CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204307Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number	204-307 (Related IND 102,177)
Submission Date	04/24/2012 (SDN 0)
Submission Type	505(b)(2)
Review Priority	Standard
Proposed Brand Name	Vituz
Generic Name	Hydrocodone and Chlorpheniramine Oral Solution
Sponsor	Cypress Pharmaceuticals, Inc.
Route of Administration	Oral
Dosage Form	Solution
Dosage Strength	Each 5 mL of Hydrocodone and chlorpheniramine oral solution oral solution contains 5 mg hydrocodone bitartrate and 4 mg chlorpheniramine maleate
OND Division	Pulmonary, Allergy, and Rheumatology Products
OCP Division	Clinical Pharmacology II
Reviewer	Arun Agrawal, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
Proposed Age and Indication	Adults 18 years of age and older: • Relief of cough associated with common cold • Relief of symptoms associated with upper respiratory allergies
Proposed Dosing Regimen	5 mL every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours

Table of Contents

1 Executive Summary

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, NDA 204-307 is acceptable.

1.2 Phase 4 Commitments

None

1.3 Summary of Clinical Pharmacology Findings

No new clinical pharmacology data were submitted for hydrocodone and chlorpheniramine oral solution per se. Data generated for Zutripro™ oral solution (NDA 22-439) containing hydrocodone, pseudoephedrine, and chlorpheniramine are used in support of hydrocodone and chlorpheniramine oral solution. Because hydrocodone and chlorpheniramine oral solution (NDA 204-307) and Zutripro™ oral solution (NDA 22-439) are exactly same formulations except that Zutripro™contains one more active ingredient (pseudoephedrine), demonstration of bioequivalence for the hydrocodone and chlorpheniramine components in the bioequivalence study supporting Zutripro™ relative to respective reference products is considered to be supportive to this product as well. This approach was discussed via a "Request for Advice" from the sponsor and the Agency agreed with this approach (for details, please see Agency correspondence dated March 07, 2012 and Clinical Pharmacology review by Dr. Ying Fan, March 05, 2012). A similar approach was used for the approval of NDA 22-422 (Rezira™) containing hydrocodone and pseudoephedrine utilizing data from the same Zutripro™ bioequivalence study (for details, please see Clinical Pharmacology review by Dr. Elizabeth Shang, May 12, 2011).

The bioequivalence of hydrocodone and chlorpheniramine components in Zutripro™ oral solution relative to respective reference solutions containing hydrocodone bitartrate (hydrocodone bitartrate and homatropine methylbromide syrup manufactured by Hi-Tech Pharmacal Co., Inc) and single-ingredient chlorpheniramine solution was demonstrated in Clinical Study No. 11058503. The 90% confidence intervals (CIs) for the geometric mean ratios of Cmax and AUC of hydrocodone and chlorpheniramine were within the 80-125% limits for bioequivalence. For completion sake, the relevant data are shown again in this review. The summary of bioequivalence statistics on pharmacokinetic parameters for hydrocodone and chlorpheniramine are provided in Table 1 and Table 2, respectively.

Table 1 Summary Statistics on Bioequivalence of Hydrocodone Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Hydrocodone Bitartrate and Homatropine Methylbromide Syrup (Reference for Hydrocodone)

Geometric Means, Ratio of Means, and 90% Confidence Intervals
Based on ANOVA of Ln-Transformed Data
Analyte: Hydrocodone (N = 98)

Parameter	Test A	Reference B	Ratio	CI*	Intra-Subject %CV
AUC0-t (pg·hr/mL)	67540.16	69723.40	0.9687	0.9465 - 0.9914	9.7130
AUC0-inf (pg·hr/mL)	69747.27	72063.25	0.9679	0.9452 - 0.9911	9.9706
Cmax (pg/mL)	10290.79	11364.25	0.9055	0.8795 - 0.9324	12.2931

* Bioequivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.
Source: Clinical Study Report, Page 37 of 75

Table 2 Summary Statistics on Bioequivalence of Chlorpheniramine Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Chlorpheniramine Solution (Reference for Chlorpheniramine)

Geometric Means, Ratio of Means, and 90% Confidence Intervals
Based on ANOVA of Ln-Transformed Data
Analyte: Chlorpheniramine (N = 97)

