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RESEARCH**

APPLICATION NUMBER:

201194Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Addendum to the Primary Clinical Pharmacology Review Dated 09/26/2011

NDA: 201194	Re-submission Date: July 14, 2011 Original submission Date(s): May 5, 2010
Brand Name	Not proposed.
Generic Name	Oxycodone Oral solution, USP, 5mg/5mL
Reviewer	Sheetal Agarwal, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCP2
OND division	DAAAP
Sponsor	VistaPharm Inc.
Relevant IND(s)	N/A
Submission Type	Standard re-submission; 505(b)(2), referencing Roxicodone® IR tablets (NDA 21-011)
Formulation; Strength(s)	Oral solution; 5 mg/5 mL
Indication	Management of moderate to severe pain where use of an opioid analgesic is appropriate.

BACKGROUND:

At the time of signing-off the primary Clinical Pharmacology review for NDA 201194 on 09/26/2011, the Division of Scientific Investigations (DSI) inspection report for pivotal BE study R11-0285 was pending. Subsequently, DSI finalized their report on 09/27/2011 (see review by Dr. Arindam Dasgupta, Ph.D. dated 09/27/2011 in DARRTS). This addendum addresses the recommendations made by Division of Scientific investigation (DSI) on the audited pivotal BE study, R11-0285.

A DSI inspection for only the analytical portion of the recently conducted pivotal BA/BE study R11-0285, conducted in the (b) (4) facility of (b) (4) research (the same analytical site used in the previously conducted BE study R09-0988 that was found to be unacceptable upon DSI inspection), was requested in consensus with the DSI team. The clinical portion of the repeat BA/BE study R11-0285 is the same as before, i.e. Fargo, ND, and the inspection team had not identified any issues with this site when tested for the first BA/BE study R09-0988 (original NDA submission).

In his review, Dr. Dasgupta concludes that the analytical data of study R11-0285 can be accepted by Agency by review and no Form FDA-483 was issued by DSI for this study.

RECOMMENDATION:

NDA 201194 is acceptable from a Clinical Pharmacology perspective providing that an agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

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/s/

SHEETAL S AGARWAL
09/28/2011

YUN XU
09/29/2011

CLINICAL PHARMACOLOGY REVIEW

NDA: 201194	Re-submission Date: July 14, 2011 Original submission Date(s): May 5, 2010
Brand Name	Not proposed.
Generic Name	Oxycodone Oral solution, USP, 5mg/5mL
Reviewer	Sheetal Agarwal, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCP2
OND division	DAAAP
Sponsor	VistaPharm Inc.
Relevant IND(s)	N/A
Submission Type	Standard re-submission; 505(b)(2), referencing Roxicodone® IR tablets (NDA 21-011)
Formulation; Strength(s)	Oral solution; 5 mg/5 mL
Indication	Management of moderate to severe pain where use of an opioid analgesic is appropriate.

Recommendation

From the viewpoint of the Office of Clinical Pharmacology, NDA 201194 re-submitted on July 11, 2011 is acceptable provided that (a) DSI inspection finds the data from pivotal BE study R11-0285 acceptable and (b) agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

Regulatory background:

VistaPharm originally submitted this 505(b)(2) NDA 201194 for Oxycodone Hydrochloride Oral Solution, 5 mg/5 mL, a marketed unapproved product, in May 2010, for the management of moderate to severe pain where use of an opioid analgesic is appropriate. Sponsor is relying on Roxicodone® (NDA 21-011; immediate-release oxycodone tablet marketed by (b)(4)) as reference for Agency's previous findings of the safety and efficacy for oxycodone IR formulation. The NDA was issued a CR letter (signed off by Dr. Sharon hertz, dated 3/3/11 in DARRTS) citing the following reasons and options for the sponsor:

“An audit performed by the Agency of the bioequivalence study, R09-0988, identified deficiencies in the methods used at the analytical site. Because of these deficiencies, the bioequivalence study cannot be relied upon to establish bioequivalence of your proposed drug product to the reference product.

This deficiency may be addressed by doing one of the following:

- 1. Provided adequate samples are available, reanalyze blood samples collected in Study*

R09-0988 and submit data establishing the bioequivalence of Oxycodone Hydrochloride Oral Solution 5 mg/5 mL with Roxicodone tablets. Ensure that the inspectional findings identified in the Agency's audit of Study R09-0988 are properly addressed in the reanalysis of blood samples.

OR

2. Conduct another pharmacokinetic study and establish the bioequivalence of Oxycodone Hydrochloride Oral Solution with Roxicodone tablets under fasting conditions using an adequately validated analytical methodology.

OR

3. Conduct a clinical development program with clinical efficacy and safety studies to support your product.”

Following the CR letter, the sponsor decided to conduct a new BE study and the PK data from the new BE study R11-0285, are discussed in this review. For the original NDA review, the reader is referred to Clinical Pharmacology review of NDA 201194 in DARRTS (signed off by Dr. Sheetal Agarwal and Dr. Suresh Doddapaneni) dated 12/13/10.

