

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205223Orig1s000

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

CLINICAL PHARMACOLOGY REVIEW

NDA	205,223
Submission Date:	05/24/2013
Brand Name	N/A
Generic Name	Metronidazole Vaginal Gel 1.3%
OCP Reviewers	Zhixia (Grace) Yan, Ph.D.
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807
Relevant IND(s)	IND 107,484
Submission Type; Code	Original NDA, Standard
Formulation; Strength(s)	Vaginal Gel 1.3% in a pre-filled applicator which delivers approximately 5 g of gel containing 65 mg of metronidazole
Indication	Treatment of bacterial vaginosis in non-pregnant women
Dosage and Administration	A single-dose, pre-filled disposable applicator administered once intravaginally at bedtime

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1. EXECUTIVE SUMMARY

Valeant Pharmaceuticals submitted a New Drug Application (NDA) for Metronidazole Vaginal Gel 1.3% for the treatment of bacterial vaginosis (BV) in non-pregnant women. Metronidazole is a nitroimidazole drug that has been marketed in the United States since 1963 for oral, intravenous, topical and vaginal administration. MetroGel-Vaginal[®] (metronidazole vaginal gel 0.75%) was approved in the US in 1992 (under NDA 20,208) for the treatment of BV. The current regimen of MetroGel-Vaginal 0.75% requires a 5-day treatment. The applicant reformulated the metronidazole vaginal gel with a higher concentration of metronidazole (1.3%) with the intent to provide a single dose formulation with equal or improved efficacy compared to currently marketed products requiring 5 to 7 days of treatment (e.g, MetroGel-Vaginal 0.75%). Metronidazole Vaginal Gel 1.3% will be provided in a single dose applicator with 5 g of gel containing 65 mg of metronidazole. Patients will be instructed to deliver the entire contents of the applicator intravaginally once at bedtime.

Clinical components of this NDA are described as follows:

- A Phase 1, single-dose pharmacokinetic (PK) study of Metronidazole Vaginal Gel 1.3% in healthy non-pregnant females between 18 and 40 years of age (MP-1601-02).
- A Phase 2 study designed to evaluate the safety and efficacy of Metronidazole Vaginal Gel 1.3% administered once daily for 1, 3, or 5, days compared with MetroGel-Vaginal 0.75% administered once daily for 5 days in treating subjects with BV (GW05-0904).
- A Phase 3, multi-center, randomized, double-blind, parallel group, vehicle-controlled study to evaluate the safety and efficacy of a single intravaginal dose of Metronidazole Vaginal Gel 1.3% compared with a single intravaginal dose of Vehicle Gel in treating subjects with BV (MP-1601-01).

Because the metronidazole vaginal gel product (MetroGel-Vaginal 0.75%) has already been approved in the US, the review for this current product will be abbreviated, and only the most relevant questions from the Question-Based Review (QBR) will be included.

1.1 Recommendations

The Office of Clinical Pharmacology, Division 4 has reviewed NDA 205,223, and it is acceptable from a clinical pharmacology perspective.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

1.3.1 Pharmacokinetics

Following a single intravaginal application of 1.3% metronidazole vaginal gel (5 g, equivalent to approximately 65 mg of metronidazole) to 20 healthy female subjects, the mean C_{\max} of metronidazole was 239 ng/mL (range of 114 to 428 ng/mL). The mean $AUC_{0-\infty}$ was 5434 ng.h/mL (range of 1382 to 12744 ng.h/mL). The average T_{\max} was 7.3 hours (range of 3.9 to 18 hours) with an average half-life of 9.65 hours. These results are comparable to those of a marketed product, MetroGel-Vaginal 0.75% (5 g, equivalent to 37.5 mg of metronidazole). Following a single intravaginal application of MetroGel-Vaginal 0.75% in healthy subjects, the mean C_{\max} of metronidazole was 237 ng/mL (range: 152 to 368 ng/mL), the mean $AUC_{0-\infty}$ was 4977 ng.h/mL (CV=57.7%). In addition, the C_{\max} and AUC following a single intravaginal application of 1.3% metronidazole vaginal gel is approximately 2% and 4%, respectively, of those reported in healthy subjects administered a single, oral 500 mg dose of metronidazole (C_{\max} = 12,785 ng/mL; $AUC_{0-\infty}$ = 125,000 ng•hr/mL). Of note, the dose of 500 mg of oral metronidazole is recommended for the treatment of BV.

