CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202810Orig1s000

SUMMARY REVIEW

MEMORANDUM

DATE: October 13, 2012

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 202810

SUBJECT: Action Memo for NDA 202810, for the use of Oxcarbazepine Extended Release Tablets as adjunctive treatment of partial seizures in patients ages 6 years and above

NDA 202810, for the use of Oxcarbazepine Extended Release Tablets as adjunctive treatment of partial seizures in patients ages (b)(4) years and above, was submitted by Supernus Pharmaceuticals, Inc., on 12/19/11. This application was submitted under Section 505(b)(2), referencing NDAs for Trileptal (oxcarbazepine) immediate release tablets and oral suspension. Trileptal is approved for mono-and adjunctive therapy for partial seizures in adults, and as adjunctive therapy for partial seizures in pediatric patients ages 2 years and above, and as monotherapy for partial seizures in pediatric patients ages 4 years and above.

Supernus has submitted the results of a single controlled trial in adults, and pharmacokinetic (PK) data in pediatric patients ages 4-16 years. In addition, they have submitted CMC and biopharmaceutics data. The application has been reviewed by Drs. Julie Neshiewat and Loretta Holmes, Division of Medication Error Prevention and Analysis (DMEPA), Sharon Williams, Division of Medical Policy Programs, Dr. Prafull Shiromani, Office of New Drug Quality Assessment (ONDQA), Dr. Sandra Suarez Sharp, ONDQA, Biopharmaceutics, Dr. Antoine El-Hage, Office of Scientific Investigations, Drs. Kofi Kumi and Satjit Brar, Office of Clinical Pharmacology, Dr. Edward Fisher, pharmacology reviewer, Dr. Ohidul Siddiqui, statistician, Dr. Steven Dinsmore, medical reviewer, and Dr. Norman Hershkowitz, neurology team leader and Cross-Discipline Team Leader (CDTL). The review team recommends that the application be approved. In this memo, I will briefly review the pertinent findings, and offer the rationale for the Division's action.

Effectiveness

As noted above, the sponsor has conducted and submitted the results of a single randomized controlled trial in adults (ages 18-65) with partial seizures. In this trial, patients were randomized to either placebo or oxcarbazepine 1200 mg or 2400 mg/day, given once a day. They entered a 4 week titration phase beginning with a daily dose of 600 mg (a dose of 1200 mg was reached at the

end of Week1 of titration, and the 2400 mg dose was reached at the end of Week 3), followed by a 12 week Maintenance Phase.

The primary outcome in this study was the median percent change in 28 day seizure frequency, using the standard modified intent-to-treat population (mITT).

Secondary outcomes included comparisons of the Seizure frequency during the Maintenance Phase only, Responder Rate (defined as a decrease of at least 50% in seizure frequency compared to baseline), Seizure-free rates, and Seizure-free rates during the Maintenance Phase only.

Results

A total of 369 patients were randomized to treatment in 88 sites in 8 countries (Bulgaria, Canada, Croatia, Mexico, Poland, Romania, Russia, and US). The following table displays the disposition of patients in the study:

	Placebo	Oxc 1200	Oxc 2400
Randomized (ITT)	121	122	123
Completed	79%	67%	58%
Discontinued Due to			
Adverse event	8%	33%	42%
Withdrew consent	5%	8%	9%

The following chart displays the results of the primary analysis of Median percent Change from Baseline in 28 Day Seizure Frequency:

	Placebo	Oxc 1200	Oxc 2400
Baseline			
Mean	27.6	18.5	37.4
Median	7	6	6
Change from Baseline			
Mean	-15.4	-29.1	-38
Median	-29	-38.2	-43
P-value		0.08	0.003

The following results for the Median Percent Change from Baseline in 28 day seizure frequency are presented by region: North America (Canada, US, Mexico) and non-North America:

	Placebo	Oxc 1200 (p)	Oxc 2400 (p)
Change from Baseline			
Median			
NA	-13.3	-34.5 (0.02)	-52.6 (0.006)
Non-NA	-33.2	-38.4 (0.6)	-41.2 (0.1)

