CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202810Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	10/19/2011
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA	202810
Applicant	Supernus
Date of Submission	12/19/2011
PDUFA Goal Date	10/19/2012
Proprietary Name / Established (USAN) names	Oxtellar XR/oxcarbazepine XR
Dosage forms / Strength	Extended Release Tablets : 150 mg, 300 mg , and 600 mg
Proposed Indication(s)	Adjunctive treatment of partial onset epilepsy in adults and children (b)(4) years and older
Recommended:	Approval for adjunctive treatment of partial onset epilepsy in adults and children 6 years and older

Cross Discipline Team Leader Review Template

1. Introduction

Oxcarbazepine (OXC) is an anticonvulsant with sodium channel blocking ability that has been approved in the United Stets and Europe for well over a decade. In the United States the proprietary version of oxcarbazepine (OXC), Trileptal, is labeled for adjunctive and monotherapy treatment of partial onset seizures (POS) for in adults. It also is indicated for the treatment of POS in children as monotherapy down to the age 4 years and as adjunctive therapy down to the age of 2 years. Based upon a single adult efficacy study in adults and a number of pharmacokinetic studies, which examine bioavailability in adults and children, the Sponsor is asking for approval of an extended release version of oxcarbazepine, Oxtellar XR, for adjunctive treatment in adults and children down to (b)(4) years of age. The proprietary version of this drug is dosed as twice daily and is believed to be efficacious for adjunctive treatment in daily dosages of 600 to 2400 mg in adults, but with a recommended dose of 1200 mg daily. Dosage for children is weight based. Oxtellar is to be used once daily.

2. Background

The division met with the Sponsor 4 times during the process of drug development, from the pre-IND to the pre-NDA phases. The resulting package, in general, concurs with the advice provided to the Sponsor. For more details the reader should see to Dr. Dinsmore's, the Medical Officer's, and review.

3. CMC/Device

CMC completed their review of Oxtellar XR and have noted that the application may be approved without any PMRs. ONDQA recommended revised drug product dissolution specifications, which were found acceptable by the applicant. The Office of Compliance inspection determined an 'Acceptable' overall recommendation. Consequently approval is recommended from a chemistry perspective.

4. Nonclinical Pharmacology/Toxicology

Not applicable as no significant new excipients are present in the drug product.

5. Clinical Pharmacology/Biopharmaceutics

The reviews were performed by Dr S. Brar (Pharmacokinetics) and Dr. K Kumi (Pharmacometrics). Drs. Bhattaram and Zhu served as Team Leaders.