A DSI inspection for only the analytical portion of the recently conducted pivotal BA/BE study R11-0285, conducted in the (b) (4) facility of (b) (4) research (the same analytical site used in the previously conducted BE study R09-0988 that was found to be unacceptable upon DSI inspection), has been requested in consensus with the DSI team keeping in mind, the fact, that the clinical portion of the repeat BA/BE study R11-0285 is the same as before, i.e. Fargo, ND, and the inspection team had not identified any issues with this site when tested for the first BA/BE study R09-0988 (original NDA submission).

At the time of finalizing this review, DSI inspection of the analytical portion of study R11-0285 is pending and an addendum to this review will be written if DSI audit finds significant issues affecting the acceptability of the data.

New BE study R11-0285 in the resubmission:

Bioequivalence in fasting conditions: Comparison with Roxicodone® IR tablet

Study R11-0285 was an open-label single-dose, randomized, two-period, two-treatment crossover study under fasted conditions comparing exposure of oxycodone from 15 mL of the Oxycodone Oral Solution 5 mg/5 mL (test product) to that of a single oral dose of Roxicodone 15 mg tablets following an overnight fast of at least 10 hours. A total of 28 healthy adult subjects (male and female) were enrolled in the study, and 25 subjects completed the study. Subjects were dosed sequentially, in groups of 3 in each of the two dosing periods for a total of two doses per subject. Subjects were administered naltrexone (1 x 50 mg tablet) with oxycodone administration.

PK: Single oral dose of the 15 mg oxycodone oral solution (15 mL of 5 mg/5 mL) is bioequivalent to a 15 mg Roxicodone tablet (1 x 15 mg) under fasting conditions. The 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean were within the 80.00% and 125.00% limits for C_{max}, AUC_{0-t}, and

AUC_{0-inf} using ln-transformed data. The test/reference ratios of geometric means were 103.21% (90% CI 97.78% -108.94%) for AUC_{0-t}, 103.27% (90% CI 97.93% - 108.90%) for AUC_{0-inf}, and 97.43% (90% CI 90.40% - 105.00%) for C_{max} (Table 1). The median (min-max) T_{max} was 1.0 h (0.5 – 2.0) for the test formulation and 1.0 h (0.75 - 3.0) for the reference formulation indicating that T_{max} values were similar for both the test and reference formulations (Table 2). It is concluded that the test oxycodone oral solution (5 mg/5 mL) is bioequivalent to the reference Roxycodone IR tablet (1 x 15 mg) under fasting conditions.

Figure 1: Mean Plasma Concentrations (ng/mL) of Oxycodone (0-24 hours) after 15 mg Oral Administration in Fasted Healthy Volunteers (n=25) Treated with Naltrexone (Semi-Log Scale)

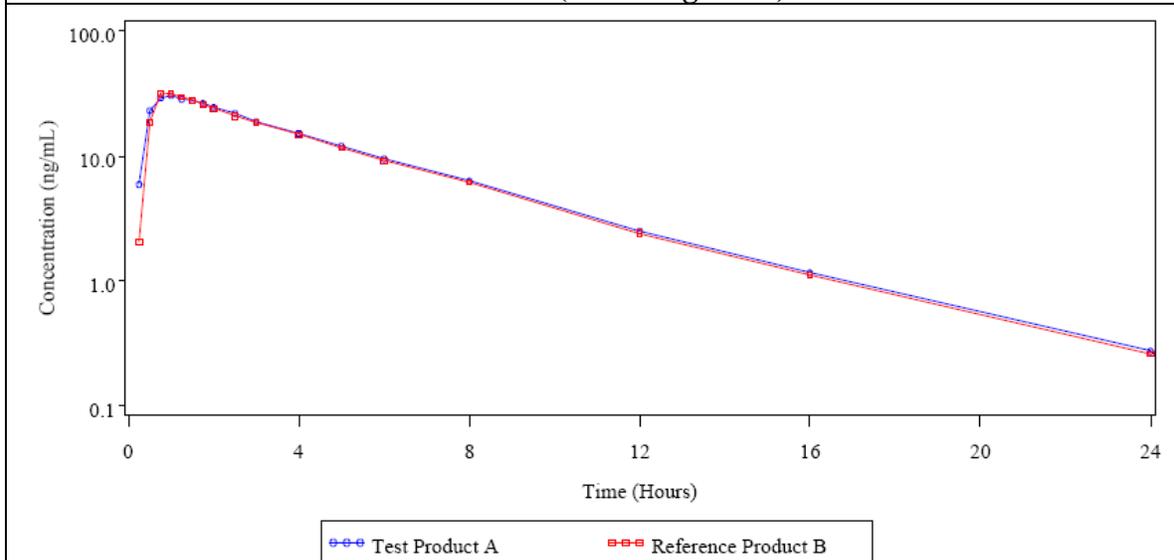


Table 1: Summary of Statistical Analysis for Study R11-0285 (N = 25)