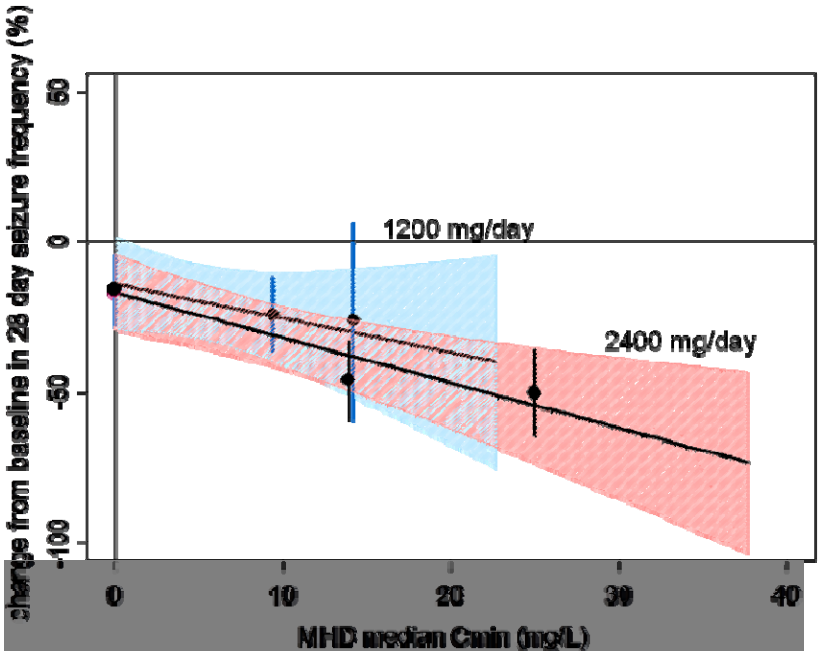
Analyses of the secondary outcomes generally show similar responses, with statistically significant and numerical, but not statistically significant, differences between the 2400 and 1200 mg doses and placebo, respectively.

Doses of 600-2400 mg/day (given as twice a day dosing) of immediate release oxcarbazepine are effective. There is a dose response, but the recommended daily dose is 1200 mg because many patients were not able to tolerate the 2400 mg daily dosing. When oxcarbazepine is given orally, it is almost completely converted to MHD, the active circulating moiety. The following chart displays the ER/IR ratio of MHD in plasma (with 90% CI) when equivalent daily doses of oxcarbamazepine ER and IR are given:

AUC (0-24)	80.8 (77.5-84.3%)
Cmax,ss	80.8 (77-84.9%)
Cmin,ss	83.7 (78.8-88.9%)

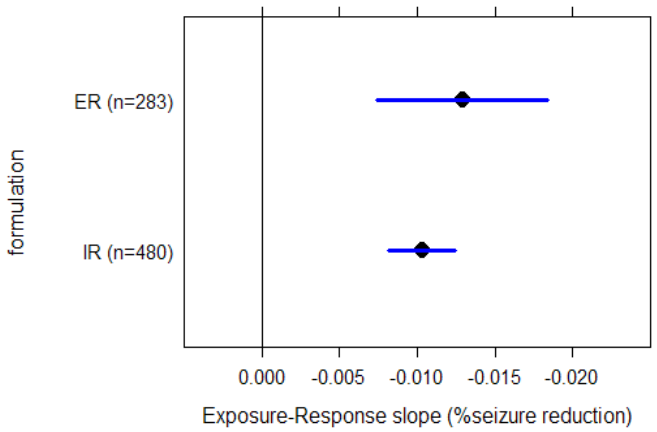
Given what is known about the effective dose range with IR oxcarbazepine and the results of the clinical trial described above (where the 1200 mg dose did not reach statistical significance compared to placebo in the primary analysis), Dr. Brar undertook various analyses of the concentration-effect relationships of the ER and IR formulations of oxcarbazepine.