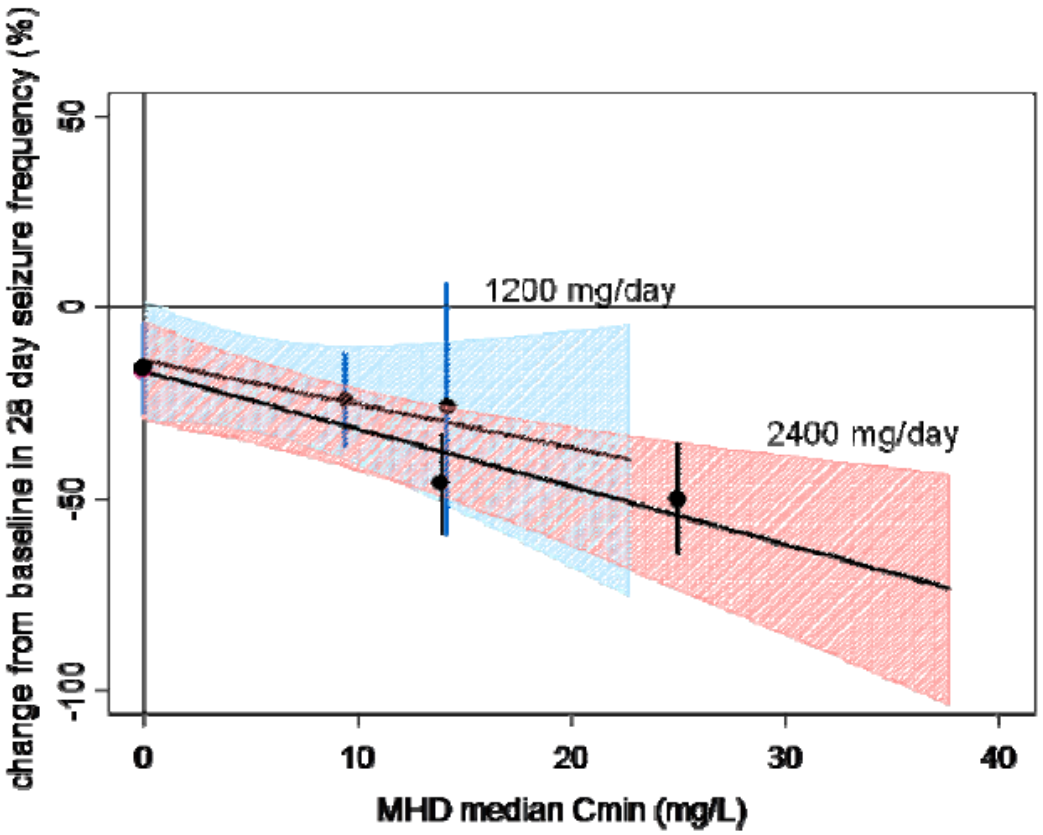
While Oxtellar XR was examined in pharmacokinetic and pharmacometric studies, much of the concentration in analyses was performed on the 10-monohydroxy derivative (MHD). This is because OXC accounts for an extremely small fraction of drug in circulation. Most of the circulating drug substance is in the form of MHD, which is believed mediate this drug's therapeutic effect.

A study examined steady state pharmacokinetic indices of Oxtellar (QD) and the RLD (BID), Trileptal, following 7 days of 1200 mg dosing. This study revealed similar indices between test and RLD for AUC, Cmax, and Cmin MHD. However, the indices were outside the normal bioequivalence standards (see the table below). The results for oxcarbazepine were well outside that compared to RLD (see table below). However, as noted above the contribution of OXC can be ignored. Nonetheless, MHD does not quite achieve bioequivalence standards.

Pharmacokinetic Parameters	Ratios of LSM and 90% Confidence Intervals (CI)	
	MHD in Plasma OXC XR vs OXC IR	OXC in Plasma OXC XR vs OXC IR
AUC(0-24)	80.8% (77.5 -84.3%)	63.8% (59.6 -68.4%)
Cmax, ss	80.8% (77.0 – 84.9%)	38.6% (33.3 – 44.8%)
Cmin, ss	83.7% (78.8 – 88.9%)	104.2% (91.5 – 118.6%)

Because of this Pharmacometrics performed a concentration response comparison between the 1200 mg/day and 2400 day dose, derived form the single efficacy study. This is presented in the figure below. In this figure the 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). The principal observation that can be gleaned from this is that the concentration response curves for both the 1200 mg and 2400 mg dose overlap.



The Sponsor provided PK data to allow the support of pediatric dosing. PK evaluated these data and noted that it demonstrated similar absorption in the pediatric populations the adult population. Using this, and based upon a previous public domain analysis on the similarity in pharmacodynamic effects between adults and children, they were able to derive appropriate weight based dosing.

These data along with the fact that Trileptal at doses of 600 mg day suggests to the Pharmacokinetics reviewer that 1200 mg is an effective dose, but that dosing between Oxtellar and the RLD are not equivalent. This will be noted in the label.

The pharmacokinetic reviewer observed that the MHD AUC is not significantly affected when Oxtellar is administered with high fat meal compared to when it is taken under fasting conditions. But, the Cmax increased about 62% after administration with food compared to under fasting conditions. Moreover, Tmax of MHD following under fed conditions occurred approximately 2.5 hours earlier than under fasting conditions. Because of this labeling

recommendations will state “Administer Oxtellar XR™ as a single daily dose taken on an empty stomach (at least 1 hour before or at least 2 hours after meals).”

