Quantitative Assessment of Additional Metrics in the Bioequivalence Evaluation of Oxcarbazepine Extended-Release Tablet

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Introduction

- OXTELLAR XR (oxcarbazepine) extended-release (ER) tablet is approved for use as an adjunctive therapy in the treatment of partial seizures in adults and children six years of age and older.
- The product specific guidance on oxcarbazepine ER tablet recommends bioequivalence (BE) evaluation in healthy subjects based on the statistical test of maximal plasma concentration (C_{max}) and area under the time-concentration curves (AUCs).[1]
- A citizen petition was submitted to the agency requesting to include partial AUCs (pAUCs) at 0-T_{max} and T_{max}-T as additional pharmacokinetic (PK) metrics for BE evaluation.[2]
- **The purpose of this study** was to conduct quantitative assessment of the appropriateness of pAUCs in the BE evaluation for oxcarbazepine ER tablet.
- We conducted PK and pharmacodynamic (PD) simulations involving four separate hypothetical test formulations of oxcarbazepine ER tablet with different release or absorption rate constants based on the PK and PD models of OXTELLAR XR.

Methods

PK and PD Models (from the NDA applicant):

- PK model of oxcarbazepine ER tablet: a combination of zero-order and first-order processes for absorption; two-compartment model for distribution and linear elimination for the clearance.[3]
- PD model of oxcarbazepine ER tablet: PD response is mainly driven by the steady state minimal concentration ($C_{min,ss}$) of the active metabolite of oxcarbazepine, 10-monohydroxy derivative (MHD).

$$PCH = PCH_0 - E_{max} \times \left[\frac{1}{1 + (C_{50} / C_{min,ss})^{\gamma}} \right]$$

where, PCH is percent change of seizure frequency from baseline under treatment and PCH_0 is PCH under placebo.

Test Formulations:

- We generated four hypothetical test formulations with different shape of PK profiles. These hypothetical test formulations (i.e., % deviation of k_a and zero order release rate from the RLD formulation) were selected based on numerous simulations to illustrate how differences in formulations may impact the BE assessment results.
  - Test formulation 1 had 13% smaller first-order absorption rate constants (k_a) compared to the reference listed drug (RLD)
  - Test formulation 2 had 13% bigger k_a compared to RLD
  - Test formulation 3 had 14% slower zero-order release rate compared to RLD
  - Test formulation 4 had 18% faster zero-order release rate compared to RLD
- The T_{max} cutoff of pAUCs, i.e. 4 hours, was selected based on the T_{max} of an approved oxcarbazepine tablet immediate release formulation.

Methods continued

BE evaluation:

- BE was claimed when the 90% confidence interval of the geometric mean ratio of BE metrics between test and RLD were within 80 – 125%.
- BE metrics: C_{max} and AUC (currently recommended) and $pAUC_{0-4hr}$ & $pAUC_{4hr-t}$ (proposed additional BE metrics).

BE and PD simulations:

- We simulated 500 BE studies (n=24 per study) for each of the four hypothetical test formulations and calculated the percentage of BE studies that pass the BE criteria under different BE metrics (C_{max} and AUC versus pAUCs).
- We simulated 1) $C_{min,ss}$ of MHD, based on a daily 1200 mg administration of the test formulations and 2) the resulting PD responses of the various $C_{min,ss}$.
- Given that adverse events associated with oxcarbazepine appear to be related to steady-state peak concentrations ($C_{max,ss}$), we also simulated $C_{max,ss}$ of oxcarbazepine and its active metabolite, MHD.
- We used NONMEM v7.3 to simulate PK and PD data of RLD and test formulations and R for evaluating BE between formulations.