Of particular interest here, Dr. Brar has determined that the PK-PD relationships for both the 1200 mg and 2400 mg doses with oxcarbazepine ER are essentially the same, as can be seen in Dr. Brar's Figure 2, Page 5 of his review:

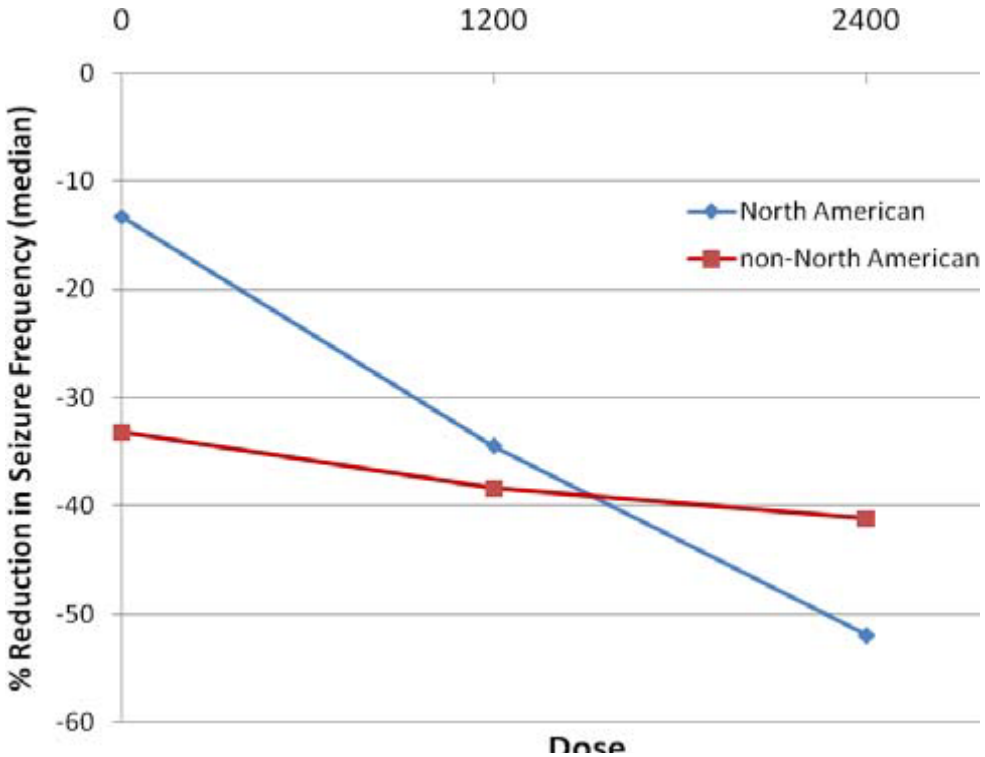


Note: For exposure-response, solid symbols and bars represent the mean and 95% confidence interval of change from baseline in 28-day seizure frequency for each MHD concentration quantile. The solid line represents the mean prediction from the linear relationship and its corresponding 95% confidence interval for the 1200 mg/day group (blue shaded region) and 2400 mg/day group (red shaded region).

Further, he has determined that the concentration-response relationship for the oxcarbazepine ER and IR formulations are also essentially identical, as seen in his Figure 7, page 14 of his review:



Finally, he describes the concentration-response relationships for the North American and non-North American site (Figure 5, page 45 of his review):

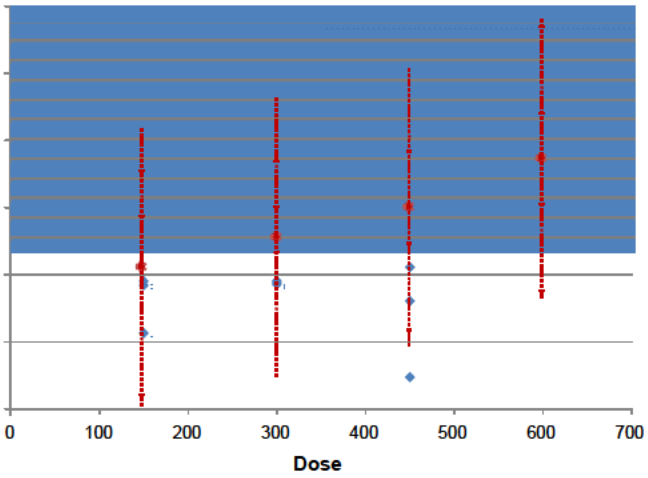


Pediatrics

The sponsor of the current application proposes that the ER formulation be approved in patients down to the age of (b)(4) years. As noted above, immediate release oxcarbazepine is approved for use as adjunctive therapy for partial seizures down to the age of 2 years. Patients below the age of 18 years old were not included in the controlled trial.

