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Single- and Multiple-Dose Bioequivalence Studies for Oxycodone Extended Release 80 mg and 5 mg Tablet. Lessons learned at Biopharma Services Inc.

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PURPOSE

The oxycodone extended release (ER) tablet (OxyContin® by Purdue Pharma L.P) provides long therapeutic duration for pain relief. The requirements of bioequivalence (BE) trials for generic drug submission for FDA and TPD require single-dose studies only, while EMA requires both, a multiple-dose study with the highest strength to demonstrate BE at steady-state, as well as a single-dose study.

OBJECTIVE(S)

Biopharma Services Inc. (BPSI) has conducted over 20 trials with doses ranging from 5 mg to 80 mg of oxycodone ER tablet using normal healthy volunteers (NHV). Four out of 20 studies were conducted as single-dose and multiple-dose trials using both the lowest (5 mg) and highest (80 mg) strengths. The objective of this presentation is to summarize pharmacokinetics (PK) and safety observations from in-house single-dose and multiple-dose trials.

METHOD(S)

- 4 pivotal studies
- Randomized, two-sequence, two-treatment, two-period, crossover trials in NHV
- 5 mg or 80 mg tablet strength (5 mg single-dose was fed study and no food effect was reported on PK of oxycodone
- Single-dose and Multiple-dose
- Safety was monitored throughout the course of the trial by evaluating reported adverse events (AE), clinical laboratory test results, vital signs, and ECG findings
- Blood samples for PK assessment were collected after oxycodone dosing
  - Single-dose sampling schedule up to 36 hours
  - Multiple dose sampling schedule (dosing interval 12 hours):
    - Prior to the first dose of oxycodone administration;
    - Pre-dose on Days prior to PK sampling day
    - On PK sampling day up to 12 hours
    - PK parameters such as maximum plasma concentration (C_{max}) and area under concentration-time curve (AUC) were determined.

Table 1. Summary of studies conducted for single and multiple-dose administration

Study	Days of Dosing	Dose Titration	Dose Reduction	Washout	Comment
5 mg SD	1	No	No	Yes	
5 mg MD	5	No	No	Yes	
80 mg SD	1	No	No	Yes	Naltrexone given
80 mg MD	13	Yes	Yes	No	Naltrexone given

RESULT(S)

- All successful BE studies with 90% confidence intervals of geometric mean ratios of C_{max} and AUC within 80.00% to 125.00%.
- The AEs observed in all single- and multiple-dose studies were either mild or moderate in nature.
- Rate of AE per subject was much higher in multiple-dose study (2.7%) than that from single-dose study (1%) for 80 mg strength
- The percentage of moderate AEs was also higher in multiple-dose trial than it observed from single-dose trial of both 80 mg and 5 mg strengths

Table 2. Summary of AEs Observed from both Single and Multiple-Dose Administration of 5 and 80 mg Oxycodone

Study	Total AE	% AE/Subject	Mild AE	Moderate AE
80 mg SD (n= 52)	54	1	52	2
80 mg MD (n=36)	94	2.7	86	8
5 mg SD (n= 36)	22	0.6	22	0
5 mg MD (n=36)	39	1.1	36	3

- Similar Median Tmax: 2 to 4 hrs with the range of 0.5 to 6 hrs when given as both single-dose and multiple-dose administration with both 5 mg and/or 80 mg strength
- Mean T1/2 of oxycodone is relatively short as 5 hrs after single-dose administration
- C_{max} and AUC of oxycodone were comparable following single-dose and multiple-dose for both 80 mg and 5 mg strengths respectively
- Comparable variability of PK parameters observed from single-dose and multiple-dose trials when given either at 80 mg or 5 mg; demonstrated in Figures 1 and 2 below

Figure 1. AUC (Mean +/- SD) from 80 mg Oxycodone after SD & MD Administrations

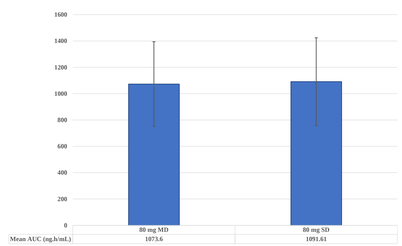
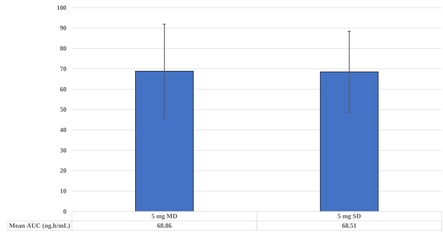


Figure 2. AUC(Mean +/- SD) from 5 mg Oxycodone after SD & MD Administrations



CONCLUSION(S)

- PK was well characterized with relatively low variability of oxycodone under both single-dose and multiple-dose conditions
- No accumulation of oxycodone after multiple-dose administration
- More AEs observed for 80 mg than that from 5 mg (either single-dose or multiple-dose conditions)
- More AEs observed when multiple doses was given comparing to AE seen from a single-dose studies
- With proper safety protection, multiple-dose of 80 mg of oxycodone clinical trial was successfully conducted in NHV
- Our experience showed 80 mg multiple-dose trial was safe in NHV and scientifically sound to be discriminative to determine BE

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