Parameter	Test	Reference	% Ratio	90% C.I.
AUC _{0-t} (ng*hr/mL)	150.91	146.22	103.21	(97.78, 108.94)
AUC _{0-inf} (ng*hr/mL)	153.33	148.48	103.27	(97.93, 108.90)
C _{max} (ng/mL)	32.53	33.39	97.43	(90.40, 105.00)

Table 2: PK Parameters for Oxycodone in Study R11-0285

Treatments (Dose, Dosage Form, Route) [Product ID]	Arithmetic Mean (%CV) Pharmacokinetic Parameters ¹ Median (Range) for T _{max}						
	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (ng- hr/mL)	AUC _{0-inf} (ng- hr/mL)	AUC _{0-t} / AUC _{0-inf}	T _{1/2} (hr)	Kel (1/hr)
Test: Oxycodone Hydrochloride Oral Solution USP 5 mg /5 mL [Lot No. 221400]	33.40 (23.45)	1.00 (0.50 – 2.00)	154.79 (22.94)	157.25 (22.99)	0.98 (0.78)	3.48 (17.02)	0.2048 (17.73)
Reference: Roxicodone 15 mg Tablet [Lot No. 957070A]	34.48 (26.57)	1.00 (0.75 – 3.00)	150.78 (24.78)	153.12 (24.89)	0.99 (0.83)	3.49 (18.37)	0.2058 (19.16)

Analytical methods: The analytical assay (AP LC/MS/MS 382.100) for determining oxycodone concentrations in plasma samples for Study R11-0285 was conducted at (b) (4). The interface used with the API 4000 LC/MS/MS was a Turbo Ionspray® that has been validated with detection in the range of 0.2000 to 125.0 ng/mL.

Quality control samples (six sets) at concentrations of low 0.6000 ng/mL (LQC), medium 7.500 ng/mL (MQC) and high 95.00 ng/mL (HQC), prepared in human plasma, were analyzed with each assay validation run to ensure acceptable assay precision and accuracy. Also included in each batch run were six (6) sets of LLOQ (0.2000 ng/mL) and ULOQ (125.0 ng/mL) samples. Intra-day precision (%CV) and accuracy (%Bias) were evaluated from the results of the QC samples processed from three (3) batch runs. The intra-day precision (%CV) from the three (3) separate analyses was within the range of 1.0 to 3.2% and the intra-day accuracy (%Bias) was within the range of 2.0 to 10.1% for oxycodone. Inter-day precision and accuracy were evaluated from the results of the back calculated calibration standard curves for all the validation runs and QC samples analyzed for three (3) batch runs. For the calibration curve standards, the inter-day precision (%CV) was within the range of 0.4 to 1.7% and the accuracy (%Bias) was within the range of -2.9 to 2.6% for oxycodone. For the QC samples, the inter-day precision (%CV) was within the range of 1.9 to 2.6% and the inter-day accuracy (%Bias) was within the range of 3.7 to 7.9%. The precision and accuracy at the ULOQ (125.0 ng/mL) and the LLOQ (0.2000 ng/mL) were evaluated. The intra-day precision (%CV) for oxycodone at the ULOQ was in the range of 0.9 to 1.7% and at the LLOQ was in the range of 4.2 to 6.4%. The intra-day accuracy (%Bias) at the ULOQ was in the range of -2.7 to 0.9% and at the LLOQ was in the range of 1.1 to 11.0%. The inter-day precision for oxycodone at the ULOQ was 1.9% and at the LLOQ was 6.3%. The inter-day accuracy at the ULOQ and LLOQ was -1.0% and 5.9%, respectively. In addition, the

stability of oxycodone in plasma during freeze-thaw cycles, extracted samples in the refrigerator and on bench top, in biological matrix at room temperature, reinjection reproducibility and long term freezer stability parameters were reported and are acceptable.

A DSI inspection for the analytical portion of study R11-0285 has been requested, and the result is pending as of 09/19/2011.

Labeling Recommendations:

The following labeling comments are proposed by this reviewer. (Deletion is shown by ~~Strike through~~, addition is shown by underline)

Highlights/ Drug Interactions:

CYP3A4 inhibitors:  (b) (4)
The CYP3A4 enzyme plays a major role in the metabolism of oxycodone, drugs that inhibit CYP3A4 activity may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. (7.4)

Highlights/ Special Populations:

 (b) (4)

Geriatric patients (8.5), Hepatic impairment (8.6) and Renal impairment (8.7): Use caution during dose selection, starting at the low end of the dosing range while carefully monitoring for side effects.

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/s/

SHEETAL S AGARWAL
09/26/2011

YUN XU
09/26/2011

Addendum to Primary Clinical Pharmacology Review Dated 12/13/2010

NDA	201194
Submission date	05/05/2010
Reviewer	Sheetal Agarwal, Ph.D.
Team leader	Suresh Doddapaneni, Ph.D.
Generic name	Oxycodone HCl, oral solution, USP, 5mg/5mL
Sponsor	VistaPharm Inc.

