving lacosamide. Dr. Villalba consequently reviewed each case, many of which an alternative explanation could be found (e.g. previous history of similar behavior). Dr Villalba suggested that the low numbers and perhaps other explainable cases undermine a casual attribution to drug use. This CDTL agrees.

The next most common SAEs in the EP S1 population for patients with epilepsy included GI disorders systems (0.6% for LCM and 0.3% for placebo-treated patients, respectively) and infections (0.5% for LCM and 0.3% for placebo-treated patients, respectively). These events were not thought to be related to treatment.

Examination of SAEs in the EP S2 pool for the epilepsy population did not reveal much additional information. A high number of injuries from fracture were noted (16 patients) and were possibly thought to be related to dizziness and ataxia, which appear to be drug related.

Serious adverse events in the DPN controlled population were similar to that reported for the epilepsy population: i.e. 6.6% (68/1023) of subjects who received lacosamide and 4.8% (14/291) of subjects who received placebo. The highest rate in the controlled database, by SOC, of serous adverse events was under the classification of cardiac disorders. There was actually a greater percent rate in placebo then in the lacosamide group (1.7% vs. 1.3%, respectively). As noted in Dr. Yasuda's, safety team leader's review, most of the cardiac conduction/rhythm abnormalities (atrial fibrillation, atrial flutter bradycardia, tachycardia etc) recorded as SAEs were reported from subjects treated with lacosamide. Serious cardiac events in the placebo group included conduction abnormalities limited to bundle branch clock but also experienced ischemia and failure. Nonetheless, it is difficult to conclude anything from this particular data in that such a population would be prone to cardiac problems and the numbers in the placebo group are rather small. As expected, and consistent with epilepsy data, the second most common SOC adverse events are under the rubric of "Nervous System Disorders" with 0.7% vs. 1.0% in placebo and lacosamide groups, respectively. There is, however, only a marginally greater rate in the lacosamide group. The common Nervous System Events included loss of consciousness, dizziness and balance disorder. This reviewer believes that generally loss of consciousness should be considered cardiac in origin unless there are positive neurologic findings. The Sponsor's categorization as neurological appears to be based upon the absence of evidence of cause, both cardiac and neurologic. This event may be better

categorized as cardiac in origin. Two patients in the controlled studies who experienced loss of consciousness as a serious event in the controlled studies were in the lacosamide treatment group, no patients were in the placebo group. A complete analysis of syncope will be discussed in greater detail below.

One serious cardiac event was noted in iv studies. Thus a 48 year old male suffered bradycardia, with heart rates down to 26 bpm, (BP 100/60) 7 minutes into infusion of 150 mg over a 15 minute period. This patient was on a beta blocker for hypertension. The patient had previously taken this dose orally with no problems. Two cardiologists, consulted by the Sponsor, evaluated the case and diagnosed it as either bradycardia with functional escape, or AV block with sinus exit block. There apparently was problematic movement artifact. Dr. Stephen Grant, the FDA cardiologist who evaluated this case, believes it is likely a vasovagal reaction. Drs Villalba and Yasuda believe that a relationship between the infusion of the drug and the profound bradycardia is biologically plausible. This reviewer agrees with the latter conclusion, but would also add that this was rapid infusion (15 min), as compared to the other tested rates (30 and 60 min), which resulted in somewhat higher concentrations (see Clinical Pharmacology). This, along with PK studies, indicates to this reviewer that rates of 30 and 60, _____ minutes should be the labeled.

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One last serious case that is of interest is a single case of hepatitis associated with nephritis that occurred 12 days after final exposure. LFTs achieved levels of 10 to 30 times the upper limits of normal and proteinuria was noted. No bilirubin was documented at the time of the event. Viral causes of hepatitis were ruled out. Both Dr Villalba and Yasuda believe that considering the multiple organ involvement this may represent a multiorgan hypersensitivity seen with other anticonvulsants (see below).

