

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206756Orig1s000

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

CLINICAL PHARMACOLOGY REVIEW

NDA: 206756	Submission Date(s): 05/23/2014
Brand Name	STIOLTO RESPIMAT
Generic Name	tiotropium / olodaterol
Reviewer	Ritesh Jain, Ph.D.
Clinical Pharmacology Team Leader	Satjit Brar, Pharm.D. Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Division of Pulmonary, Allergy and Rheumatology Products
Sponsor	Boehringer Ingelheim
Submission Type; Code	NDA; Standard
Formulation; Strength(s)	Inhaler; Each actuation from the STIOLTO RESPIMAT inhaler delivers 2.5 mcg tiotropium and 2.5 mcg olodaterol. Two actuations equal one dose.
Proposed Indication	The long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

1 EXECUTIVE SUMMARY	2
1.1 RECOMMENDATION	3
1.2 PHASE IV COMMITMENTS	3
1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS	3
1.3.1 Has the dosing regimen of tiotropium and olodaterol combination product been adequately explored? ⁴	
1.3.2 Is there a drug-drug interaction between tiotropium and olodaterol in the combination product? .	6
1.3.3 Labeling Recommendations: None	7

List of Figures and Tables:

FIGURE 1: TROUGH FEV1 RESPONSE (L) AT DAY 8, DAY 15 AND DAY 29 FOLLOWING ADMINISTRATION OF TIOTROPIUM 5 MCG DOSE ALONE (BLUE COLUMN) AND FDC OF TIOTROPIUM 5 MCG DOSE WITH OLODATEROL 2.5 MCG , 5 MCG AND 10 MCG DOSE (GREEN, GREY AND YELLOW COLUMN RESPECTIVELY)	5
FIGURE 2: TROUGH FEV1 RESPONSE (L) AT DAY 29 FOLLOWING ADMINISTRATION OF OLODATEROL 5 MCG AND 10 MCG DOSE ALONE (RED COLUMN) AND FDC OF OLODATEROL OF 5 MCG AND 10 MCG DOSE WITH TIOTROPIUM 1.25 MCG, 2.5 MCG AND 5 MCG DOSE (GREEN, GREY AND YELLOW COLUMN RESPECTIVELY)	6
FIGURE 3: GEOMETRIC MEAN RATIOS AND THEIR ASSOCIATED 90% CONFIDENCE INTERVALS FOR TIOTROPIUM AND OLODATEROL PHARMACOKINETIC PARAMETERS FOLLOWING ADMINISTRATION OF THE TIOTROPIUM/OLODATEROL FDC PRODUCT AND INDIVIDUAL OLODATEROL AND TIOTROPIUM ADMINISTRATION	7

1 Executive Summary

Boehringer Ingelheim Pharmaceuticals, Inc. has submitted a 505(b)(1) New Drug Application (NDA 206756) for fixed dose combination (FDC) of tiotropium and olodaterol respimat[®] inhalation spray. Tiotropium and olodaterol respimat[®] is a fixed dose combination of tiotropium, a long-acting muscarinic antagonist (LAMA) and olodaterol, a long-acting beta2-adrenergic agonist (LABA). The FDC product is indicated for long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The proposed dose for FDC product is 5 mcg (for both components) once daily.

At the time of NDA submission, both tiotropium respimat[®] (TR) and olodaterol respimat[®] (OR) were under review by Agency as individual agents. Both TR and OR are approved under NDA 021936 and NDA 203108, respectively. Both products have been approved as monotherapies for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The approved dose for individual product TR and OR is 5 mcg once daily.

In this NDA, the clinical development program for tiotropium and olodaterol respimat[®] FDC product consists of:

- Three (3) Phase 2 dose ranging trials (1237.4, 1237.9, and 1237.18) in COPD patients,
- Two (2) Phase 3 replicated 52-week factorial design safety and efficacy trials in COPD patients (1237.5 and 1237.6),
- One 6 week serial spirometry trial in COPD patients (1237.20),
-  (b) (4)
- 
- A drug-drug interaction study (1237.3).

The clinical pharmacology aspects of tiotropium and olodaterol as monotherapies have been comprehensively investigated in the respective monotherapy clinical programs, and have been reviewed under NDA 021936 for tiotropium (DARRTS date 08/29/2014 by Dr. Yunzhao Ren) and NDA 203108 for olodaterol (DARRTS date 01/17/2013 by Dr. Ping Ji).