Background:

VistaPharm submitted this 505(b)(2) NDA 201194 on 05/05/2010 seeking approval of Oxycodone Hydrochloride Oral Solution, 5 mg/5 mL, a marketed unapproved product, for the management of moderate to severe pain where use of an opioid analgesic is appropriate. Sponsor is relying on Roxicodone® Tablets (NDA 21-011; immediate-release oxycodone tablets marketed by (b) (4) to refer to the Agency’s previous findings of safety and efficacy. Approval of this product is dependent on successful demonstration of bioequivalence (BE) to the reference Roxicodone Tablets.

Study R09-0988 (clinical site: Cetero Research, Fargo, ND and analytical site: (b) (4)) demonstrated BE of the test Oxycodone Oral Solution (5 mg/5 mL) to the reference Roxicodone® IR Tablets, under fasting conditions, Since this was a pivotal BE study, Division of Scientific Investigations (DSI) inspection of this study was required. At the time of the completion of the Clinical pharmacology review of this NDA (review dated 12/13/2010), report of DSI inspection was pending and acceptability of the Clinical Pharmacology data in the NDA was deferred pending ‘acceptable’ DSI inspection findings.

DSI Inspection Findings:

In his review dated 02/03/2011, Dr. Xikui Chen of DSI identified the following 2 issues with respect to BE study R09-0988:



Following evaluation of the inspectional findings, Dr. Chen made the following recommendation:

Recommendation:

Based on the identified issues and the recommendation to not accept the data from Study R09-0988 in the DSI review, data obtained from this study cannot be accepted to conclude demonstration of BE of Oxycodone Oral Solution (5 mg/5 mL) to Roxicodone® IR Tablets. The following deficiencies and remedial actions to address the deficiencies from a clinical pharmacology perspective should be conveyed to the sponsor, VistaPharm Inc.:

Clinical Pharmacology deficiency to be conveyed to the sponsor:

An audit performed by the Agency of the bioequivalence study R09-0988 identified analytical methodology related deficiencies at the analytical site. Because of these deficiencies, data obtained from this study cannot be relied upon to establish bioequivalence of your proposed drug product, Oxycodone HCl Oral Solution, 5mg/5mL, to the reference product, Roxicodone® (oxycodone hydrochloride tablets).

These deficiencies may be addressed in either one of the following two ways:

Provided adequate subject samples from bioequivalence study R09-0988 are still available, reanalyze the samples for oxycodone and submit data establishing bioequivalence of Oxycodone Hydrochloride Oral Solution, 5 mg/mL with Roxicodone® (oxycodone hydrochloride tablets). Ensure that the inspectional deficiencies identified in Agency's audit of study R09-0988 are properly addressed in the reanalysis of the subject samples.

OR

Conduct another pharmacokinetic study to establish bioequivalence of Oxycodone Hydrochloride Oral Solution, 5mg/5mL with Roxicodone® (oxycodone hydrochloride tablets) under fasting conditions using adequately validated analytical methodology.

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/s/

SHEETAL S AGARWAL
02/08/2011

SURESH DODDAPANENI
02/08/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	NDA 201194		Proposed Brand Name	Oxycodone HCl, oral solution, USP, 5mg/5mL
OCP Division (I, II, III, IV, V)	II		Generic Name	Oxycodone HCl, oral solution, USP, 5mg/5mL
Medical Division	DAAP		Drug Class	Opioid
OCP Reviewer	Sheetal Agarwal		Proposed Indication(s)	Management of moderate to severe pain where use of an opioid analgesic is appropriate.
OCP Team Leader	Suresh Doddapaneni		Dosage Form	Oral solution; 5 mg/5 mL
Pharmacometrics Reviewer			Dosing Regimen	
Date of Submission	May 5, 2010		Route of Administration	Oral
Estimated Due Date of OCP Review			Sponsor	VistaPharm
Medical Division Due Date			Priority Classification	S
PDUFA Due Date	April 30, 2011			
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	3	3	1 fasted and 1 fed BE study submitted referencing Roxicodone IR tablets and 1 bioanalytical report
replicate design; single / multi dose:				
Food-drug interaction studies	X			
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Pediatric development plan		1	1	(b) (4)
Literature References				
Total Number of Studies	4	4	4	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

SHEETAL AGARWAL

Reviewing Clinical Pharmacologist

Date

SURESH DODDAPANENI

Team Leader/Supervisor

Date

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/s/

SHEETAL S AGARWAL
01/19/2011

SURESH DODDAPANENI
01/19/2011

CLINICAL PHARMACOLOGY REVIEW

NDA: 201194	Submission Date(s): May 5, 2010
Brand Name	N/A
Generic Name	Oxycodone HCl, oral solution, USP, 5mg/5mL
Reviewer	Sheetal Agarwal, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	DCP2
OND division	DAAP
Sponsor	VistaPharm Inc.
Relevant IND(s)	N/A
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Oral solution; 5 mg/5 mL
Indication	Management of moderate to severe pain where use of an opioid analgesic is appropriate.