Results

- The percentage of simulated trials (passing rate) that passed the BE criteria for different BE metrics is presented in Table 1. All four test products had comparable C_{max} and AUC as compared to those of the RLD as shown by high passing rate (i.e., greater than 80%) for C_{max} and AUC metrics. However, they had different early $pAUC_{0-4hr}$, as evidenced by low passing rate for the $pAUC_{0-4hr}$ metric (Table 1).
- The PD response (percent reductions of seizure frequency) for all test formulations was similar to that of RLD (Table 2). The difference in seizure frequency between the RLD and the test formulations was less than 2%. Table 2 shows products that meet FDA's BE criteria based on conventional BE metrics are expected to have similar PD responses, despite of the differences in the early $pAUC_{0-4hr}$.
- The $C_{max,ss}$ of both oxcarbazepine and MHD were similar between test formulations and the RLD as demonstrated in Table 3. The differences in $C_{max,ss}$ of oxcarbazepine and MHD between the RLD and the test formulations were less than 7% and 1%, respectively. These results suggested a similar risk profile of adverse events between test formulations and RLD.
- The modeling and simulation results of oxcarbazepine ER tablet were included in the FDA's response to the citizen petition.[4]

Table 1. Percentage (%) of the simulated BE studies that passed the BE criteria under conventional BE metrics (C_{max} and AUC_t) and proposed additional pAUC metrics (AUC_{0-4hr} and AUC_{4hr-t}).

Product	C_{max}	AUC_t	AUC_{0-4hr}	AUC_{4hr-t}
OXTELLAR XR to OXTELLAR XR (as control)	100	100	100	100
Test Formulation 1 to OXTELLAR XR	84	100	68	100
Test Formulation 2 to OXTELLAR XR	81	100	72	100
Test Formulation 3 to OXTELLAR XR	97	100	18	100
Test Formulation 4 to OXTELLAR XR	98	100	53	100

Table 2. Simulated steady-state trough concentrations ($C_{min,ss}$) of the active metabolite, MHD and the percent change of seizure frequency over 28 days (PD response) following administration of once a day 1200 mg ER tablets for 28 days.

Product	$C_{min,ss}$ of MHD (ug/mL)	Percent change of seizure frequency over 28 days (%)
OXTELLAR XR	16.11	-53.79
Test Formulation 1	16.34	-54.24
Test Formulation 2	15.87	-53.17
Test Formulation 3	16.21	-54.01
Test Formulation 4	16.00	-53.54

Table 3. Simulated steady-state concentrations of oxcarbazepine and an active metabolite, MHD following oxcarbazepine 1200 mg ER tablets administration

a. Oxcarbazepine Concentrations

Product	Dosage	T_{max} (hours)	$C_{max,ss}$ (ug/mL)	$C_{min,ss}$ (ug/mL)
OXTELLAR XR	1200 mg ER once a day	3.4	0.729	0.191
Test Formulation 1		3.5	0.684	0.199
Test Formulation 2		3.4	0.780	0.185
Test Formulation 3		4.1	0.705	0.193
Test Formulation 4		2.9	0.748	0.190

b. MHD concentrations

Product	Dosage	T_{max} (hours)	$C_{max,ss}$ (ug/mL)	$C_{min,ss}$ (ug/mL)
OXTELLAR XR	1200 mg ER once a day	9.5	20.99	16.11
Test Formulation 1		9.5	20.78	16.34
Test Formulation 2		9.0	21.22	15.87
Test Formulation 3		10.0	20.97	16.21
Test Formulation 4		9.0	21.00	16.00

Conclusions

- Simulation results support that generic oxcarbazepine ER tablets that are bioequivalent to OXTELLAR XR based on C_{max} and AUC metrics would have similar clinical performance, despite of the differences in the early $pAUC_{0-4hr}$.
- Our analysis shows that there is no sufficient scientific support to include pAUCs as additional PK metrics in a BE assessment of generic oxcarbazepine ER tablet products.

References

1. Product specific bioequivalence guidance on oxcarbazepine extended release tablet
2. Citizen petition is available at https://www.regulations.gov/document?D=FDA-2015-P-2830-0001
3. FDA Clinical Pharmacology Biopharmaceutics Review of Oxtellar XR (oxcarbazepine) Extended Release Tablets, NDA 202810, (October 19, 2012), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202810Orig1s000ClinPharmR.pdf
4. Citizen petition response from FDA is available at https://www.regulations.gov/document?D=FDA-2015-P-2830-0022

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