In this current NDA application, the clinical pharmacology program includes only a drug-drug interaction study between tiotropium and olodaterol (Study 1237.3). The results of this study demonstrate that that olodaterol and tiotropium have no drug-drug interaction when administered as a FDC product (Figure 3). This drug-drug interaction study was also submitted with the olodaterol monotherapy program and the results of the study are in the approved olodaterol product label. Also, the Sponsor used to-be-marketed dose (5/5 mcg) and to-be-marketed formulation in the pivotal Phase III trials. Therefore, clinical pharmacology trials related to formulation development such as bioequivalence,

relative bioavailability, dose proportionality or dose strength equivalence studies, were not needed.

The dosing regimen of olodaterol and tiotropium has been adequately explored in this application. The three Phase 2 trials in this NDA, demonstrated that olodaterol and tiotropium when administered in combination showed better FEV1 response as compared to olodaterol or tiotropium when administered alone as a monotherapy. Sponsor's assessment on the dose-response relationship observed in the Phase 2 trials, and the selection of 5 mcg olodaterol doses in combination with 2.5 mcg and 5 mcg tiotropium doses for the Phase 3 evaluation seems adequate. Please refer to Medical review by Dr. Robert Lim for further details on the Phase 3 study efficacy and safety results.

In addition in this NDA, the Phase 2 and Phase 3 trials evaluated only once daily (QD) dosing regimen for this fixed dose combination product of olodaterol and tiotropium. The rationale for QD dosing regimen is supported by the study results in the monotherapy programs, where QD dosing regimen was found to be most appropriate in regards to the pertinent pulmonary endpoints. Please refer to Clinical Pharmacology review of NDA's 021936 (DARRTS dated 08/29/2014 by Dr. Yunzhao Ren) and NDA 203108 (DARRTS dated 01/17/2013 by Dr. Ping Ji) for further details on QD dosing regimen.

In summary, this application is acceptable from a clinical pharmacology standpoint and this review will primarily summarize the results of the Phase 2 dose ranging trials and the results of the DDI study.

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2), has reviewed the clinical pharmacology data submitted under this NDA, and finds it acceptable.

1.2 Phase IV Commitments

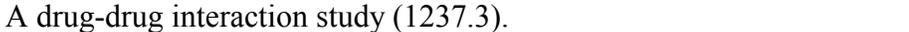
None

1.3 Summary of Important Clinical Pharmacology Findings

The purpose of the current application (NDA 206756) is to seek the marketing approval for fixed dose combination (FDC) of tiotropium and olodaterol respimat[®] inhalation spray. Both tiotropium respimat[®] inhalation spray and olodaterol respimat[®] inhalation spray are approved under NDA 021936 and NDA 203108, respectively. Both products have been approved as monotherapies for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The approved dosing regimen for the individual products for both TR and OR is 5 mcg once daily.

The clinical program for tiotropium and olodaterol respimat[®] FDC product consists of:

- Three (3) Phase 2 dose ranging trials (1237.4, 1237.9, and 1237.18) in COPD patients,

- Two (2) Phase 3 replicated 52-week factorial design safety and efficacy trials in COPD patients (1237.5 and 1237.6),
- One 6 week serial spirometry trial in COPD patients (1237.20),
-  (b) (4)
- 
- A drug-drug interaction study (1237.3).

1.3.1 Has the dosing regimen of tiotropium and olodaterol combination product been adequately explored?

The dosing regimen of olodaterol and tiotropium has been adequately explored in this application. The three Phase 2 trials in this NDA, demonstrated that olodaterol and tiotropium when administered in combination showed better FEV1 response as compared to olodaterol or tiotropium when administered alone as a monotherapy. To characterize the dose-response of the combination product versus the dose-response of the mono products given once daily, sponsor conducted three Phase 2 dose ranging trials. The Phase 2 clinical program was designed to (i) characterize the dose-response for olodaterol in combination with tiotropium and confirm its comparability with the dose response for olodaterol monotherapy (1237.4), and (ii) characterize the dose-response for tiotropium in combination with olodaterol and confirm its comparability with the dose-response for tiotropium monotherapy (1237.18). These trials included tiotropium doses of 1.25, 2.5 and 5 mcg in combination with olodaterol 5 mcg and 10 mcg (1237.18), and olodaterol doses of 2, 5 and 10 mcg in combination with tiotropium 5 mcg (1237.4).

In the Phase 2 clinical trials, it is clearly demonstrated that olodaterol and tiotropium when administered in combination showed better FEV1 response as compared to olodaterol or tiotropium when administered alone as a monotherapy (see below). Thus, based on the dose-response relationship observed in the Phase 2 trials, the selection of 5 mcg olodaterol doses in combination with 2.5 mcg and 5 mcg tiotropium doses for the Phase 3 evaluation seems adequate. Please refer to Medical review by Dr. Robert Lim for further efficacy and safety details on the Phase 3 study results.