The final conclusion of the review is that the new formulation should be approved as a once a day dosing, but with the above caveats noted. No PMRs are recommended.

6. Clinical Microbiology

Does not apply.

7. Clinical/Statistical- Efficacy

Dr Dinsmore performed the clinical review and Dr Siddiqui performed the statistical review**.**

As a 505b2 application based and upon the fact that the oxcarbazepine in the IR formulation is already approve for the treatment of POS the Sponsor was only required to perfom a single adequately controlled trial. A bioequivalence study was also requested (see above). The Study performed is typical of the type of studies requested by this division for approval. Study 301 was multicenter, double blind randomized, parallel group, placebo-controlled study which evaluated oxcarbazepine ER as add on therapy in patients from age 18 to 65 years old who had refractory epilepsy. The three arms included once a day dosing (with meals before bedtime) of placebo, 1200 mg OXC ER and 2400 mg OXC ER. The trial included an 8 week baseline period followed by a 16 week treatment period, which consisted of an initial 4 week titration phase (400 mg/day weekly titration) and a 12 week maintenance phase. Patients were permitted to continue into an open label extension phase if they so desired. Each arm of the study examined 121 to 123 patients. In his review Dr Dinsmore notes that demographic variables are reasonably well divided amongst treatment arms. However, he notes a lager mean seizure frequency in the 2400 mg group, but observed that this is driven by two outliers and indeed the median seizure frequencies are rather close. Off note, 19% of studies were form the United States. A majority of studied patients were form Eastern Europe and Russia. Approximately 27%, 33% and 42%% discontinued because any reason during the trial in the placebo, 1200 mg/day and 2400 mg/day treatment arms, respectively. Dr Dinsmore notes that although in the 2400 mg/day arm it compares favorably with the pivotal study for Trileptal approval where 73were noted at this dose to discontinue. As noted by Dr Dinsmore, approximately 8%, 15%, and 30% of patients discontinued because for adverse events treatment during the trial in the placebo, 1200 mg/day and 2400 mg/day treatment arms, respectively.

The primary endpoint t was the percent change in seizure frequency during the treatment phase, as compared to the baseline phase. The analysis set was a modified intent to treat that consisted of all patients with measurable treatment phase endpoints in an LOCF type analysis. A Wilcoxin Rank Sum test was used to analyze the data. The p value was set to 0.05. I hierarchical analysis was used, starting at the highest dose, to prevent the error of multiple comparisons.

The table below, which is transcribed form Dr Siddiqui's review, presents the primary endpoint results. Both dosages produced an effect of similar magnitude, but only the 2400 mg dosage was statistically significant. Other analyses performed by the Sponsor and Dr Siddiqui on frequency derived secondary endpoints (responder rate analysis), a variety of sensitivity analyses (analysis of completers)and a variety of different methods to analyze the data (e.g. parametric analysis of the log transformed data) revealed similar results. .

Statistic	SPN-8040 2400mg/d (N=123)	SPN-804O 1200mg/d (N=122)	Placebo (N=121)
N	111	109	117
Mean (SD)	-38.03 (53.11)	-29.14 (69.84)	-15.43 (67.34)
Median	-42.90	-38.20	-28.70
Min, Max	-100.0, 212.8	-100.0, 556.1	-100.0, 333.6
p-value versus placebo[a]	0.003	0.078	
Hodges-Lehmann Estimate	-18.30	-10.30	
95% Confidence Interval	(-30.40, -5.80)	(-22.30, 1.20)	

Source: Study report

[a] *Wilcoxon rank-sum test of the median percentage change in partial seizure frequency per 28 days during the 16-week Treatment Phase (Titration + Maintenance Periods) relative to the 8-week Baseline Phase.*

Dr S notes that no subgroup analysis for race as there was an insufficient non-Caucasian patient in subgroup analyses Dr Siddiqui concludes that there was no marked group differences when gender, region, type of seizure (partial. Secondary generalized, complex partial) was analyzed.

