# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 22-272Orig1s014

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

**Clinical Pharmacology Review**

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| IND: | 29,038 SDN 693, 753 |
| Date Received: | 9/17/2010, 9/4/2012 |
| Product Name: | OxyContin Tablets |
| Active Ingredient: | Oxycodone HCl |
| Sponsor: | Purdue Pharma |
| Type of Submission: | Abuse Liability Clinical Study Reports |
| Reviewer: | Srikanth C. Nallani, Ph.D. |

**Background:**

Purdue Pharma LP conducted five clinical studies to evaluate the abuse potential of their developmental tamper resistant formulation of oxycodone extended release tablets (OTR). These studies were submitted to IND 029038 on September 16, 2010.

1. **OTR-1016** entitled "A Randomized, Open-Label, Single-Dose, Crossover Study of the Effects of Various Tampering Methods on Exposure to Oxycodone in Fasting Healthy Subjects".
2. **OTR-1018** entitled "A Single-Center, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Crushed and Intranasally Administered Oxycodone HCl Tamper Resistant Tablets".
3. **OTR-1019** entitled "Relative Attractiveness of Oxycodone TR: Comparative Assessment of Tampering Potential and Recreational Drug User Preferences for Different Opioid Formulations".
4. **OTR-1021** entitled "A Randomized, Single-Blind, 3-Way Crossover Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Crushed Intranasal Oxycodone Tamper Resistant Tablets (OTR) and OxyContin® in Healthy Adults".
5. **OTR-1022** entitled "Single-Center, Randomized, Cross-Over Study in Recreational Opioid Users to Evaluate the Safety of Crushed and Intranasally Administered OTR and OC Placebo Tablets".

Studies OTR-1016, OTR-1018 and OTR-1021 are reviewed in this memo with particular focus on pharmacokinetic disposition of oxycodone following administration of intact oxycodone extended release formulations (OxyContin tablets (OC) or tamper resistant tablets (OTR)) or administration of tablet contents following various methods of abuse (chewing, grinding followed by intranasal administration). Sponsor compares systemic exposure (Cmax and AUC) of oxycodone in blood following several treatments.

## 1. Study OTR-1016

**Study Title:**

A Randomized, Open-Label, Single-Dose, Crossover Study Of The Effects Of Various Tampering Methods On Exposure To Oxycodone In Fasting Healthy Subjects

**OBJECTIVES:**

The objectives of this study were as follows:

Primary: To characterize the pharmacokinetic (PK) profiles and metrics for each treatment.

Secondary: To assess the safety and tolerability of the oxycodone treatments administered under naltrexone blockade.

**METHODOLOGY:**

Part A: Randomized, open-label, single-dose, 8-treatment, 5-period, incomplete block, crossover study in fasting healthy adult male and female subjects.

Parts B and C: Randomized, open-label, single-dose, 4-period, 2-treatment replicated design in fasting healthy adult male and female subjects.

Part A: Subjects were randomized to a treatment sequence. All sequences included the immediate-release oxycodone reference solution. All treatments were administered orally with a total fluid volume of 240 mL in the fasted state.

**Test Treatments:**

Part A:

Treatment A: OTR 40 mg tablet swallowed intact

Treatment B: OTR 40 mg tablet chewed and swallowed

Treatment C: OTR 40 mg tablet particle size reduced by crushing via mortar and pestle, and swallowed

Treatment D: OTR 40 mg tablet particle size reduced by crushing via mortar and pestle, chewed, and swallowed

Treatment E: OTR 40 mg tablet pre-softened in water, chewed, and swallowed

Treatment F: OxyContin® 40 mg tablet (OC formulation) swallowed intact

Treatment G: OxyContin® 40 mg tablet chewed and swallowed

*Reference Treatment:*

Treatment H: Immediate-release 40 mg oxycodone solution

There were 5 Periods for Part A. Study drug was administered in each period according to the random allocation schedule (RAS).

Part B:

Treatment B: OTR 40 mg tablet chewed and swallowed

Treatment G: OxyContin® 40 mg tablet chewed and swallowed (Under vigorous chewing conditions as established in Part A)

Part C:

Treatment B: OTR 40 mg tablet chewed and swallowed

Treatment G: OxyContin® 40 mg tablet chewed and swallowed (Under normal chewing conditions with duration times established in the chewing qualification session prior to Part C.)