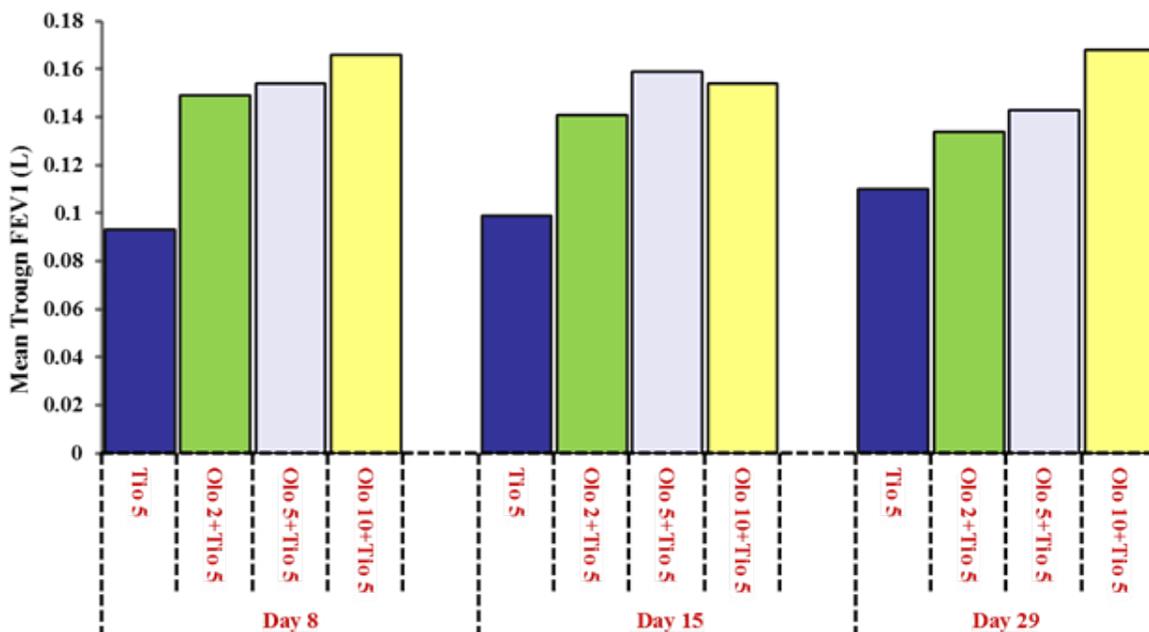
In addition in this NDA, the Phase 2 and Phase 3 trials evaluated only once daily (QD) dosing regimen for this fixed dose combination product of olodaterol and tiotropium. The rationale for QD dosing regimen is supported by the study results in the monotherapy programs, where QD dosing regimen was found to be most appropriate in regards to the pertinent pulmonary endpoints. Please refer to Clinical Pharmacology review of NDA's 021936 (DARRTS dated 08/29/2014 by Dr. Yunzhao Ren) and NDA 203108 (DARRTS dated 01/17/2013 by Dr. Ping Ji) for further details on QD dosing regimen.

Olodaterol dose-response study (Study 1237.4)

Olodaterol dose response was evaluated in trial 1237.4, which was a 4-week, parallel group study in patients with moderate / severe COPD. The primary efficacy endpoint for this trial was the trough FEV1 response [L] after 4 weeks of treatment. At day 29, a dose-

response for olodaterol in combination with tiotropium 5 mcg was observed. In addition, when compared to tiotropium alone, a higher FEV1 response was observed with tiotropium in combination with olodaterol dose of 5 mcg and 10 mcg. (Figure 1)

Figure 1: Trough FEV1 response (L) at Day 8, Day 15 and Day 29 Following Administration of Tiotropium 5 mcg Dose alone (blue column) and FDC of Tiotropium 5 mcg Dose with Olodaterol 2.5 mcg , 5 mcg and 10 mcg Dose (green, grey and yellow column respectively).

