T2312

Challenge with New FDA Requirement for Partial AUCs for Bioequivalence Assessment of Modified-Release Products

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Purpose

Single dose studies under both fasting and fed state are generally required by FDA to demonstrate Bioequivalence (BE) for modified-release (MR) formulations on AUC_t, AUC_{inf}, and C_{max}. The 90% confidence interval (CI) of the geometric mean ratios (T/R) of AUC_t, AUC_{inf}, and C_{max} must be within the acceptable range of 80.00% to 125.00% to prove the same rate and extend of absorption of the active moiety of the two products.

FDA recently requested BE demonstration on additional partial AUC (pAUC) for certain products including an immediate-release (IR) and modified-release component such as Dexmethylphenidate extended-release (ER) capsules, Mesalamine delayed-release (DR) capsules, Methylphenidate ER tablets, Naltrexone (ER suspension, Intramuscular), and Zolpidem ER tablets which IR component is necessary for rapid onset of the pharmacological effect while the DR component is destined to sustain it.

Methods

Retrospective analyses from successful studies conducted for both Methylphenidate ER tablets and Zolpidem ER tablets in which the pAUC criteria were applied. All studies applied are single dose, 2 way crossover trial to assess the BE in healthy subjects. The Test/Reference (T/R) ratios of geometric means and the 90% CI approach were used to investigate BE. For studies analyzed, the 90% CI of the T/R ratio of geometric mean of AUC_t, AUC_{inf}, and C_{max} was within 80.00% to 125.00%. The same criterion applies for specific pAUCs.

Different pAUCs of different compounds required with the details below as per the FDA BE guidance.

For Methylphenidate ER tablets under fasting state:

- AUC_{0-3} for early onset of response during the early part of the once-daily dosing interval;
- AUC_{3-7} for sustaining the response in the middle of the once-daily dosing interval and where for patients (children) taking this medication, this would correspond to the early afternoon time to ensure the completion of the school day after lunch; and
- AUC_{7-12} for maintenance of the response in late stage of the once-daily dosing interval. For children taking this medication, this would correspond to the late afternoon time to ensure the completion of homework and other after-school activities.

For Zolpidem ER tablets, the $AUC_{0-1.5}$ and $AUC_{1.5-t}$, have been determined to be the most appropriate parameters for evaluation of the drug bioavailability responsible for the sleep onset and sleep maintenance phases, respectively.

The T/R ratio and 90% CI of the geometric mean T/R ratios for pAUCs were calculated with the above specified pAUCs for Methylphenidate and Zolpidem respectively.

Figures 1 & 2 Early Partial AUCs for Methylphenidate

Figure 1. Methylphenidate ER Tablets

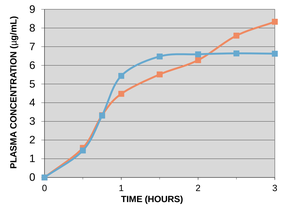

Figure 2. Methylphenidate ER Tablets

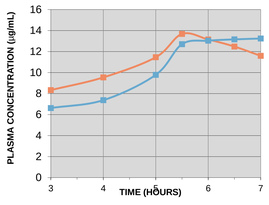

Figure 3 Early Partial AUCs for Zolpidem

Figure 3. Zolpidem ER Tablets

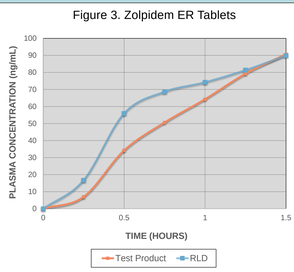

Table 1 Summary of Comparison AUCs of Zolpidem

	T/R	90% CI	ISCV
AUC_t	~ 95%	within 80 - 125%	<20%
$AUC_{0-1.5}$	< 80%	outside 80 - 125%	50 -200%
$AUC_{1.5-t}$	~ 95%	within 80 - 125%	<20%

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Results and Discussion

Methylphenidate:

Our investigations showed that ISCVs for AUC_{0-3}, AUC_{3-7}, and AUC_{7-12} were below 20%, which were comparable to those obtained from AUC_t. However, in some cases, the T/R ratios of pAUCs (e.g. 0-3h, 3-7h, and 7-12 h) were significantly different between the test and reference products, while the T/R ratios of of AUC_t were close to 100% and the 90% CI for AUC_t were entirely within 80.00% to 125.00%. Meanwhile, the 90% CIs of those pAUCs were either within or outside the acceptable range of 80.00% to 125.00%.

The difference shape of the pharmacokinetic profile of the methylphenidate products can result in different therapeutic effect in particular time duration through the day. The Figures 1 and 2 showed the difference of the early time of the PK profiles between the test and reference products.

Zolpidem:

Our results indicated that the intra-subject coefficient variability (ISCV) of $AUC_{1.5-t}$ were similar to what obtained from the AUC_t, and the T/R ratios and 90% confidence intervals for $AUC_{1.5-t}$ were also within 80.00% to 125.00%.

The results for $AUC_{0-1.5}$ showed that the intra-subject coefficient variability (ISCV) of $AUC_{0-1.5}$ were much higher (range from 50% to 200%) than those obtained from AUC_t. Such high ISCV might introduce difficulty to demonstrate BE using a sample size estimated originally on AUC_t, AUC_{inf}, and C_{max}. In addition, the T/R ratios of $AUC_{0-1.5}$ were not optimum showing significant difference between the test and reference products, while the T/R ratios for AUC_t were close to 100%. Meanwhile, the 90% CIs of $AUC_{0-1.5}$ were not within 80.00% to 125.00%.

The difference in early T_{max} can lead to either lack of the efficacy and the acute AEs.

The Figure 3 and Table 1 illustrated the difference of the early $AUC_{0-1.5}$ for both test and reference products.

Conclusion

The additional pAUC metrics of BE assessment for drug with both IR and ER components may ensure the therapeutic equivalence between the products.

The results of our retrospective data analysis of pAUC showed that the ISCVs can be significantly higher and the T/R ratios significantly different when using multiple pAUCs for specific compounds such as Zolpidem and Methylphenidate. Consequently, the impact on the sample size could be significant and the generic development of the product with pAUC requirement may be more challenging.

Reference

1. FDA Draft Guidance on Methylphenidate Hydrochloride Extended Release Tablets, November 2014
2. FDA Draft Guidance on Zolpidem Extended Release Tablets, October 2011
3. FDA Draft Guidance on Dexmethylphenidate Hydrochloride Extended Release Capsules, March 2015
4. FDA Draft Guidance on Naltrexone, Extended Release Suspension, intramuscular, September 2015