Discontinuations

A very obvious dose dependent discontinuation rate was observed for discontinuations resulting from adverse events in the EP S1 pool with 8.2%, 10.7%, 17.1%, and 34.7% such discontinuations in the placebo, LCM 200mg/day, LCM 400mg/day, and LCM 600mg/day groups, respectively. Most discontinuations occurred during the titration phase. Like serious events, the most common cause of discontinuations were grouped under the SOC of nervous system disorders, with 2.5% withdrawing in the placebo group and 9.9% in the combined lacosamide groups for which there was also a dosage dependency. The most common nervous SOC, by preferred term, in descending order, were dizziness, ataxia, convulsion, and tremor. Except for convulsions, drug treated groups experienced greater rates than the placebo treated groups and there appeared to be a dose dependency. Dizziness and ataxia are rather common for this class of agents (i.e. sodium blocking anticonvulsants).

Discontinuations classified as CNS SOC in the epilepsy EP S1 pool was followed by GI disorders (3.2% drug Vs 0.8% placebo), general, Eye disorders (1.7% Vs 0.3% placebo), Psychiatric (1.6 % drug Vs 0%) and Ear and labyrinth disorders (1.4% drug Vs 1.0% placebo). Off interest no patients discontinued for reasons of cardiac disorders in placebo (0 of 364), but 0.4%(4 of 944 patients) did so in the lacosamide group. The numbers from a cardiac signal may be too small, but this will be further discussed below. The most common contributing adverse

event preferred term associated with GI was vomiting and nausea, contributing to over 90% of reporting. These symptoms are not uncommon for this class of agents (i.e. sodium blocking anticonvulsants). Visual preferred terms that contributed to the SOC were predominately diplopia and blurred vision, whereas vertigo and vestibular disorders contributed to all Ear and labyrinth disorders. Similar adverse events have been reported for other agents in this class of anticonvulsants. The overall rate of dropouts in EP S2 was similar to EP S1. Similar events led to drop out in the DNP database. Syncope led to dropout in both the EP and DNP populations and will be discussed below.

Common Adverse Events

A larger percent of patients experienced adverse events in the drug as compared to the placebo population in the EP S1 population (81% in drug Vs 65% in placebo). Common adverse events, greater in drug than placebo, were of similar nature as those reported that lead to discontinuations: e.g. dizziness ataxia, nausea, vomiting, diplopia, vision blurred, etc. Fatigue somnolence, headache and memory impairment was also noted and occurred more frequently in drug than placebo. Adverse events generally followed a relatively obvious dose dependency. Events occurred in both, the titration and maintenance phase, but they were more frequent in the titration phase, particularly for those that were clearly dose related. Dr. Yasuda, safety team leader, noted that common adverse events in the DNP population were similar to the epilepsy population.

Laboratory Findings

Standard blood chemistries, hematology and urinalyses were collected throughout the studies. Dr Villalba notes that "evaluation of routine chemistry, hematology laboratory measurements and urinalyses did not reveal major issues of clinical concern in patients with partial-onset seizures..." She, however, notes that there was a slightly greater rate of ALT elevations 2X ULN in the control database for low dose, but this was not observed for higher doses or for AST. In EP S1 population ALT/AST >3X ULN occurred in 0.7% on LCM Vs 0% on placebo, and was not associated with abnormal bilirubin. The elevations were reversible on withdrawal of LCM (although in 1 case the patient was lost to follow-up). Similar elevations of LFTs have been noted with other anticonvulsants. This CDTL believes that this can be labeled in the adverse event section (laboratories). No cases of liver failure were observed in either the epilepsy database or in the diabetic neuropathic pain population. Of note one patient was observed with markedly elevated LFTs associated with nephritis, which was interpreted as a multiorgan hypersensitivity and will be discussed below. One additional patient had a transient elevation of bilirubin associated with rash and mild eosinophilia. The bilirubin was elevated barely above the upper limit of normal and resolved within days of drug discontinuation. Because of the skin and eosinophila, Dr Villalba considered this as a potential multiorgan hypersensitivity response.