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1 Executive Summary

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, NDA 201194 submitted on May 5, 2010 is acceptable provided that (a) DSI inspection finds the data from pivotal BE study R09-0988 acceptable and (b) agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

VistaPharm submitted this 505(b)(2) NDA 201194 for Oxycodone Hydrochloride Oral Solution, 5 mg/5 mL, a marketed unapproved product, for the management of moderate to severe pain where use of an opioid analgesic is appropriate. Single-ingredient oxycodone hydrochloride immediate-release oral tablets are approved in the US in strengths ranging from 5 mg to 30 mg for management of moderate to severe pain where the use of an opioid analgesic is appropriate. Sponsor is relying on Roxicodone® (NDA 21-011; immediate-release oxycodone tablet marketed by (b) (4) to refer the Agency's previous findings of the safety and efficacy.

The clinical and clinical pharmacology database for this NDA consists of two bioavailability/bioequivalence (BA/BE) studies, study R09-0988 and study R09-0989. These studies are randomized, single-dose, two-period, two-treatment crossover studies in naltrexone blocked healthy male and female volunteers designed to establish BE of the oral solution (5 mg/5 mL) to Roxicodone® IR tablet, under fasting and fed conditions. Whereas study R09-0988 tests for BE of test to reference under overnight fasting conditions, study R09-0989 tests for BE of test to reference in the presence of a high fat, high calorie meal.

Bioequivalence in fasting conditions: Comparison with Roxicodone® IR tablet

Single oral dose of the 15 mg oxycodone oral solution (15 mL of 5 mg/5 mL) is bioequivalent to a 15 mg Roxicodone® tablet (1 x 15 mg) under fasting conditions. The 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean were within the 80.00% and 125.00% limits for C_{max}, AUC_{0-t}, and AUC_{0-inf} using ln-transformed data. The test/reference ratios of geometric means were (b) (4) for C_{max}. The median (min-max) T_{max} was (b) (4) for the test formulation and (b) (4) for the reference formulation indicating that T_{max} values were similar for both the test and reference formulations.

Bioequivalence in fed conditions: Comparison with Roxicodone® IR tablet

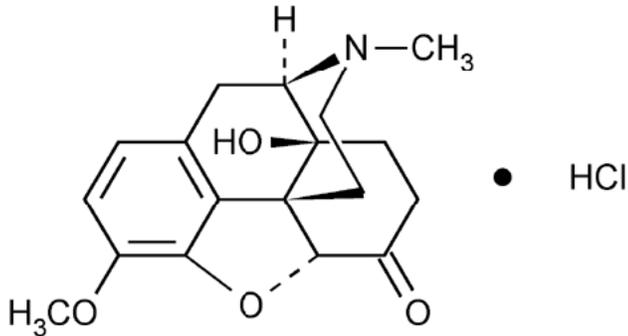
Single oral dose of the 15 mg oxycodone oral solution (15 mL of 5 mg/5 mL) is not bioequivalent to a 15 mg Roxicodone® tablet (1 x 15 mg) under fed conditions. The extent of exposure (AUC) values were similar for both test and reference formulations, however the mean peak plasma value (Cmax) was slightly (b) (4) for test as compared to the reference formulation. The 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean were within the 80% and 125% limits for AUC0-t, and AUC0-inf using ln-transformed data. The 90% confidence interval about the ratio of the test geometric mean to the reference geometric mean was not within the 80% and 125% limits for Cmax using ln-transformed data. The test/reference ratios of geometric means were (b) (4) for Cmax. The median (min-max) Tmax was (b) (4) for the test formulation and (b) (4) for the reference formulation indicating that there was a slight delay in oxycodone absorption (b) (4) in fed conditions.

At the time of finalizing this review, DSI inspection of study R09-0988 is pending and an addendum to this review will be written if DSI audit finds significant issues affecting the acceptability of the data.

2 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product?

Table 1: Physical-Chemical Properties of Oxycodone Hydrochloride	
Drug Name	Oxycodone Hydrochloride
Chemical Name	4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
Structure	
Molecular Formula	C ₁₈ H ₂₁ NO ₄ ·HCl
Molecular Weight	351.82
Melting Point	218°C -223°C (range not to exceed 2°C)
Appearance	White to off-white, fine crystalline powder
Solubility	Up to 0.18 g/mL in water (pH 6.5-6.6); ~0.10 g/mL in water (pH>6.6)

The components and composition of the drug product, oxycodone HCl solution 5 mg/5 mL is listed in **Table 2**.

Table 2: Components and Composition of Oxycodone HCl Oral Solution, 5 mg/5 mL				
Oxycodone HCl Oral Solution, USP, 5mg/5mL				
Formula Ingredient	Provider	Function	Strength	
			Per mL	(b) (4)
Oxycodone HCl, USP	(b) (4)	Active	1.00 mg	(b) (4)
Poloxamer 188, NF			(b) (4)	
Sodium Benzoate, NF/FCC				
Citric Acid Anhydrous, USP				
Glycerin Natural (b) (4) USP				
Sorbitol Solution 70%, USP				
FD&C Red #40				
Raspberry Flavor (b) (4)				
Purified Water, USP				

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Oxycodone is a pure agonist opioid whose principle therapeutic action is analgesic. Oxycodone capsule is indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Oxycodone solution is intended for oral administration. The proposed dosing regimen is 5 to 15 mg every 4 to 6 hours as needed.