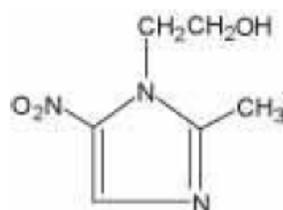
2. ABBREVIATED QUESTION-BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Metronidazole is a nitroimidazole (2-[2-methyl-5-nitro-1*H*-imidazol-1-yl] ethanol), $C_6H_9N_3O_3$; MW=171) with a structure as depicted in Figure 2.1.1-1 below:

Figure 2.1.1-1. Chemical Structure of Metronidazole



Metronidazole vaginal gel 1.3% is [REDACTED]^{(b) (4)} gel with a pH of ~4.0, and it contains metronidazole and the excipients: purified water, polyethylene glycol, propylene glycol, polycarbophil, benzyl alcohol, methyl paraben and propyl paraben (**Table 2.1.1-1**).

Table 2.1.1-1. Drug Product Components and Composition

Component	Function	Quality Standard	Quantity (% w/w)
Metronidazole	Active	USP	1.3
Polyethylene Glycol 400	(b) (4)	NF	(b) (4)
Propylene Glycol		USP	
Benzyl Alcohol		NF	
Methylparaben		NF	
Propylparaben		NF	
Polycarbophil		USP	
Purified Water		USP	

USP= United States Pharmacopeia

NF=National Formulary

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

Metronidazole is a nitroimidazole classified as both an antibiotic and as an anti-protozoal agent. The exact mechanism of action is unknown, but likely involves reduction by low-redox potential electron transport proteins with the resultant reactive species causing DNA disruption and inhibition of nucleic acid synthesis. Metronidazole Vaginal Gel 1.3% is proposed for the treatment of BV in non-pregnant women.

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

Metronidazole Vaginal Gel 1.3% will be provided in a single dose applicator with 5 g of drug product containing 65 mg of metronidazole. Patients will be instructed to deliver the entire contents of the applicator intravaginally once at bedtime.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

There was one Phase 1 study (MP-1601-02) evaluating the pharmacokinetics of metronidazole following a single intravaginal application of 1.3% metronidazole vaginal gel (5 g, equivalent to approximately 65 mg of metronidazole) to 20 healthy female subjects.

The efficacy of the single application of Metronidazole Vaginal Gel 1.3% was evaluated in one Phase 2 (GW05-0904) and one Phase 3 (MP-1601-01) studies (Table 2.2.1-1).

Table 2.2.1-1. Overview of Clinical Efficacy Trials for of Metronidazole Vaginal Gel 1.3% in the Treatment of BV

Study No.	Design	Metronidazole Vaginal Gel 1.3% Regimen	Comparator Regimen	Population Size
MP-1601-01	Phase 3 -Randomized -Double-blind -Parallel -Vehicle-controlled	a single dose at bedtime	Vehicle Vaginal Gel	Metronidazole Vaginal Gel 1.3%: N=325 Vehicle Vaginal Gel: N=326
GW05-0904	Phase 2 -Open-label -Dose-ranging -Randomized	QD x 1 day QD x 3 day QD x 5 day	MetroGel-Vaginal 0.75% QD x 5 days	<i>MetroGel-Vaginal Gel 0.75%</i> QD x 5 days: N=49 <i>Metronidazole Vaginal Gel 1.3%</i> QD x 1 day: N=43 QD x 3 day: N=48 QD x 5 day: N=49

Note: Adapted from Module 2.5, Clinical Overview

2.2.2 Exposure-response

2.2.2.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Phase 2 Trial: Regimens of Metronidazole Vaginal Gel 1.3% QD for 1, 3, and 5 days were evaluated in a dose-ranging Phase 2 trial (**Table 2.2.2-1**). The primary efficacy endpoint was the proportion of subjects with the therapeutic cure (clinical cure and a bacteriological cure) at the TOC/EOS visit.