Vital signs

Dr Villalba notes that for study of tablets there was little or no effect on vital signs (SBP, DBP, heart rate, and weight), with therapeutic doses of LCM oral tablet in the epilepsy population.

While orthostatic changes were not measured in phase 2/3 studies, they were measured in the QTc study in healthy volunteers and there was no evidence of orthostatic hypotension in doses up to 800 mg/day.

Dr Villalba notes that in general the intravenous study design, presumably the lack of placebo control and small size, does not allow adequate safety comparisons with regard to vital signs. It is however noteworthy that 10% of patients receiving the 15-minute infusion and 2.5% of those receiving the 30-minute infusion presented at least one measurement of marked hypotension (SBP < 90 and drop \geq 20mmHg or DBP <50 and drop \geq 15 mmHg), perhaps suggesting an increased rate of hypotension with more rapid infusion. As noted above, there was a potential episode of arrhythmia, or vaso-vagal reaction with the more rapid infusion rates (15 minutes).

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Adverse Events of Interest

Cardiac Adverse Events

As noted above, cardiac conduction abnormalities were identified in the non-clinical program. Because of this the Sponsor was asked to specifically discuss and analyze cardiac adverse events. Consistent with this the formal thorough QT (TQT) study revealed a dose-dependent increase in PR interval was observed. The maximum mean changes in PR interval on Day 6 (steady-state), observed at 1 hour post-dose, were 6.3ms, 13.6ms, and 18.2ms for the placebo, lacosamide 400 mg and lacosamide 800mg groups, respectively. There was no evidence in this study of an effect on the QRS interval. As noted above these changes were not associated with changes in blood pressure. The TQT study demonstrated a shortening of the QTc. At Tmax on day 6, the mean change in QTcI from baseline for LCM 400 mg/day compared to placebo was -9.4 msec with an upper one-sided 95% CI of -4.2; for 800 mg/day the values were -7.4 and -3.3 msec, respectively. This CDTL reviewer is under the impression that this is likely related to the ability of this drug to block sodium channels and indeed this CDTL reviewer has seen other TQT studies with similar channel activity produce similar QT prolongation. The significance of this shortening is not well understood, although it is known that patients with genetic short QT syndromes are at risk of ventricular fibrillation (without Torsades) and sudden death. Moreover, according to the IRT review of the TQT study, adequate data upon which to base a recommendation regarding labeling for products that shorten the QT interval do not currently exist. There was no obvious signal for this in the database to indicate sudden death or ventricular fibrillation (other than appear to be explainable by SUDEP).

Dr. Villalba notes the percentage of patients with *any* potentially cardiac-related adverse event is 5.0% for lacosamide and 2.3% for placebo in EP S1. The difference was driven by a higher rate of rhythm and conduction disorders, mainly PR and QRS prolongation in the LCM group. There were 4 cases of first degree AV block in the LCM group (0.4%) vs 0% on placebo. Three subjects taking LCM presented conduction disorders that led to dropout (2 cases of bradycardia and 1 PR prolongation in a patient with sick sinus syndrome) in the EP S1 population. There were no cases of second degree AV block or serious arrhythmias in EP S1 or

EP S2 populations. In the DNP database, there was 1 case of second degree AV block in a patient with prolonged PR at baseline taking LCM 400 mg daily during the DNP open label studies, and an additional patient who had second degree AV block during telemetry monitoring after a syncopal episode during LCM titration with a dose of 600 mg. No QRS prolongation was observed in the DNP controlled database. In the placebo controlled studies in DNP there were 5 AEs of first degree AV block, 4 of atrial fibrillation, 3 of atrial flutter, and 1 nodal rhythm, all in the LCM treatment group. No such cases were observed in the placebo group.