Parameter	Test A	Reference D*	Ratio	CI**	Intra-Subject %CV
AUC0-t (pg·hr/mL)	159719.72	155681.52	1.0259	0.9992 - 1.0534	11.0456
AUC0-inf (pg·hr/mL)	181409.61	174224.49	1.0412	1.0174 - 1.0657	9.6529
Cmax (pg/mL)	6923.48	6789.48	1.0197	0.9946 - 1.0456	10.4537

*N=96 for AUC0-inf for Reference product D.
**Bioequivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.
Source: Clinical Study Report, Page 41 of 75

2 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Sponsor submitted NDA 204-307 for hydrocodone and chlorpheniramine oral solution on April 24, 2012. Zutripro™ NDA 22-439 was originally submitted on November 6, 2008 (SDN 1) through 505(b)(2) pathway; first resubmission (SDN 11) occurred on December

10, 2009 in response to the Complete Response (CR) Letter of September 18, 2009 for the original NDA, while the second resubmission (SDN 22) occurred on December 8, 2010 in response to the CR Letter of June 11, 2010. In this resubmission, data from a new single dose bioequivalence study (Study No. 11058503) was submitted demonstrating that each active ingredient in Zutripro™ is bioequivalent to the corresponding components in the respective reference products (for details, please see Clinical Pharmacology review by Dr. Elizabeth Shang, May 12, 2011).

2.1.2 What is the status of pediatric studies and/or any pediatric plan for study?

Sponsor proposed usage of hydrocodone and chlorpheniramine oral solution in patients 18 years of age and older. Sponsor requested waiver for children below 6 years of age based on the fact that the proposed product contains hydrocodone which is contraindicated for use in children less than 6 years of age due to the risk of fatal respiratory depression. Sponsor also requested deferral for pediatric studies in 6-17 year old patients. Sponsor's proposed pediatric plan and Division's assessment were presented to Pediatric Review Committee (PeRC) on October 10, 2012. PeRC agreed with the waiver of studies in children less than 6 years of age and a deferral for studies in patients 6-17 years of age. PeRC members asked the Division to evaluate if efficacy can be extrapolated from adults to pediatric population or an efficacy study in pediatric population is needed.

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

Adults 18 years of age and older: 5 mL orally every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.

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?

The Clinical Pharmacology program consisted of a single-dose bioequivalence study (Study No. 11058503). This study was an open-label, single-dose, randomized, four-period cross-over study under fasting conditions. The objectives of the study were to determine and compare the rate and extent of absorption of hydrocodone, pseudoephedrine, and chlorpheniramine from Zutripro™ oral solution to that from homatropine methylbromide/hydrocodone bitartrate (manufactured by Hi-Tech Pharmacal Co, Inc.), pseudoephedrine solution, and chlorpheniramine solution. Ninety-eight healthy adult subjects completed the study. The study results showed bioequivalence for the hydrocodone, pseudoephedrine, and chlorpheniramine components of the Zutripro™.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Hydrocodone and chlorpheniramine were measured in the plasma samples.

2.2.3 What are the single dose pharmacokinetic parameters?

The arithmetic mean plasma pharmacokinetic parameters for Test product and Reference product are summarized in Table 3 and Table 4.

Table 3 Arithmetic Mean (SD) of Plasma Pharmacokinetic Parameters of Hydrocodone Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Hydrocodone Bitartrate and Homatropine Methylbromide Syrup (Reference)

Summary of Pharmacokinetic Parameters
Untransformed Data
Analyte: Hydrocodone (N = 98)

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)	
	Test A	Reference B
AUC0-t (pg·hr/mL)	69401.3314 ± 16433.6643 (23.6792)	71785.3004 ± 18328.4015 (25.5322)
AUC0-inf (pg·hr/mL)	71759.8232 ± 17539.3146 (24.4417)	74293.9576 ± 19573.8121 (26.3464)
Cmax (pg/mL)	10616.4388 ± 2634.2446 (24.8129)	11829.5000 ± 3598.8372 (30.4226)
Tmax (hr)	1.3806 ± 0.5513 (39.9328)	1.2248 ± 0.4929 (40.2400)
Kel (1/hr)	0.1440 ± 0.0229 (15.8926)	0.1414 ± 0.0204 (14.4431)
T½ (hr)	4.9246 ± 0.7340 (14.9041)	5.0060 ± 0.7424 (14.8294)