Dr S concludes that "In conclusion, 2400mg SPN-804O administered QD demonstrated an effective treatment for refractory partial epilepsy, and 1200mg QD demonstrated numerically better than placebo in reducing the partial seizure frequency."

The lack of statistical significance of the 1200 mg dose is a bit surprising in that the IR formulation demo started effects at both 600 and 1200 mg/day. Dr Dinsmore noted that one of the contributing factors in this is that the placebo group from Eastern Europe exhibited a very large "placebo effect," which lessened the overall treatment effect. I agree that this is a factor, although it would be expected to affect both the 2400 mg and 1200 mg dose in a similar fashion. But one may consider that such an effect would decrease the size of effect as well as increase the overall variability of the study and thereby lessen the expected power of the trial. Another important factor in concluding efficacy is that a concentration response analysis performed by Pharmacometrics (see above) demonstrated overlapping curves concentration response curves. This is also supported by the previous demonstrated that even the low dose

of 600 mg/day of the IR formulation produces an efficacious response. However, it cannot be assumed that the doses of the present formulation are equipotent to those of IR. Moreover, because of this a single recommended dosage will not be noted in the label, but a dosage range will be recommended 1200 mg/day to 2400 mg/day.

8. Safety

Dr Dinsmore performed the primary safety review.

As noted above, oxcarbazepine has been marketed for over a decade in the form of an IR formulation. As a result there is substantial clinical trials and post marketing experience. There were approximately 260 patients exposed to oxcarbazepine in the present application in initial phase 1 pharmacokinetic studies. Most of these were single dose exposures in adults. Some of these studies examined earlier forerunners to the final ER formulation. One study examined 18 pediatric patients with multiple exposures. The principal study from which safety data was obtained includes the above described Multicenter, double-blind, placebo-controlled, three-arm, parallel group in adult patients (study 301) and its open label extension (study 302), which included 369 patients on drug and 248 on placebo. The duration of the latter study was 3 months with target doses of 1200 and 2400 mg/day; patients were permitted to continue treatment during an extension period. Dr Dinsmore's analyses revealed reveals that 206 subjects had exposure greater than 3 months and less than 6 months and 109 subjects had exposures for an interval greater than 9 months and less than 12 months. There was a a total of 289 patient years of exposure. While these values are below ICH guidelines for new medicinal entities, prior trial and post-marketing experience provide sufficient experience to allow the review of this new formulation.

Two deaths were observed in the complete trial data base. One related to metastatic ovarian cancer, identified 2 days after randomization in study 301, and the second related to multiple seizures and pulmonary embolus, identified 147 days into study 302 that may be . Dr. Dinsmore concludes that both cases do not appear to be related to drug, and I agree.

Approximately 8% of patients on oxcarbazepine experienced serious adverse events as compared to 7% of patients on placebo in Study 301.Six additional reports of serious adverse events were observed in the extension trial (study 302). Dr. Dinsmore examined the serious adverse events and could not identify a new signal above beyond that already known for oxcarbazepine. He does notes 2 ischemic strokes in the complete database that originated from one site in Romania, but feels this could not be associated with drug treatment, at least one patient had prior existing risk factors. I agree with his conclusions.

Of normal subjects studied in phase 1 trials Dr. Dinsmore notes reasons for discontinuation involved non-serious rash and hyponatremia, both of which are known and described in the label of the reference drug. Dr. Dinsmore notes that discontinuations in epilepsy control trials at both studied doses, 1200 mg/day and 2400 mg/day, closely reflected that seen in the IR. The most common reason, like the IR product, for discontinuations included mostly those related to neurotoxicity, including dizziness, vomiting, diplopia, headache and somnolence. My own comparison, using the label for IR as reference, suggests a substantially lower rate of

discontinuation at the 2400 mg/day with the XR formulation (i.e. 65% as compared to 30%). This difference cannot be assumed to indicate better tolerability as this is a cross study comparison and it cannot be assumed that these doses are equipotent in efficacy. The overall rate of discontinuations was 16% in the 1200 mg/day and 30% in the 2500 mg/day group.