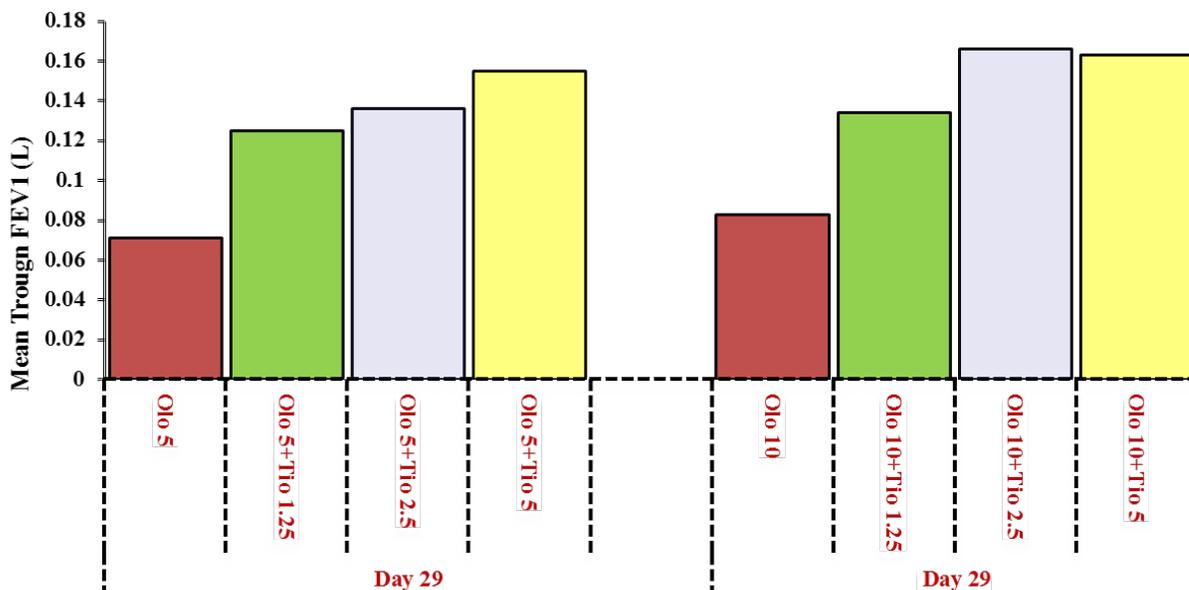


Tiotropium dose-response study (Study 1237.18)

The dose-response for tiotropium in combination with olodaterol was evaluated in trial 1237.18, a 4-week, incomplete cross-over study in patients with moderate / severe COPD, which included tiotropium doses of 1.25 mcg, 2.5 mcg and 5 mcg in combination with olodaterol 5 mcg and olodaterol 10 mcg.

There was a stepwise, dose-ordered increase in lung function response for tiotropium dose of 1.25 mcg, 2.5 mcg, and 5 mcg in combination with both olodaterol 5 mcg and olodaterol 10 mcg (Figure 2). In addition, prior to initiation of the Phase III program for tiotropium/olodaterol FDC, the Phase III clinical program for olodaterol was completed, demonstrating similar efficacy for olodaterol 5 mcg and olodaterol 10 mcg. Therefore, for the pivotal Phase 3 trials only 5 mcg olodaterol doses in combination with 2.5 mcg and 5 mcg tiotropium doses seems appropriate.

Figure 2: Trough FEV1 response (L) at Day 29 Following Administration of Olodaterol 5 mcg and 10 mcg Dose alone (red column) and FDC of Olodaterol of 5 mcg and 10 mcg Dose with Tiotropium 1.25 mcg, 2.5 mcg and 5 mcg Dose (green, grey and yellow column respectively)