2.2 General Clinical Pharmacology

2.2.1. What is known about the PK characteristics of oxycodone in general?

When administered orally, oxycodone is well absorbed. About 60% to 87% of an oral dose of oxycodone reaches the systemic circulation in comparison to a parenteral dose. Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone. The formation of noroxycodone is mainly mediated by CYP3A4 and the formation of oxymorphone is mediated by CYP2D6. Oxymorphone is a known analgesic that is marketed in parenteral form in the US. However, although possessing analgesic activity, oxymorphone is present in plasma only in low concentrations (about 15% of administered dose), after oral administration of oxycodone. Oxycodone and its metabolites are excreted primarily via the kidney. Food has been shown to have no significant effect on the extent of absorption of oxycodone. However, studies have demonstrated the peak plasma concentrations, of oxycodone, increased by as much as 25% when administered with a high-fat meal. Following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk. Precautions should be taken for special populations. Apparent elimination half-life of oxycodone is 3.5 to 4 hours. Oxycodone and its metabolites are excreted as urine as both conjugated and unconjugated metabolites.

2.2.2. Were the active moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?

Oxycodone analgesic activity is primarily due to the parent compound oxycodone, only the parent compound was measured in the 2 BA/BE studies.

2.3 Intrinsic Factors

2.3.1. What is the pediatric plan?

In line with the Agency's current policy with respect to pure opioids, sponsor would be required to conduct pharmacokinetics studies in children of all ages and efficacy studies in children up to 2 years of age. At this time, sponsor is requesting deferral of pediatric studies since adult studies are complete and ready for approval. This seems reasonable and the required pediatric studies will have to be conducted as post marketing requirements.

2.4 Extrinsic Factors

Two articles related to drug-drug interactions with oxycodone were published subsequent to the approval of the reference Roxicodone Tablets Product. These articles are: (1) Hagelberg NM et al., Voriconazole drastically increases exposure to oral oxycodone. *Eur J Clin Pharmacol.* 2009;65:263-271 and (2) Nieminen TH et al., Rifampin greatly reduces the plasma concentrations of intravenous and oral oxycodone. *Anesthesiology.* 2009;110:1371-1378. Since the findings from these studies are relevant to all oxycodone products, Agency has been incorporating these findings into oxycodone package inserts as appropriate. As such, package insert of this product will also be updated with these metabolism and drug-drug interaction data.

2.5 General Biopharmaceutics

2.5.1 *Is the proposed oxycodone oral solution bioequivalent to the reference immediate release oral tablet following single dose administration in fasting conditions?*

When administered as a 15 mg dose (15 mL of 5 mg/5 mL) in the fasted state, the oxycodone plasma concentration-time profiles for test oxycodone oral solution and reference Roxicodone® IR tablet are similar (Figure 1). Box plots comparing C_{max}, AUC_t and AUC_{inf} values are shown in Figure 2. The statistical analysis results for the assessment of bioequivalence between the two are presented in the Table 3. Results showed that the ratio of the geometric means for log transformed C_{max} and AUC values as well as its corresponding confidence intervals fell within the range of 80% to 125%. PK Parameters for oxycodone are presented in Table 4. The T_{max} values for both test and reference are similar. It is concluded that the test oxycodone oral solution (5 mg/5 mL) is bioequivalent to the reference Roxicodone® IR tablet (1 x 15 mg) under fasting conditions.

Figure 1: Mean Plasma Concentrations (ng/mL) of Oxycodone after 15 mg Oral Administration in Fasted Healthy Volunteers (n=26) Treated with Naltrexone.