Table 2.2.2-1 Summary of Therapeutic Cure Rate at Test of Cure/End of Study

	Metronidazole			
	0.75% QD x 5 Days (N=49)	1.3% QD x 1 Day (N=43)	1.3% QD x 3 Days (N=48)	1.3% QD x 5 Days (N=49)
Therapeutic cure				
Cured, n (%)	10 (20.4)	13 (30.2)	12 (25.0)	16 (32.7)
Failed, n (%)	39 (79.6)	30 (69.8)	36 (75.0)	33 (67.3)
95% CI for cure rate	(10.2, 34.3)	(17.2, 46.1)	(13.6, 39.6)	(19.9, 47.5)

Note: Adapted from Module 2.5, Clinical Overview

When Metronidazole Vaginal Gel 1.3% was applied daily for 1, 3, or 5-days, the medication provided comparable or numerically greater investigator/microbiology-assessed cure rates than the MetroGel-Vaginal 0.75% formulation given daily for five days. A single dose of Metronidazole Vaginal Gel 1.3% appeared to have the highest patient acceptability and was the

dose taken forward to the Phase 3 study.

2.2.2.2 What are the characteristics of the exposure-response relationships (dose-response, concentration response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Phase 2 Trial: There were no deaths and no subject was discontinued from the study due to an adverse event (AE). No clinically important differences were observed in the incidence of TEAEs across treatment groups. Most AEs were mild or moderate in severity and were assessed as unrelated to study treatment. Overall, the most commonly reported AEs (occurring in $\geq 2\%$ of subjects in any group) were vulvovaginal candidiasis and headache. There did not appear to be an increase in adverse events associated with the increased number of doses.

2.2.3 What are the PK characteristics of the drug and its major metabolite?

2.2.3.1 What are the single dose and multiple dose PK parameters?

Single-Dose: Following a single intravaginal application of 1.3% metronidazole vaginal gel (5 g, equivalent to approximately 65 mg of metronidazole) to 20 healthy female subjects, the mean C_{\max} of metronidazole was 239 ng/mL (range of 114 to 428 ng/mL). The mean $AUC_{0-\infty}$ was 5434 ng.h/mL (range of 1382 to 12744 ng.h/mL). The average T_{\max} was 7.3 hours (range of 3.9 to 18 hours) with an average half-life of 9.65 hours.

Multiple-Dose: Metronidazole Vaginal Gel 1.3% is intended as a single dose administration and repeated administration was not evaluated.

2.3 General Biopharmaceutics

2.3.1 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on the absorption, distribution, or bioavailability of Metronidazole Vaginal Gel 1.3% was not evaluated.

2.4 Analytical Section

2.4.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Metronidazole was quantified in human plasma by a validated LC-MS/MS assay and the assay was acceptable for intended purposes. See **Table 2.4.1-1** for details.

Table 2.4.1-1. Summary of the Analytical Method for Quantification of Metronidazole

	Plasma	Comment
Validation Report	MED-R2122	
Clinical Study	MP-1601-02	
Method	LC-MS/MS	
Analyte	Metronidazole	
Internal Standard	Metronidazole-d ₄	
Linearity, r ²	≥0.996	Satisfactory
Standard Curve (ng/mL)	1-500	Satisfactory
LLOQ (ng/mL)	1	Satisfactory
QC Samples (ng/mL)	3, 150, 375	Satisfactory
Accuracy, %Nominal Concentration	90.4-103.2%	Satisfactory
Precision, %CV	0.5-10.7%	Satisfactory
Stability		
At -20 °C	516 days in human plasma	Satisfactory
At 4°C	41 days in 50:50 methanol:water	Satisfactory

3. DETAILED LABELING RECOMMENDATIONS

The following proposed package insert has been marked by revisions made by the Reviewer, indicated with ~~red strikethrough font~~ for deleted text and underlined blue text for inserted text.