Source: Clinical Study Report, Page 36 of 75

Table 4 Arithmetic Mean (SD) of Plasma Pharmacokinetic Parameters of Chlorpheniramine Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Chlorpheniramine Solution (Reference)

Summary of Pharmacokinetic Parameters
Untransformed Data
Analyte: Chlorpheniramine (N = 97)

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)	
	Test A	Reference D*
AUC0-t (pg·hr/mL)	170939.1008 ± 60670.6833 (35.4926)	169040.6387 ± 73085.0690 (43.2352)
AUC0-inf (pg·hr/mL)	200844.9726 ± 96259.5622 (47.9273)	190371.4343 ± 81311.4355 (42.7120)
Cmax (pg/mL)	7203.6392 ± 1979.3166 (27.4766)	7108.8763 ± 2067.1756 (29.0788)
Tmax (hr)	3.4692 ± 1.5764 (45.4380)	3.8637 ± 3.5482 (91.8341)
Kel (1/hr)	0.0323 ± 0.0106 (32.7556)	0.0334 ± 0.0100 (30.1088)
T½ (hr)	24.1356 ± 10.0853 (41.7858)	22.6116 ± 6.6990 (29.6264)

*N=96 for AUC0-inf, Kel, and T½ for Reference product D.
Source: Clinical Study Report, Page 40 of 75

2.3 General Biopharmaceutics

2.3.1 What is the relative bioavailability of the formulations (Reference and Test) based on the pivotal bioequivalence studies? Was the bioequivalence demonstrated between the two formulations?

The bioequivalence of hydrocodone and chlorpheniramine components of Zutripro™ was demonstrated under fasting condition as evident by the observation that the 90% CI ratios of the geometric means for C_{max}, AUC_{0-t}, and AUC_{0-inf} were within the limits for bioequivalence (80-125%) (Table 1 and Table 2).

2.3.2 What is the effect of food on the bioavailability of the drug from the dosage form?

No specific pharmacokinetic studies to determine the effect of food on the pharmacokinetics of hydrocodone and chlorpheniramine were submitted in this NDA. As a post meeting comment in the minutes of the January 14, 2008 pre-IND meeting (IND (b) (4) the Agency agreed that no food effect study was needed with the proposed oral solution formulation since it did not contain any food sensitive excipient such as sorbitol or mannitol.

2.4 Analytical Section

2.4.1 What bioanalytical methods are used to assess concentrations?

The analytical portion of this study was conducted at (b) (4)

2.4.1.1 Hydrocodone

Plasma concentrations of hydrocodone were measured by a validated method utilizing high performance liquid chromatography-tandem mass spectrometry. The method for the analysis of hydrocodone in human heparinized plasma was validated over the range of 100-20,000 pg/mL. Summary of plasma hydrocodone bioanalytical validation methods is listed in Table 5. The results of sample analysis on hydrocodone are provided in Table 6. The results are acceptable as evidenced by QC sample precision and accuracy within ± 15%.

Table 5 Analytical Method Validation Summary for Hydrocodone

	Hydrocodone (pg/mL)
	(b) (4)
Standard Concentrations	
Linear Range	
Corelation Coefficient (r)	
Accuracy Across Standard Curve Concentrations (%)	
QC Concentrations (pg/mL)	
Intra-Run Precision (%CV) of QC Samples	
300	
3000	
16000	
Intra-Run Accuracy of QC Samples	
300	
3000	
16000	
Inter-Run Precision of QC Samples (%CV)	
300	
3000	
16000	
Inter-Run Accuracy of QC Samples (%CV)	
300	
3000	
16000	
Recovery (%)	
Analyte	
300	
3000	
16000	
Internal standards	
Stabilities in Plasma	
Room Temperature	
Refrigerated (4°C)	
Frozen (-20°C)	
Frozen (-80°C)	
Freeze-Thaw Stability	
Processed Batch Stability	
Processed Sample Stability	
Dilution Accuracy (4X High QC, i.e. 64,000 pg/mL)	
x5	
x10	