In order to consider whether or not he ER formulation is effective in pediatric patients (and, if so, what the effective dose range is), Dr. Brar, has examined the concentration- (and dose-) response in the pediatric population.

As described earlier, the sponsor performed a pharmacokinetic study in 17 pediatric patients ages 4-16, examining plasma MHD concentrations resulting from doses of 150, 300, 450, and 600 mg. Simulations were then performed to determine plasma levels that would result in adults given those same doses. The following graphic displays a comparison of the derived plasma MHD Cmin levels expected to occur in adults at these doses with the actual levels occurring in pediatric patients given these doses (with ranges):



It is clear that the levels achieved in adults at a given dose are comparable to those achieved in the pediatric patients. Given that we know that the concentration-response relationships for the treatment of partial seizures are the same in both adults and pediatric patients (based on previously performed analyses of adjunctive therapy data for Trileptal, which served as part of the basis for the approval of pediatric monotherapy for that drug), it is clear that dosing recommendations can be provided for pediatric use for the ER formulation (see Dr. Brar's review, page 49, Table 3 for specific dosing recommendations).

Safety

Safety data has been submitted for 950 unique individuals who have received at least one dose of oxcarbazepine ER. A total of 569 subjects received at least one dose of 1200 mg/day, with 99 patients receiving this dose for between 3-6 months, and 92 patients receiving this dose for between 6-18 months. A total of 128 patients received a dose of 2400 mg/day, with 48 patients receiving this dose for greater than 3 months.

No new safety signals emerged in this database that are not already known to occur with immediate release oxcarbazepine. However, it is instructive to compare the rates of common adverse events with the ER product and the IR product at equivalent daily doses, as seen in the following chart:

	1200 IR	2400 IR	Pla	1200 ER	2400 ER	Pla
Event (%)						
Dizziness	32	49	13	20	41	15
Diplopia	30	40	5	10	13	4
Vomiting	25	36	5	6	15	9
Nausea	25	29	10	12	12	12
Somnolence	28	36	12	12	14	9
Ataxia	17	31	5	3	1	1
Nystagmus	20	26	5	3	3	1
Gait Abnl	10	17	1	3	0	1
Vertigo	12	15	2	-	-	-

It is clear that, in general, the incidence of common adverse events is considerably lower at a given dose with the ER as compared to the IR formulation.

Comments

The sponsor has submitted the results of a single controlled trial of oxcarbazepine ER comparing the effectiveness of single daily doses of 1200 mg, 2400 mg, and placebo as adjunctive therapy in patients with partial seizures. The study clearly demonstrates the effectiveness of the 2400 mg dose, though the 1200 mg-placebo contrast did not reach statistical significance. However, concentration-response relationships of the 1200 mg and 2400 mg/day doses are the same, and the concentration-response relationships of the ER and IR formulations are the same. Therefore, it is reasonable to conclude that the 1200 mg/day dose of the ER formulation is effective (it is worth noting that the placebo response in this study was considerably greater than in the !R study; -29% and -8% median % change in seizure frequency, respectively; the placebo response in the North American centers in this study (-13%) was much closer to that seen in the IR study).

Regarding pediatrics, although no patients below the age of 18 were included in the controlled trial, concentration-response analyses and simulations established that similar doses in adults and pediatric patients yielded similar plasma levels of MHD, and we know from previous analyses of Trileptal that adults and pediatric patients have similar concentration-response analyses. For these reasons, it is reasonable to conclude that oxcarbazepine ER is effective in pediatric patients,

and dosing recommendations can be written for these patients that will result in therapeutic levels.

Regarding safety, no new safety signals emerged in this database. However, it is clear that the incidence of common adverse reactions is substantially lower with the ER formulation compared to the IR formulations, despite the cross-study comparison.

Finally, the sponsor has proposed that the indication include patients as young as (b)(4) years old. Although the safety and effectiveness data would support such a lower age level, the pill sizes are such that it would be difficult for patients below the age of 6 to swallow the drug safely. For this reason, we will restrict the lower age to 6 years old.

For these reasons, then I will issue the attached Approval letter, with labeling that we and the sponsor have agreed to.

Russell Katz, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
10/19/2012