Affected sections include the following:

- **Clinical Pharmacology (12)**

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Following a single, intravaginal 5 g dose of TRADENAME (equivalent to 65 mg of metronidazole) to 20 healthy female subjects, a mean maximum serum metronidazole concentration (C_{max}) of 239 ng/mL was observed (range: 114 to 428 ng/mL). The average time to achieve this C_{max} was 7.3 hours (range: 4 to 18 hours). This C_{max} is approximately 2% of the mean maximum serum concentration reported in healthy subjects administered a single, oral 500 mg dose of metronidazole (mean C_{max} = 12,785 ng/mL).

The extent of exposure [area under the curve (AUC)] of metronidazole, when administered as a single intravaginal 5 g dose of TRADENAME (equivalent to 65 mg of metronidazole), was 5,434 ng•hr/mL (range: 1382 to 12744 ng•hr/mL). This AUC_{0-∞} is approximately 4% of the reported AUC of metronidazole following a single oral 500 mg dose of metronidazole (approximately 125,000 ng•hr/mL).

APPENDIX 1: Individual Study Reviews
STUDY NO.: MP-1601-02

AN OPEN-LABEL STUDY OF THE PHARMACOKINETICS OF METRONIDAZOLE VAGINAL GEL, 1.3%

Date(s): 10 July 2012 – 04 Aug 2012

Investigator(s): Philip LaStella, MD

Clinical Site: TKL Research, Inc., 4 Forest Avenue, Paramus, NJ 07652

Analytical Site

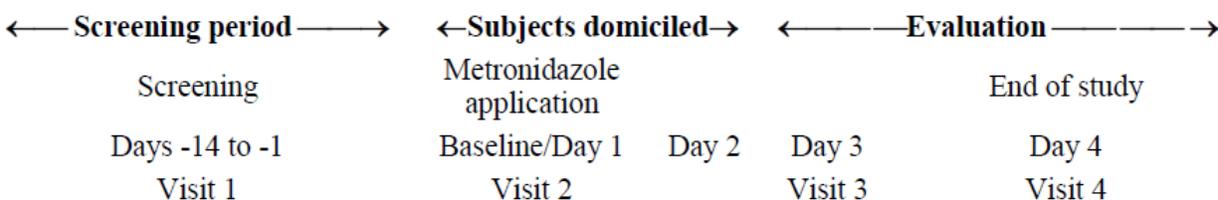
(b) (4)

OBJECTIVE: To assess the single-dose pharmacokinetics (PK) of metronidazole vaginal gel 1.3%.

METHODS

Study Design: This was an open-label PK study. A schematic overview of the trial is provided in **Figure 1**. Briefly, eligible female subjects were domiciled at the study center from Day 1 through Day 2. Subjects remained in a reclined position for at least six hours after study product was applied. Blood samples for the determination of plasma concentrations of metronidazole were obtained up to 72 hours postdose.

Figure 1. Schematic overview of trial MP-1601-02



Inclusion/Exclusion Criteria: Healthy females, 18-40 years of age, body mass index (BMI) < 29.9 kg/m², non-smoking, non-pregnant, non-lactating, and within the second or third week of their menstrual cycle were enrolled. Subjects who were menopausal or post-menopausal, or had a history of alcohol abuse or drug dependence within the last year, or received systemic or intravaginal antifungal, antibacterial or antiparasitic drugs within 14 days prior to the first dose of study medication were excluded.

Drug Products: Metronidazole vaginal gel 1.3% was supplied in prefilled applicators. Each applicator contained approximately 5 g, equivalent to 65 mg metronidazole.