The cases of PR prolongation and heart block are expected, based upon what is known about this drug's physiological effect. The reviewer of the Division of Cardio-Renal Products (DCRP) suggested that the increase in PR may result in clinically significant AV block and is particularly important in patients with pre-existing AV nodal disease and/or who are co-administered agents that block the AV node. DCRP recommends obtaining an ECG after LCM is titrated to steady state in such patients. They also suggested this effect may be potentiated in patients with myocardial injury (e.g. ischemia) because the associated increase in depolarization that may enhance sodium channel blockade. DCRP believes that patients with diabetes and/or cardiovascular disease may be at increased risk of atrial fibrillation and/or atrial flutter following treatment with LCM. These will be addressed in labeling. Dr Yasuda suggests that a REMS might be considered. It is, however, noteworthy that a number of other medications (e.g. beta blockers, calcium channel blockers) can produce similar PR interval changes.

This information should be included in the Warnings section of the label

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Syncope

Dr. Villalba noted that 11 cases of treatment emergent syncope/loss of consciousness were identified in the epilepsy population, three of them in the controlled phase (two on LCM and one on placebo). The difference in the placebo trials does not allow the conclusion of a signal. Nonetheless, Dr Villalba noted that 27 cases of syncope were identified in the neuropathic pain population, 13 of them during the controlled studies (all in the LCM treatment group) and 14 in the open label studies. Most cases of syncope in the development program occurred at LCM doses of 600 mg/day. Four subjects presented syncope during the phase 1 studies

. This suggested a signal for syncope, particularly in the neuropathic pain population. In one of the DNP cases, the patient had 2nd degree AV block identified with telemetry monitoring. This particular sensitivity to a potential cardiac event is consistent with DCRP's contention that injured cardiac tissue may be more prone to this drug's cardiac effect. Two cases had documented orthostatic hypotension on the same day of the event. Unfortunately most patients did not have ECGs performed or measurements of orthostatic blood pressure at the time of (or closely after) the syncope and consequently the mechanism is unclear. Based on the known effects of LCM in cardiac conduction, Dr. Villalba and Yasuda believe that an LCM-related cardiac cause for syncope cannot be ruled out. This CDTL agrees. In addition, Dr. Villalba suggests that if future clinical studies are performed, orthostatic changes in blood pressure should be measured, especially in patients who experience syncope or pre-syncope. In addition, both recommend that Holter monitoring should be considered in future clinical

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“myocarditis (toxic damage to the myocardium) and alcoholic intoxication and toxic damage of the liver.” However, investigator noted that the subject had no history of alcohol abuse. The date of onset of the toxic damage of the liver was unknown. Information received indicated that the actual date of the last dose of medication is unknown. This led Dr Villalba to conclude that, while the presentation of this syndrome after over one year of exposure is unusual, multiorgan hypersensitivity cannot be ruled out.

The Sponsor was also requested to search their clinical trial database to identify any other potential multiorgan hypersensitivity cases. Two cases were identified, which Dr. Vallbal believed may represent mild or aborted reactions. Many cases identified do not provide adequate information to draw any conclusions. Both cases involved rash and eosinophilia and elevated LFTs which resolved on drug discontinuation.

Based upon this information, both Dr Villalba and Yasuda believe that this syndrome should be described in the Warnings section. This reviewer agrees.

9. Advisory Committee Meeting

No AC is considered necessary.

10. Pediatrics

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_____ The Sponsor will be expected to pursue a pediatric indication. The study of pediatric patients over 1 month will be deferred and that under 1 month will be waived, as is the policy of this division.

11. Other Relevant Regulatory Issues

Financial Disclosure

The Sponsor has provided financial interest information for clinical investigators participating in studies included in this NDA. According to this, the \$25,000 threshold for “payments of other sorts” was not exceeded in the case of any investigator. Moreover, no clinical investigator participating in the covered studies has a proprietary interest in lacosamide. The Sponsor has also determined that no clinical investigator participating in the covered studies has a significant equity interest in Schwarz by using direct to investigator questionnaires.

