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RESEARCH**

APPLICATION NUMBER:

22-556Orig1s000

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

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 22-556 Resubmission Amendment (SDN- 0016)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DPAADP		
Applicant:	Tris Pharma	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	--	Supervisor (acting): Richard Lostritto, Ph.D	
Generic Name:	Carbinoxamime ER Oral Suspension	Date Assigned:	January 16, 2013
Indication:	Allergic rhinitis	Date of Review:	March 4, 2013
Formulation/strengths	Extended Release suspension, 4 mg/5 mL		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Oct 10, 2012 Feb 14, 2013	Oct 10, 2012 Feb 14, 2013	January 16, 2013	March 2013
Type of Submission:	Resubmission Class 2 (Response to the CR letter)		
Type of Consult:	- Dissolution acceptance criteria		

REVIEW SUMMARY:

The Applicant has developed Carbinoxamine ER Oral Suspension as a 12-hour extended release formulation indicated for the treatment of allergic rhinitis. Carbinoxamine Maleate Oral Solution (4mg/5mL), manufactured by Mikart Inc., (Brand Name-Palgic) is being used as the Reference Product for the development and for bioavailability studies. According to the Applicant, the ER properties of this product are controlled by the diffusion of drug through the controlled release polymer (Sodium polystyrene sulfonate).

Carbinoxamine ER Oral Suspension was originally submitted on Dec 9, 2010, and due to several CMC deficiencies received a CR letter on Oct 11, 2011. The Biopharmaceutics Reviewer¹ found the NDA acceptable from a biopharmaceutics perspective and the following dissolution acceptance criteria were agreed upon with the Applicant on July 14, 2011.

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Carbinoxamine	ER Suspension	USP Paddle	50	900 mL 0.4 M KH ₂ PO ₄ at 37°C	1 hr: (b) (4) 3 hrs: (b) (4) 6hrs: (b) (4) 12 hrs: NLT (b) (4)

In the present submission, it was noted that the Applicant changed the dissolution acceptance criteria range for the 3 hours time point for stability testing as follows:

¹ Biopharmaceutics review for NDA 22556 entered in DARRTS by Dr. Sandra Suarez on 09/05/11.

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Carbinoxamine	ER Suspension	USP Paddle	50	900 mL 0.4 M KH ₂ PO ₄ at 37°C	1 hr: (b) (4) (b) (4) 6hrs: (b) (4) 12 hrs: NLT (b) (4)

On a teleconference dated February 8, 2013, Tris Pharma was informed that there was no justification/data submitted to support the change to the dissolution acceptance criteria. The FDA added that the new limits should also be supported and justified by in vivo bioequivalence and/or exposure-response information otherwise the original agreed upon criteria should be restored. The Applicant agreed to maintain the 3-hours dissolution criteria of (b) (4)% as originally discussed in the teleconference dated July 13, 2011. On February 14, 2013, the Applicant submitted the updated specifications table for the drug product reflecting the previously approved dissolution acceptance criteria.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 22-556 and its amendment submitted on Oct 10, 2012 and Feb 14, 2013, respectively and found this NDA acceptable from the Biopharmaceutics perspective.

The following dissolution method and acceptance criteria have been agreed upon with the Applicant (refer to submission dated February 14, 2013).

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Carbinoxamine	ER Suspension	USP Paddle	50	900 mL 0.4 M KH ₂ PO ₄ at 37°C	1 hr: (b) (4) 3 hrs: (b) (4) 6hrs: (b) (4) 12 hrs: NLT (b) (4)

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
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/s/