Pharmacokinetic Assessment: Blood samples were collected for pharmacokinetic analysis of metronidazole at predose, and 1 (± 5 min), 2 (± 5 min), 3 (± 5 min), 4 (± 5 min), 5 (± 5 min), 6 (± 5 min), 7 (± 5 min), 8 (± 5 min), 9 (± 5 min), 10 (± 5 min), 12 (± 5 min), 18 (± 5 min), 24 (± 5 min), 48 (± 2 hours), and 72 (± 2 hours) hours after application of the study product. Blood samples were analyzed for plasma concentrations of metronidazole using a validated LC-MS/MS method (**Table 1**). Pharmacokinetic parameters (C_{max} , T_{max} , $t_{1/2}$, AUC_{0-t} , $AUC_{0-\infty}$) were calculated from the plasma concentration data using non-compartmental analysis.

Table 1. Summary of the analytical method for quantification of metronidazole.

	Plasma	Comment
Validation Report	MED-R2122	
Clinical Study	MP-1601-02	
Method	LC-MS/MS	
Analyte	Metronidazole	
Internal Standard	Metronidazole-d ₄	
Linearity, r ²	≥0.996	Satisfactory
Standard Curve (ng/mL)	1-500	Satisfactory
LLOQ (ng/mL)	1	Satisfactory
QC Samples (ng/mL)	3, 150, 375	Satisfactory
Accuracy, %Nominal Concentration	90.4-103.2%	Satisfactory
Precision, %CV	0.5-10.7%	Satisfactory
Stability At -20 °C At 4°C	516 days in human plasma 41 days in 50:50 methanol:water	Satisfactory Satisfactory

Safety Assessment: Adverse events and concomitant medications were collected throughout the study. Routine clinical laboratory assessments (serum chemistry, hematology, and urinalysis) were conducted at screening and 24 hours postdose.

RESULTS AND CONCLUSIONS

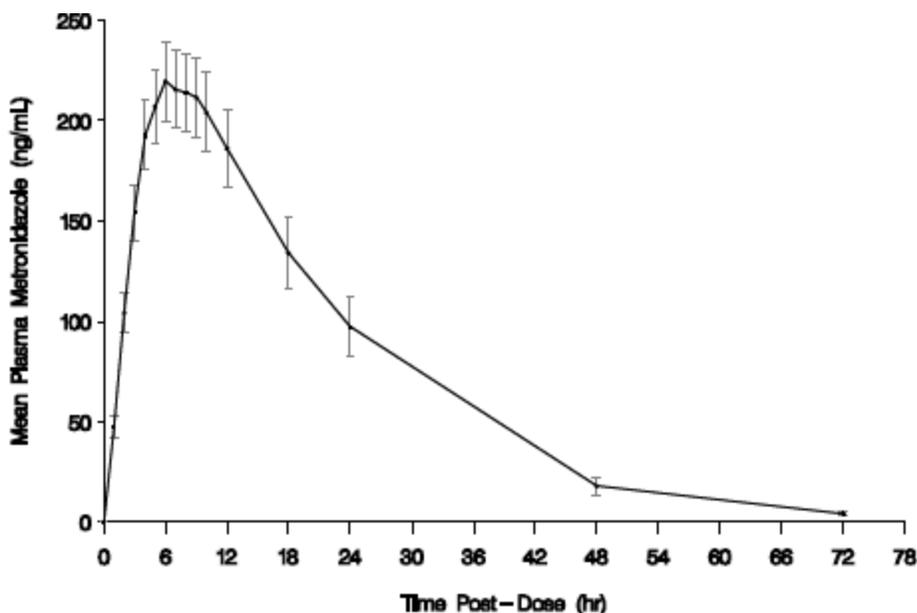
Study Population: In total, 20 subjects were enrolled and completed the study (**Table 2**).

