CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Sheetal Agarwal, Ph.D.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: **04/29/09**	IND No.: 29,038 SDN.:687	Related NDA Nos. 20-553 (SDN 351), 22-272 (SDN 60)	Submission Date: 04/16/2010	
NAME OF DRUG: Oxycontin	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	
NAME OF THE SPONSOR: Purdue Pharma				

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW):*
☒ PHASE IV RELATED		DDI study protocol employing Oxycontin 10 mg (ER) with 200 mg bid ketoconazole

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ . See comments below
☐Medical ☐Chemist ☐Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ . See submission cover letter
☐Micro ☐Pharmacometrics ☐Others		☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

The submitted study protocol OTR1023 for a drug-drug interaction study employing Oxycontin and ketoconazole as a Phase 4 post marketing commitment for approval of Oxycontin is acceptable from a Clinical Pharmacology perspective. No further action is indicated at this time.

BACKGROUND:

This review pertains to the final drug-drug interaction protocol # OTR1023 submitted to the Agency on 04/16/2010. This DDI study is designed to fulfill the Post Marketing Commitment outlined in the Agency's letter dated September 2, 2009 in reference to the approval of supplement # S-060 that was submitted on December 13, 2007. A draft of protocol OTR1023 was submitted on September 11, 2009 (NDA 20533/SDN 340) and reviewed by Dr. Sayed Al Habet (see review in DARRTS dated 09/30/00).

The following Clinical Pharmacology related comment was conveyed to the sponsor at the time of initial review of the draft protocol:

"Although, a drug interaction is expected between ketoconazole and oxycontin, the magnitude of resulting increase in oxycodone exposure is unknown. In order to protect the healthy volunteers participating in this study from the opioid side effects resulting from a potential interaction, we advice that you provide naltrexone blockade to the participating volunteers. We recommend that naltrexone at a dose of 50 mg be administered during the study at the following time points in relation to oxycontin dosing: 12 hours pre-dose, 12 hours, 24 and 36 hours post-dose."

It should be noted that the final protocol does not contain any major amendments to the study design reviewed by Dr. Al Habet which would materially affect the clinical pharmacology assessments.

Purdue did not include naltrexone blockade in their final protocol but provided an acceptable rationale to the Agency via email on April 27, 2010 to the project manager, Ms. Lisa Basham. Dosing in this study was planned to be started on April 28, 2010. Attachment 1 is an extract of Purdue's rationale, while attachment 2 contains the final protocol synopsis.

ATTACHMENT 1: RATIONALE PROVIDED BY PURDUE PHARMA FOR NOT INCLUDING NALTREXONE BLOCKADE IN THE DRUG-DRUG INTERACTION STUDY

[April 26, 2010] FDA Comment on proposed study OTR1023:

"Although, a drug interaction is expected between ketoconazole and OxyContin, the magnitude of resulting increase in oxycodone exposure is unknown. In order to protect the healthy volunteers participating in this study from the opioid side effects resulting from a potential interaction, we advise that you provide naltrexone blockade to the participating volunteers. We recommend that naltrexone at a dose of 50 mg be administered during the study at the following time points in relation to OxyContin dosing: 12 hours pre-dose, 12 hours, 24 and 36 hours post-dose."

[April 27, 2010] PPLP Response:

OTR1023 is a drug-drug interaction study in which 10 mg OxyContin (oxycodone hydrochloride controlled-release [CR]) tablets will be administered to subjects with and without concomitant ketoconazole administration to assess the impact of this potent azole CYP3A4 inhibitor on oxycodone pharmacokinetics. We considered inclusion of naltrexone blockade in protocol OTR1023 but elected not to include it based upon the considerations summarized below.

In a published report, Hagelberg et al (Eur J Clin Pharmacol. 2009 Mar;65(3):263-71 attached in email) examined the interaction between oxycodone and the potent azole CYP3A4 inhibitor voriconazole in 12 healthy subjects. Oxycodone was administered as single 10 mg immediate-release (IR) capsule (Oxynorm) doses. In the presence of voriconazole, mean peak oxycodone (Cmax) increased from 18.1 to 30.5 ng/mL. This corresponds to a 1.7-fold increase in Cmax on average (range 1.4 – 2.4x). Mean total oxycodone exposure (AUCinf) increased from 102 to 363 ng.h/mL. This corresponds to a 3.6-fold increase in AUCinf on average (range 2.7 – 5.6x).