Source: LC-MS/MS-Assay Validation Report VAL-RPT-1261 Rev1

Table 6 Plasma Assay Parameters for Hydrocodone

	Hydrocodone
Lower Limit of Quantitation (pg/mL)	(b) (4)
Assay Range (pg/mL)	
Linearity (correlation coefficient)	
Precision (%CV)	
Accuracy (%Theoretical)	

2.4.1.2 Chlorpheniramine

Plasma concentrations of chlorpheniramine were measured by a validated method utilizing the technique of protein precipitation, followed by high performance liquid chromatography-positive ionization electrospray-tandem mass spectrometry. The method for the analysis of chlorpheniramine in human heparinized plasma was validated over the range of 100-20,000 pg/mL. Summary of plasma hydrocodone bioanalytical validation methods is listed in Table 7. The results of sample analysis on chlorpheniramine are provided in Table 8. The results are acceptable as evidenced by QC sample precision and accuracy within ± 15%.

Table 7 Analytical Method Validation Summary for Chlorpheniramine

	Chlorpheniramine (pg/mL)
	(b) (4)
Standard Concentrations	
Linear Range	
Corelation Coefficient (r)	
Accuracy Across Standard Curve Concentrations (%)	
QC Concentrations (pg/mL)	
Intra-Run Precision (%CV) of QC Samples	
300	
3000	
16000	
Intra-Run Accuracy of QC Samples	
300	
3000	
16000	
Inter-Run Precision of QC Samples (%CV)	
300	
3000	
16000	
Inter-Run Accuracy of QC Samples (%CV)	
300	
3000	
16000	
Recovery (%)	
Analyte	
300	
3000	
16000	
Internal standards	
Stabilities in Plasma	
Room Temperature	
Refrigerated (4°C)	
Frozen (-20°C)	
Frozen (-80°C)	
Freeze-Thaw Stability	
Processed Batch Stability	
Processed Sample Stability	
Dilution Accuracy (4X High QC, i.e. 64,000 pg/mL)	
x5	
x10	

Source: LC-MS/MS-Assay Validation Report VAL-RPT-1266 Rev 0

Table 8 Plasma Assay Parameters for Chlorpheniramine

	Chlorpheniramine
Lower Limit of Quantitation (pg/mL)	(b) (4)
Assay Range (pg/mL)	
Linearity (correlation coefficient)	
Precision (%CV)	
Accuracy (%Theoretical)	

3 Detailed Labeling Recommendations

None

4 Appendix

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	204-307	Brand Name	TRADENAME
OCP Division (I, II, III, IV, V)	II	Generic Name	Hydrocodone and Chlorpheniramine oral solution
Medical Division	DPARP	Drug Class	Cough and allergy medicine
OCP Reviewer	Arun Agrawal, Ph.D.	Indication(s)	Relief of cough associated with common cold and relief of symptoms associated with upper respiratory allergies
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Oral solution
Pharmacometric Reviewer		Dosing Regimen	Adults 18 years of age and older: 5 mL every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours
Date of Submission	April 24, 2012	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Cypress Pharmaceutical, Inc
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	February 22, 2013		

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	2	2	Referred to NDA 22-439: One BE study, 2 bioanalytical method validation reports and 1 bioanalytical report

Tabular Listing of All Human Studies	X	1	1	Referred to NDA 22-439
HPK Summary	X	1	1	Referred to NDA 22-439
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	Referred to NDA 22-439: Hydrocodone assay validation (VAL-RPT-1262 Rev: 1); Chlorpheniramine assay validation (VAL-RPT-1266 Rev: 0); and Bioanalytical Report (BR1053)
I. Clinical Pharmacology	X	1	1	Referred to NDA 22-439
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	1	1	Referred to NDA 22-439
Healthy Volunteers-				
single dose:	X	1	1	Referred to NDA 22-439 (Study No. 11058503)
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	1	1	Referred to NDA 22-439 (Study No. 11058503)
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				Waiver requested for 0 to <6 year old, Deferral requested for 6 to <18 year old
Literature References	X			
Total Number of Studies	X	2	2	Referred to NDA 22-439: Hydrocodone assay validation (VAL-RPT-1262 Rev: 1); Chlorpheniramine assay validation (VAL-RPT-1266 Rev: 0); and Bioanalytical Report (BR1053)