Clinical Site Inspections

Of the 3 pivotal efficacy trials, DSI inspected 2 sites in protocols SP754 and SP755. With one exception no problem was identified and sites were found to be completely acceptable. One site in Croatia inspected for protocol SP755 revealed a single protocol violation. Thus, one patient was maintained in the protocol at the studied dose, although he was initially tapered with an intent to withdraw the medication due too that adverse event. This CDTL does not believe this single event should adversely effect the conclusions of this study. Inspections of clinical pharmacology studies were performed and study conduct was found to be acceptable (see above).

CSS Scheduling

After evaluating both non-clinical and clinical abuse Data, CSS concluded that the present NME should be granted a Schedule IV. Data that led to this conclusion included: 1) Positive subjective responses similar to alprazolam, 2) high rate of the reporting of euphoria in phase 1 studies, 3) Animal discrimination studies revealing partial generalization to abused substances. No physical dependence or animal self administration was observed nor was there any receptor binding data that would indicate this drug belongs to a class of commonly abused substances. The division met with the Sponsor on 9/29/08 where this issue was discussed.

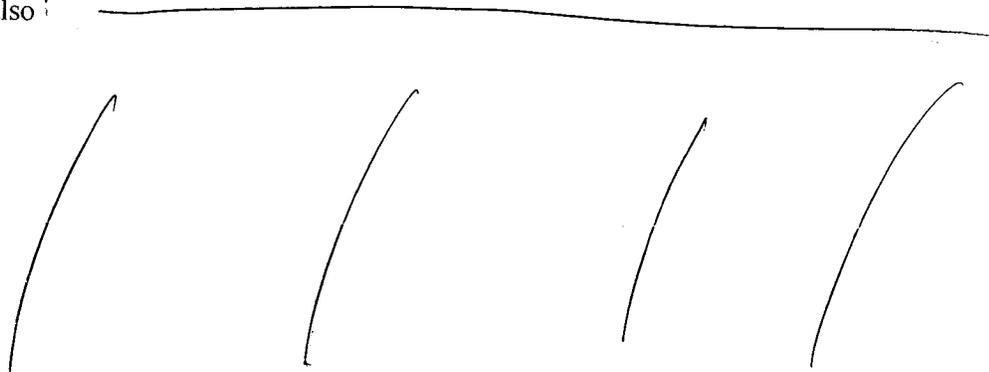
Division of Medication Error Prevention (DMEP) Review

The Division of Medication Error Prevention found the proprietary name "Vimpat" acceptable. That division does recommend that the following informtion be conveyed to the Sponsor:

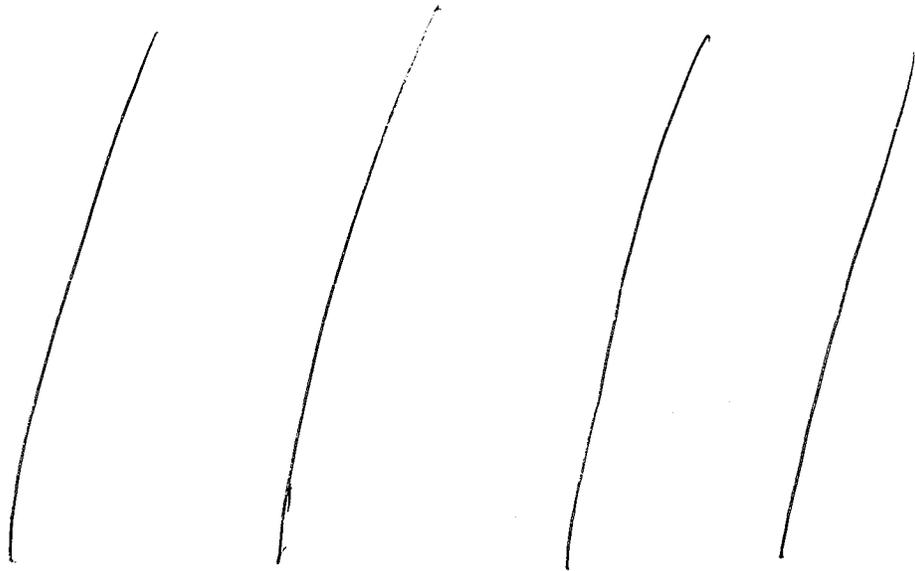
"Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained from a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity."