Adverse events were described by Hagelberg et al as follows:

> "All subjects completed the study. Eight of the 12 subjects experienced adverse events on day 3. Adverse events were headache (n=5), nausea (n=3), vomiting (n=1), dizziness (n=2), extreme fatigue (n=1) and itch (n=1). Three subjects received paracetamol (1,000 mg) for headache 12 h after oxycodone dosing, and one received tropisetrone 2 mg iv for nausea 5 h after dosing. All cases of nausea or vomiting were reported during the voriconazole phase. Number of reports of headache did not differ between voriconazole and control phases."

PPLP concluded that although the increase in oxycodone exposure following co-administration with voriconazole was associated with more AEs, there were no significant safety concerns raised by the observed AEs following the administration of 10 mg IR oxycodone under CYP3A4 inhibition, beyond those applicable whenever an opioid is administered under experimental conditions.

We hypothesize that since ketoconazole and voriconazole are both potent azole CYP3A4 inhibitors, they will have similar effects on oxycodone pharmacokinetics. We further hypothesize that the magnitudes of the increases in Cmax and AUC noted by Hagelberg et al are the best available predictions of the

effects of these CYP3A4 inhibitors on sirolimus exposure in healthy subjects. Voriconazole produced increases in sirolimus exposure of 7-fold and 11-fold for Cmax and AUC, respectively (Vfend Package Insert attaached in email). Ketoconazole produced increases in sirolimus exposure of 4.4-fold and 11-fold for Cmax and AUC, respectively (Floren et al. Clin Pharm Ther (1999) 65, 159–159 attached in email).

In OTR1023, oxycodone is administered in CR form as a 10 mg OxyContin dose. In the absence of CYP3A4 inhibition, this dose is expected to produce a mean Cmax of approximately 9.4 ng/mL and an AUCinf of approximately 108 ng.h/mL. It should be noted that this expected peak exposure (Cmax) is approximately 50% of that expected for a 10 mg IR oxycodone dose, while total oxycodone exposure (AUCinf) is similar for CR and IR formulations. Thus, use of a CR dosage form (OxyContin) provides a 2-fold reduction in expected Cmax, with and without CYP3A4 inhibition. Since the intensity of opioid AEs is typically related to Cmax, this margin is relevant to the safety and tolerability of oxycodone dosing in OTR1023.

In a prior PPLP single-dose crossover study OC93-0801 [submitted to IND 29,038 on October 7, 1994, Serial Number 188]), both 20 and 40 mg OxyContin doses and 20 mg IR oxycodone doses were administered to healthy subjects (n=24) without naltrexone blockade. Mean oxycodone Cmax and AUC following 40 mg OxyContin administration were 39.3 ng/mL (range 23.9 – 87.5) and 421 ng.h/mL (range 244 – 921), respectively. The OC93-0801 study report states that most AEs were mild or moderate in intensity and that there were no discontinuations due to adverse experiences. It further states that a dose-response was observed between 20 mg (n=22) and 40 mg (n=24) OxyContin doses, with 97 and 197 AEs reported, respectively, for the two treatments.

The prior safety and tolerability experience in OC93-0801 with 40 mg OxyContin administered without naltrexone represents the safety and tolerability that is expected in OTR1023 assuming ketoconazole were to produce approximately a 4-fold increase in Cmax (vs. the 1.7-fold increase noted with voriconazole) and AUC (vs. the 3.6-fold increase noted with voriconazole).

Administration of 50 mg naltrexone blockade is believed by our investigators to be associated with tolerability issues, reflected by reported AEs, and can even lead to subject discontinuations in rare instances.

While exclusion of naltrexone is advantageous in permitting a 'cleaner' assessment of the effect of ketoconazole on oxycodone pharmacokinetics, this consideration only applies if the conclusion is reached that naltrexone blockade is not required to minimize the opioid agonist effects anticipated in this study. Based upon the considerations summarized above, we concluded that naltrexone blockade is not required in this study. Therefore co-administration of naltrexone was not included in protocol OTR1023.

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