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

/s/

ARUN AGRAWAL
10/31/2012

SURESH DODDAPANENI
10/31/2012

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

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**204-307**	**Brand Name**	**TRADENAME**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Hydrocodone and Chlorpheniramine oral solution**
Medical Division	**DPARP**	**Drug Class**	**Cough and allergy medicine**
OCP Reviewer	**Arun Agrawal, Ph.D.**	**Indication(s)**	**Relief of cough associated with common cold and relief of symptoms associated with upper respiratory allergies**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Oral solution**
Pharmacometric Reviewer		**Dosing Regimen**	**Adults 18 years of age and older: 5 mL every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours**
Date of Submission	**April 24, 2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Cypress Pharmaceutical, Inc**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**February 22, 2013**		

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**	**2**		**Referred to NDA 22-439: One BE study, 2 bioanalytical method validation reports and 1 bioanalytical report**
Tabular Listing of All Human Studies	**X**	**1**		**Referred to NDA 22-439**
HPK Summary	**X**	**1**		**Referred to NDA 22-439**
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**		**Referred to NDA 22-439: Hydrocodone assay validation (VAL-RPT-1262 Rev: 1); Chlorpheniramine assay validation (VAL-RPT-1266 Rev: 0); and Bioanalytical Report (BR1053)**

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

I. Clinical Pharmacology	X	1		**Referred to NDA 22-439**
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	1		**Referred to NDA 22-439**
Healthy Volunteers-				
single dose:	X	1		**Referred to NDA 22-439 (Study No. 11058503)**
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	1		**Referred to NDA 22-439 (Study No. 11058503)**
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				**Waiver requested for 0 to <6 year old, Deferral requested for 6 to <18 year old**
Literature References	X			

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

Total Number of Studies	X	**2**		**Referred to NDA 22-439: Hydrocodone assay validation (VAL-RPT-1262 Rev: 1); Chlorpheniramine assay validation (VAL-RPT-1266 Rev: 0); and Bioanalytical Report (BR1053)**

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			Referred to NDA 22-439
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Referred to NDA 22-439
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			Referred to NDA 22-439
5	Has a rationale for dose selection been submitted?	X			Referred to NDA 22-439
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			Referred to NDA 22-439
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			Referred to NDA 22-439
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			Referred to NDA 22-439
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			Referred to NDA 22-439
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			Referred to NDA 22-439
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	Requested waiver for 0 to <6 years of age, and deferral for 6 to <18 years of age.
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			Referred to NDA 22-439
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_____

Background:

This NDA filing review is for Hydrocodone and Chlorpheniramine oral solution submitted under 505(b)(2) of the FDC Act. Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and physiological dependence. Chlorpheniramine is an antihistamine drug (H1 receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Clinical Pharmacology Study:

Sponsor conducted a BE study (Study # 11058503) for Zutripro oral solution containing Hydrocodone, Pseudoephedrine and Chlorpheniramine (NDA 22-439, approved on June 8, 2011). Sponsor used data for Hydrocodone and Pseudoephedrine from Zutripro BE study for the approval of Rezira (NDA 22-442 approved on June 8, 2011), and has now submitted NDA 204-307 utilizing data for Hydrocodone and Chlorpheniramine from Zutripro BE study. This approach was deemed reasonable by the Division (March 7, 2012).

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

The bioequivalence of hydrocodone, chlorpheniramine, and pseudoephedrine components in Zutripro oral solution formulation relative to respective reference solutions containing hydrocodone bitartrate (hydrocodone bitartrate and homatropine methylbromide syrup manufactured by Hi-Tech Pharmacal Co., Inc), single-ingredient chlorpheniramine solution, and pseudoephedrine solution was demonstrated in Study 11058503. The 90% confidence intervals for the geometric mean ratios of C_{max} and AUC of hydrocodone, chlorpheniramine, and pseudoephedrine were within the 80-125% limits for bioequivalence.

This NDA is fileable from a clinical pharmacology perspective.

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

None

Arun Agrawal, Ph.D.

Reviewing Clinical Pharmacologist Date

Suresh Doddapaneni, Ph.D.

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/

ARUN AGRAWAL
06/18/2012

SURESH DODDAPANENI
07/02/2012