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DMEP also :



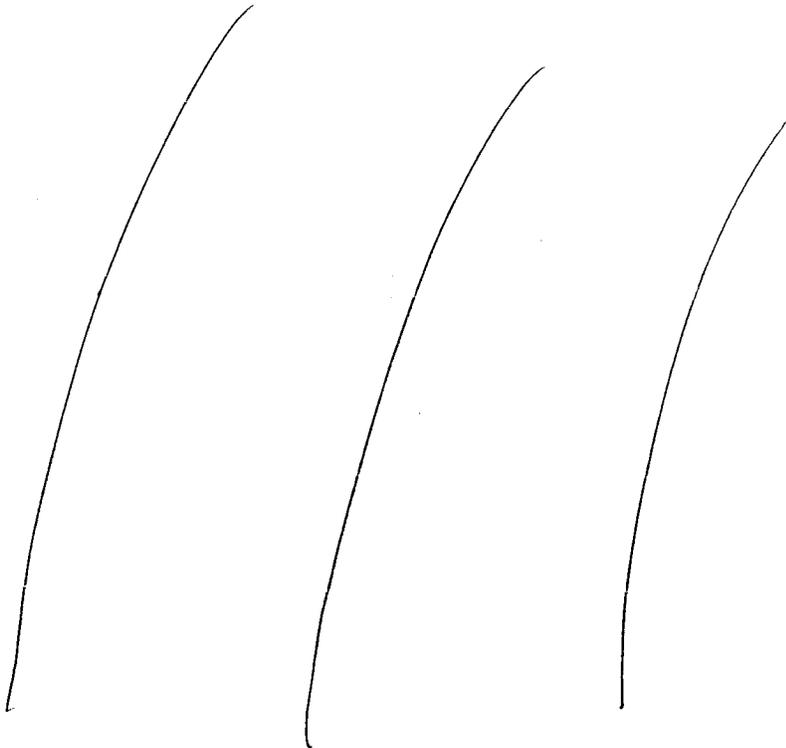
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OSE Review Label and Labeling Risk Assessment found

OSE had the following recommendations to reduce medication errors:

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12. Labeling

The reader is referred to the label that is included in the approval letter.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The CDTL recommends approval for Tablets (22253) and iv solution (22254).

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Risk Benefit Assessment

There exists general agreement within the team that risk benefit ratio indicates that this drug should be approved.

Recommendation for Postmarketing Risk Management Activities

There is general agreement in the team that a MedGuide should be distributed for the issue of suicidal ideation, as it will be for other anticonvulsant drugs.

There is some difference in opinion regarding the issue of a MedGuide for Multiorgan hypersensitivity. Dr Villabla, in her review, notes that "MedGuide may help reduce the risk of serious multiorgan hypersensitivity reactions further." It should, however, be noted that this syndrome has been identified in with many anticonvulsants (indeed it was once referred to as anticonvulsant hypesentivity syndrome) and while it is included in the label of these agents no MedGuide had been adapted. Dr Villabla notes in her review that there is no way, at the present time, to determine if this syndrome is more or less common with this agent as compared to others. For these reasons this CDTL feels a MedGuide is not absolutely necessary. Meetings with Dr. Katz and Dr Temple indicate they concur.

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_____ and labeling in the Warnings section is recommended. _____

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Pediatric(PREA)

Cross Discipline Team Leader Review

The study of pediatric patients over 1 month will be deferred and that under 1 month will be waived.

Recommended Comments to Applicant

These are noted in the body of this review above. The reader should also examine the letter, which this reviewer concurs with.

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/s/

Norman Hershkowitz
10/28/2008 12:51:46 PM
MEDICAL OFFICER