*Reference Treatment:*

Parts B and C: none

**Study drugs (OTR, OC, and IR oxycodone solution) were prepared and administered as follows:**

1. For intact dosing (Part A), the OTR and OxyContin® tablets were swallowed whole with 240 mL of water.

2. Particle size reduction of OTR tablets by crushing via mortar and pestle (Part A only) was performed per standardized procedures. Following particle size reduction, subjects directly swallowed or chewed and swallowed the tablet contents as described below.

3. Pre-softening of OTR tablets (Part A only) was performed per standardized procedures. Following tablet softening in water, subjects chewed and swallowed the softened tablet as described below. Just prior to administration of the softened tablet, the water used to soften the tablet was administered, followed by administration of a rinse of the tablet softening container. Upon completion of chewing, subjects received the remaining volume of water.

4. For each 'chewed and swallowed' treatment in Parts A and B, subjects were required to chew the administered intact tablet (OC or OTR), crushed tablet (OTR), or softened tablet (OTR) vigorously for up to (b) (4). Chewing stopped once (b) (4) whichever occurred first. During chewing, subjects were allowed to swallow accumulated saliva and small particulates ad libitum.

Subjects informed site staff upon completion of chewing/particle size reduction if this occurred prior to the end of the (b) (4) chewing period, and immediately after chewing stopped, the remaining dosing solution was administered.

Otherwise chewing stopped at the end of (b) (4) and the remaining tablet or tablet fragments were swallowed with the remaining dosing solution.

For Part B, the duration of chewing in minutes and seconds following vigorous chewing for each subject was recorded.

5. For each 'chewed and swallowed' treatment in Part C, subjects were required to chew the administered intact tablet (OC or OTR), using "normal" non-vigorous chewing techniques. Chewing duration data from the chewing qualification session was used to obtain the maximum duration of chewing (in minutes and seconds) for each subject for

Part C. Once the subject reached his/her maximum chewing duration time, they were instructed to swallow the dose followed by 240 mL of water.

6. For immediate-release oxycodone solution administration (Part A only), subjects received study drug in the appropriate volume of the oxycodone oral solution, followed by dosing cup rinses with an additional quantity of water sufficient to bring the total volume administered to 240 mL.

7. Study drug (test or reference treatment) was administered following a 10-h overnight fast. Subjects continued fasting from food for 4 h following dosing.

8. Subjects were standing or in an upright sitting position while receiving their dose of study drug. Following dosing, subjects remained in an upright position for a minimum of 4 h.

Fasting was not required for non-dosing study days.

Subjects received naltrexone HCl 50 mg tablets with 240 mL of water at -13, -1, 11, 23, and 35 h relative to each study drug dosing.

**Endpoints/Criteria for Evaluation:**

***Pharmacokinetic:***

Plasma concentrations of oxycodone were analyzed to determine the following PK metrics: area under the plasma concentration-time curve from h 0 to the last measurable plasma concentration (AUCt), area under the plasma concentration-time curve extrapolated to infinity (AUCinf), maximum observed plasma concentration (Cmax), time to maximum plasma concentration (tmax), apparent plasma terminal phase half-life ($t_{1/2Z}$), lag time was estimated as the timepoint immediately prior to the first measurable plasma concentration value ($t_{lag}$), and apparent terminal phase rate constant ($\lambda Z$).

***Safety:***

Safety was assessed using recorded adverse events (AEs), clinical laboratory test results, vital signs results, pulse oximetry, physical examinations, and electrocardiograms.

**Bioanalytical Methods:**

Plasma concentrations of oxycodone were quantified by using a validated liquid chromatography tandem mass spectrometric method ((b) (4) SOP TM.664,(b) (4) Report # 4141.090806.1).

**Statistical Analysis:**

For Part A, oxycodone AUCt, AUCinf, and Cmax, a mixed-model analysis of variance (SAS PROC MIXED) was used to compare logarithmic-transformed (base e) values for each comparison. The 90% confidence intervals were estimated for the ratios (test/reference) of exponentiated LS means from all 28 pairwise treatment comparisons. Additionally, a secondary analysis on normalized metrics (indexed by subjects' own metric values from the Immediate-release 40 mg oxycodone solution treatment) was also performed.

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