Table 2. Demographic characteristics of enrolled subjects

	N = 20
Age	
Mean (SD)	27.2 (5.4)
Median	27.5
Minimum, Maximum	19, 37
Sex	
Female	20 (100.0%)
Race	
Asian	1 (5.0%)
Black or African American	5 (25.0%)
White	14 (70.0%)
Ethnicity	
Hispanic or Latino	5 (25.0%)
Not Hispanic or Latino	15 (75.0%)
Height (cm)	
Mean (SD)	165.1 (7.8)
Median	164.5
Minimum, Maximum	152.0, 179.0
Weight (kg)	
Mean (SD)	69.8 (8.5)
Median	69.5
Minimum, Maximum	55.0, 85.0
BMI (kg/m²)	
Mean (SD)	25.7 (3.1)
Median	26.9
Minimum, Maximum	18.3, 29.4

Pharmacokinetics: The geometric mean concentration-time profile of metronidazole following a single application of Metronidazole vaginal gel 1.3% was shown in **Figure 2**.

Figure 2. Mean concentration-time profile of metronidazole following a single application of Metronidazole vaginal gel 1.3% in healthy female subjects



Following a single intravaginal application of 1.3% metronidazole vaginal gel (5 g, equivalent to approximately 65 mg of metronidazole) to 20 healthy female subjects, the mean C_{max} of metronidazole was 238.95 ng/mL (range of 113.93 to 428.44 ng/mL). The mean $AUC_{0-\infty}$ was 5433.52 ng.h/mL (range of 1382 to 12744 ng.h/mL). The average T_{max} was 7.31 hours (range of 3.92 to 18.00 hours) with an average half-life of 9.65 hours. These results are comparable to those of a marketed product, MetroGel-Vaginal 0.75% (5 g, equivalent to 37.5 mg of metronidazole). Following a single intravaginal application of MetroGel-Vaginal 0.75% in healthy subjects, the mean C_{max} of metronidazole was 237 ng/mL (range: 152 to 368 ng/mL), the mean $AUC_{0-\infty}$ was 4977 ng.h/mL (CV=57.7%).

Safety: There were six adverse events reported by two subjects. None of the AEs were treatment-related, serious, or led to the subject's discontinuation from the study. There was one severe AE (headache) which resolved without sequelae. None of the hematology, serum chemistry, or urinalysis safety lab results were considered clinically significant. All other tests conducted during the study (UPT, urine cotinine, urine drug screen, and saliva alcohol) yielded negative results.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

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/s/

ZHIXIA YAN
01/16/2014

PHILIP M COLANGELO
01/16/2014

**CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST
FOR NDA/BLA SUBMISSIONS**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

NDA/BLA Number	205223	Brand Name	
OCP Division (I, II, III, IV, V)	DCP4	Generic Name	Metronidazole Vaginal Gel 1.3%
Medical Division	DAIP	Drug Class	Antineoplastic/Antileishimianial
OCP Reviewer	Seong Jang, PhD	Indication(s)	Treatment of bacterial vaginosis in non-pregnant women
OCP Team Leader	Phil Colangelo, PhD	Dosage Form	Vaginal Gel 1.3% in a pre-filled applicator which delivers approximately 5 g of gel containing 65 mg of metronidazole
Pharmacometrics Reviewer	NA	Dosing Regimen	A single-dose, pre-filled disposable applicator administered once intravaginal at bedtime
Date of Submission	May 24 2013	Route of Administration	Intravaginal
Estimated Due Date of OCP Review	December 24, 2013	Sponsor	Valeant Pharmaceuticals
Medical Division Due Date	January 24, 2014	Priority Classification	
PDUFA Due Date	March 24, 2014	AC Meeting (if applicable)	

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS -				
single dose:	X			
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:				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	X	1		
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:				The same formulation as been used from clinical development
replicate design; single / multi dose:				
Food-drug interaction studies				
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				
Literature References				
TOTAL NUMBER OF STUDIES		2		

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

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	The same basic capsule formulation has been used throughout clinical development
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	

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

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, the submission is fileable from a clinical pharmacology perspective.

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

Not applicable.

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

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

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

/s/

SEONG H JANG
07/12/2013

PHILIP M COLANGELO
07/12/2013