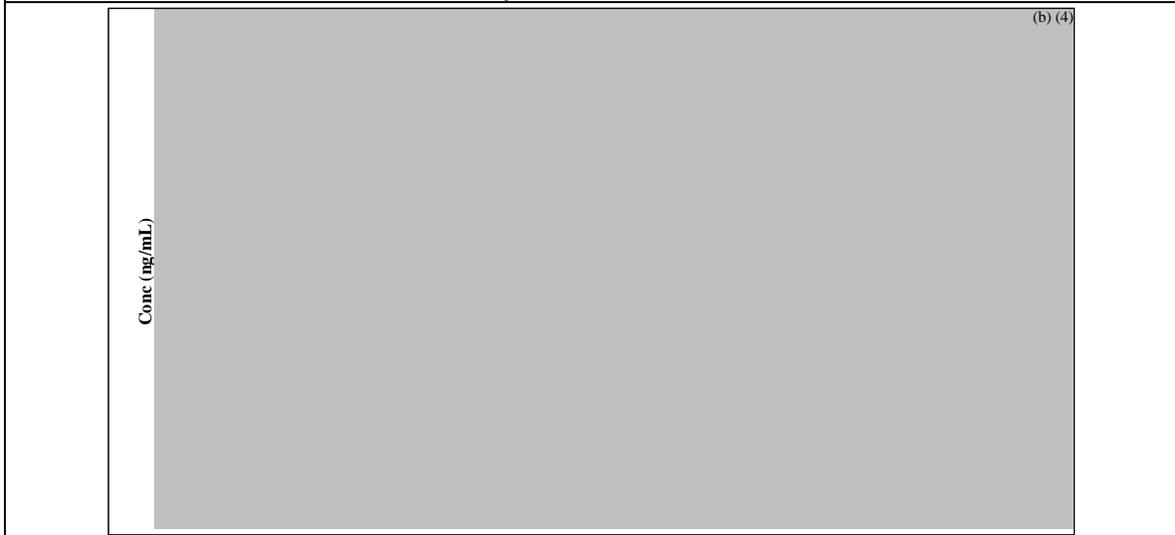


Figure 2: Box Plots for PK Parameters for Oxycodone in the Fasted BE Study R09-0988

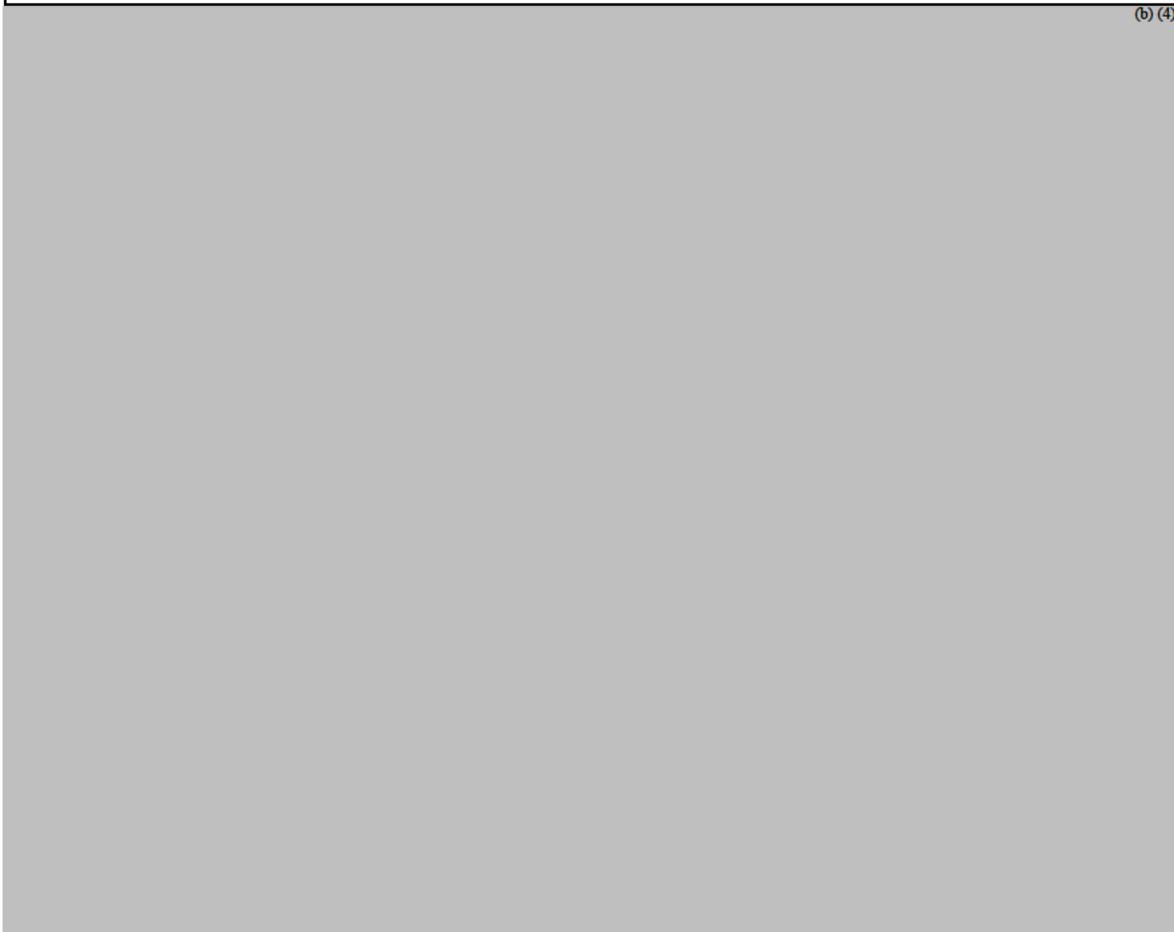


Table 3: Summary of Statistical Analysis for Study R09-0988 (N = 26)

Ln-Transformed Data						
Variable	Least Squares Mean		Geometric Mean			90 % Confidence Interval
	Test	Reference	Test	Reference	% Ratio	(Lower Limit, Upper Limit)
C _{max}	(b) (4)					
AUC _{0-t}						
AUC _{0-inf}						

Table 4: PK Parameters for Oxycodone in Study R09-0988			
Variable	Least Squares Mean		
	Test	Reference	% Ratio
C _{max}	(b) (4)		
AUC _{0-t}			
AUC _{0-inf}			
T _{max}			
Kel			
t _{1/2}			

2.5.2 Does food affect the bioavailability of oxycodone from the oral solution?

BE study R09-0989, compared absorption of oxycodone from both test oxycodone oral solution and reference Roxicodone® IR tablet under fed conditions. Prior to each dose, subjects fasted at least 10 hours, then consumed a standardized high-fat, high-calorie breakfast 30 minutes prior to drug administration.