Approximately 55% of patients experienced any adverse event in the placebo group of study 301 as compared to 56% and 69% in the 1200 mg/day and 2400 mg/day groups, respectively. A dose response was noted for the preferred terms "Dizziness", Somnolence", "Headache", "Diplopia", and "Asthenia". Additional adverse events observed in the open label trials included hyponatremia and infections; such adverse events are labeled for the IR product. In sum, this Oxtellar XR product exhibited a similar common adverse event profile as did the referenced label IR product,

No significant changes were observed in alteration in red blood cells. A very subtle signal was observed in some white blood cell indices, which Dr. Dinsmore did not believe represented a true signal. I should note that the Warnings and Precautions section of the label for the IR products note "Rare reports of pancytopenia, agranulocytosis, and leukopenia have been seen in patients treated with Trileptal during post-marketing experience." No platelet signal awas appreciated.

Dr. Dinsmore did not observe a signal from the chemistry labs except for that of hyponatremia, which is presently labeled in the Warnings and Precautions section for the reference drug.

No consistent alterations in blood pressure were noted. Dr. Dinsmore note as subtle change in body temperature with a drop in drug treatment mean of about 0.1 degrees Fahrenheit. There was no clinically significant treatment emergent reduction in body temperature. However, because of currently labeled notation of reduced T4 levels, Dr Dinsmore recommends post-marketing vigilance. I do not believe this would be helpful as the signal was extremely subtle and could not be further elucidated form post-marketing data.

No obvious consistent changes in EKG were apparent.

No other special clinical changes were noted that were not otherwise expected based upon the present labeling for the referenced drug.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

PK extrapolation from adults was performed to determine pediatric dosing. As noted above, the extrapolation was made possible by previous PK/PD published work. The extrapolation used a comparison of Oxtellar XR PK studies in children and adults. Using this, dosing could be derived for children down to 6 years old. While the Sponsor requested pediatric labeling for adjunctive treatment down to (b) (4) 6 years will be permitted because of concerns about the ability of young children to swallow the tablets. Patients younger then 1 month

were waived as too few patients are diagnosed at this age and such studies are therefore impracticable. Studies in patients 1 month to 6 years of age were deferred because the formulation is ready for marketing. Such studies will be included in the PREA requirements and include the following:

- A prospective, randomized, controlled, double-blind, efficacy/safety study of Oxcarbazepine ER for the adjunctive the treatment of partial onset seizures in children ages 1 month to < 2 years. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon Video/EEG data.

- Deferred pediatric trial under PREA: A prospective, randomized, controlled, double-blind, efficacy/safety study of Oxcarbazepine ER for the adjunctive the treatment of partial onset seizures in children ages 2 to <6. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon diary data.

- A clinical trial to examine pharmacokinetics and tolerability in children ages 6 months to 4 years using an age appropriate extended release formulation.

- A clinical trial to examine pharmacokinetics and tolerability in children ages 1 month to 6 months using an age appropriate extended release formulation.

These studies were designed in consultation with PERC.

11. Other Relevant Regulatory Issues

Financial Disclosure

Dr. Dinsmore examined the Financial Disclosure documentation and noted there were a few cases where information was not provided. In reading his review these constitute a very small percentage of studies, and would likely not affect the final results (only 1.5% of total investigative personnel represented by sub-investigators). Furthermore, the Sponsor attempted to contact such individuals, but was unsuccessful.

DSI inspected 3 sites. While they found minor infractions, none where considered to threaten the integrity of the trial.

12. Labeling

See label.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Approval will be recommended down to age 6 years.

Risk Benefit Assessment: Risk benefit are adequate for approval and are similar to those of the referenced labeled drug.

Recommendation for Postmarketing Risk Management Activities: None.

Recommendation for other Postmarketing Study Commitments Other then the PREA requirements there are no PMRs or PMCs.

Recommended Comments to Applicant: None..

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/s/

NORMAN HERSHKOWITZ
10/19/2012