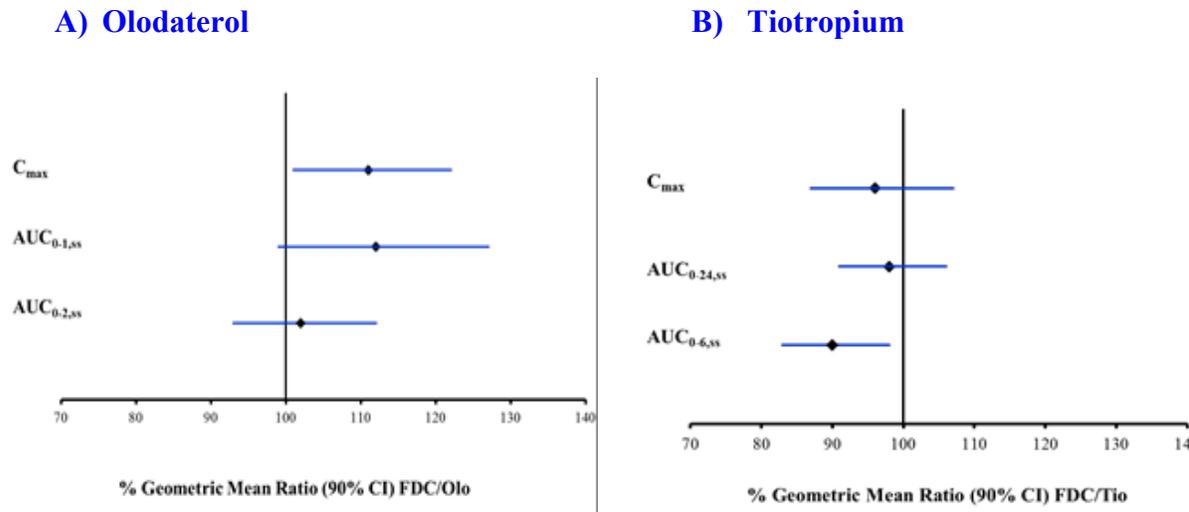


1.3.2 Is there a drug-drug interaction between tiotropium and olodaterol in the combination product?

Drug-Drug interaction study (1237.3) showed no clinical meaningful drug interaction between tiotropium and olodaterol. In the drug-drug interaction study patients with chronic obstructive pulmonary disease (COPD) FDC (Tiotropium+Olodaterol 5/10 mcg; Test), olodaterol 10 mcg (Reference 1) or tiotropium 5 mcg (Reference 2) once daily via the RESPIMAT inhaler for 21 days -. The primary endpoint for the assessment of tiotropium steady state exposure was $Ae_{0-24,ss}$, while $C_{max,ss}$, $AUC_{0-4,ss}$ and $AUC_{0-6,ss}$ were evaluated as supportive parameters. The primary endpoints for the assessment of olodaterol steady state exposure were $C_{max,ss}$ and $AUC_{0-1,ss}$, while $AUC_{0-2,ss}$ and $Ae_{0-24,ss}$ were evaluated as supportive parameters.

The Test/Reference ratios of the PK parameters between the FDC and olodaterol monotherapy or tiotropium monotherapy were all close to 100% (90–98%). Altogether, these results indicate that systemic exposure to olodaterol after inhalation of the FDC was not relevantly different to the exposure after inhalation of olodaterol monotherapy. Also, systemic exposure to tiotropium after inhalation of the FDC was not relevantly different to the exposure after inhalation of tiotropium monotherapy.

Figure 3: Geometric Mean Ratios and Their Associated 90% Confidence Intervals for Tiotropium and Olodaterol Pharmacokinetic Parameters Following Administration of the Tiotropium/Olodaterol FDC product and individual Olodaterol and Tiotropium Administration.



Reviewers Comment: This drug-drug interaction study was also submitted with the olodaterol monotherapy program and the results of the study are in the approved olodaterol product label. Please refer to the clinical pharmacology review of NDA 203108 for further detail on this DDI study (DARRTS dated 01/17/2013 and by Dr. Ping Ji.

In conclusion, from a clinical pharmacology standpoint there was no clinically significant drug-drug interaction and this NDA is acceptable.

1.3.3 Labeling Recommendations: None.

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

/s/

RITESH JAIN
01/23/2015

SATJIT S BRAR
01/23/2015

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

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

	Information		Information	
NDA/BLA Number	206756		Brand Name	Stiolto Respimat
OCP Division (I, II, III, IV, V)	II		Generic Name	tiotropium/olodaterol
Medical Division	Division of Pulmonary, Allergy, and Rheumatology Products		Drug Class	LAMA/LABA
OCP Reviewer	Dinko Rekcic, Ph.D.		Indication(s)	COPD
OCP Team Leader	Satjit Brar, Pharm.D., Ph.D.		Dosage Form	Inhaler
Pharmacometrics Reviewer	NA		Dosing Regimen	5µg once daily
Date of Submission	5/22/14		Route of Administration	Inhalation
Estimated Due Date of OCP Review	1/24/15		Sponsor	Boehringer Ingelheim
Medical Division Due Date	1/24/15		Priority Classification	standard
PDUFA Due Date	5/22/15			

Clin. Pharm. and Biopharm. 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:	X	2		U07-1057, U06-1541
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		U07-1939
multiple dose:	X	1		U08-2169
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:	X	1		U09-1422
In-vivo effects of primary drug:	X	1		U09-1422
In-vitro:				
Subpopulation studies -				
ethnicity:	X	1		U13-2350
gender:				
pediatrics:				
geriatrics:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

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

renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				U09-1588, U10-3444, U11-1790
Phase 3:	X	7		U13-1759, U13-1760, U13-1917, c02094185, c02094318, U13- 1763, U13-1762
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:				
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	X	1		c02407862
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		16		

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			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

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

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
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		
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.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

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

/s/

DINKO REKIC
07/23/2014

SATJIT S BRAR
07/23/2014