The statistical analysis results for the assessment of bioequivalence between test and reference when administered with food are presented in the Table 5. Results showed that the point estimates and their 90% CIs were contained within the acceptance range of 80% to 125% for AUC_{0-t}, and AUC_{0-inf}. However, the C_{max} for the test formulation was lower than that for the reference formulation, having a lower confidence interval limit of (b) (4). PK Parameters for oxycodone are presented in Table 6. The median (min-max) T_{max} was (b) (4) for the test formulation and (b) (4) for the reference formulation. It is concluded that the test oxycodone oral solution (5 mg/5 mL) is not bioequivalent to the reference Roxicodone® IR tablet (1 x 15 mg) under fed conditions. Although, effect of food on the absorption of oxycodone from the oxycodone oral solution was not tested by administering it under fasted and fed conditions in the same study, data obtained in study R09-0989 shows that presence of food is not expected to have a clinically significant impact on the absorption of oxycodone from oxycodone oral solution.

Table 5: Summary of Statistical Analysis for Study R09-0989 (N = 24)						
Ln-Transformed Data						
PK Variable	Least Squares Mean		Geometric Mean			90 % Confidence Interval (Lower Limit, Upper Limit)
	Test	Reference	Test	Reference	% Ratio	
C _{max}	(b) (4)					(b) (4)
AUC _{0-t}						
AUC _{0-inf}						

Table 6: PK Parameters for Oxycodone in Study R09-0989			
PK Variable	Least Squares Mean		
	Test	Reference	% Ratio
C _{max}	(b) (4)		
AUC _{0-t}			
AUC _{0-inf}			
T _{max}			
Kel			
T _{1/2}			

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess concentrations?

The analytical assays for Studies R09-0988 and R09-0989 were conducted at (b) (4) to determine the plasma concentrations of oxycodone in the study samples. The analysis was performed by an API 4000 LC/MS/MS system. The interface used with the API 4000 LC/MS/MS was a Turbo Ionspray®. The positive ions were measured in MRM mode. The analyte was quantitated using a liquid-liquid extraction procedure. Analytical method used in both studies was AP LC/MS/MS 382.100. Following extraction, 5.0 µL of each sample was injected onto a LC/MS/MS system. The data was acquired by and integrated on Applied Biosystems “Analyst” version 1.4.1 Software. Linear regression, with 1/x² weighting, performed in Watson LIMS version 6.4.0.02™ for Windows, was used to obtain the best fit of the data for the

calibration curves. The lower limit of quantitation (LLOQ) was 0.2000 ng/mL and the upper limit of quantitation (ULOQ) was 125.0 ng/mL. The intra-day precision (%CV) from the three (3) separate analyses was within the range of 1.0 to 3.2% and the intra-day accuracy (%Bias) was within the range of 2.0 to 10.1% for oxycodone. For the QC samples, the inter-day precision (%CV) was within the range of 1.9 to 2.6% and the inter-day accuracy (%Bias) was within the range of 3.7 to 7.9%. The mean recovery of oxycodone from plasma was 86.6% and the precision (%CV) was 5.3%. The mean recovery of internal standard from plasma was 87.2% and the precision (%CV) was 5.2%.

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4 Appendix

4.1 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology <i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	NDA 201194	Proposed Brand Name	Oxycodone HCl, oral solution, USP, 5mg/5mL	
OCP Division (I, II, III, IV, V)	II	Generic Name	Oxycodone HCl, oral solution, USP, 5mg/5mL	
Medical Division	DAAP	Drug Class	Opioid	
OCP Reviewer	Sheetal Agarwal	Proposed Indication(s)	Management of moderate to severe pain where use of an opioid analgesic is appropriate.	
OCP Team Leader	Suresh Doddapaneni	Dosage Form	Oral solution; 5 mg/5 mL	
Pharmacometrics Reviewer		Dosing Regimen		
Date of Submission	May 5, 2010	Route of Administration	Oral	
Estimated Due Date of OCP Review		Sponsor	VistaPharm	
Medical Division Due Date		Priority Classification	S	
PDUFA Due Date	April 30, 2011			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE		2	2	1 fasted and 1 fed BE study submitted referencing Roxycodone IR tablets
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods		1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				

Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
-				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies	X			
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan		1		
Literature References				
Total Number of Studies	2	4	4	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

SHEETAL AGARWAL

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEETAL S AGARWAL
12/13/2010

SURESH DODDAPANENI
12/13/2010