SANDRA SUAREZ
03/06/2013

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03/06/2013

CLINICAL PHARMACOLOGY REVIEW

<i>NDA</i>	22-556	<i>Submission Date</i>	12/08/2010 (SDN0) 10/04/2012 (SDN016)
<i>Brand Name</i>	Karbinal		
<i>Generic Name</i>	Carbinoxamine oral suspension		
<i>Reviewer</i>	Ping Ji, Ph.D.		
<i>Team Leader</i>	Suresh Doddapaneni, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology-II		
<i>OND Division</i>	Division of Pulmonary, Allergy, and Rheumatology Products		
<i>Sponsor</i>	Tris Pharmaceuticals		
<i>Relevant IND(s)</i>	102,091		
<i>Submission Type; Code</i>	505 (b) (2)	S	
<i>Formulation; Strength(s)</i>	4 mg carbinoxamine maleate per 5 mL suspension		
<i>Indication</i>	<p>The proposed indications include:</p> <p>Seasonal and perennial allergic rhinitis</p> <p>Vasomotor rhinitis</p> <p>Allergic conjunctivitis due to inhalant allergens and foods</p> <p>Mild, uncomplicated allergic skin manifestations of urticaria and angioedema</p> <p>Dermatographism</p> <p>As therapy for anaphylactic reactions <i>adjunctive</i> to epinephrine and other standard measures after the acute manifestations have been controlled</p> <p>Amelioration of the severity of allergic reactions to blood or plasma</p>		
<i>Proposed Dosing Regimen</i>	<p>Adult Dosage:</p> <p>██████████^{(b) (4)} (6 to 16 mg) every 12 hours</p> <p>Child's Dosage (approximately 0.2 to 0.4 mg/kg/day):</p> <p>Two to three years – ██████████^{(b) (4)} (3 to 4 mg) every 12 hours</p> <p>██████████^{(b) (4)} – ██████████^{(b) (4)} (3 to 8 mg) every 12 hours</p> <p>██████████^{(b) (4)} – ██████████^{(b) (4)} (6 to 12 mg) every 12 hours</p>		

Table of Contents

Table of Contents	2
1. Executive Summary	3
1.1. Recommendations	3
1.2. Phase IV Commitments	3
2. Question-Based Review	5
2.1. General Attributes	5
2.2. General Clinical Pharmacology	6
2.3. Analytical Section	8
3. Detailed Labeling Recommendations	10

1. EXECUTIVE SUMMARY

1.1. Recommendations

This resubmission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

1.2. Phase IV Commitments

None.

1.2.1. Summary of Clinical Pharmacology and Biopharmaceutics Findings

(b) (4) ER oral suspension, subject of NDA22556, was developed by Tris Pharmaceuticals for the treatment of allergic symptoms. This program is supported with two BA/BE studies in healthy subjects: a single dose study that compared the Test and Reference Products under fasted conditions and evaluated the food effect on the Test Product (M1FT08001) and a multiple dose study that compared the Test and Reference Products at steady state under fasted conditions (M1FT08002). The Test Product is bioequivalent with the Reference Product after both single dose and multiple doses under fasted condition. Food has no effect on the Test Product.

Since these two BA/BE studies were pivotal for approval, an OSI inspection was requested during the original review cycle. However, OSI declined to inspect the studies, based on inspectional findings at the (b) (4) bioanalytical site in (b) (4) (see Dr. Dasgupta's memo dated 9/20/11) and recommended that these data be not accepted. In the Complete Response Letter, this issue was cited as a deficiency. Subsequently, inspection of the clinical component of these bioavailability studies was conducted by ORA inspector in the time period (4/21 to 5/5, 2011). In the OSI memo related to these inspectional findings (see Dr. Chen's memo dated 9/11/12), the following was recommended;

Following evaluation of the inspectional observations for Studies M1FT08001 and M1FT08002, the DBGC reviewer recommends:

- 1. The miscarriage for Subject #5 should be considered an adverse event possibly related to drug product dosing or other study activities.*
- 2. DPARP and DCPII should evaluate whether to exclude this subject from pharmacokinetic evaluations.*
- 3. DPARP should contact the sponsor and request an independent third-party data integrity audit, using the FDA-approved plan, for the bioanalytical portions of studies M1FT08001 and M1FT08002.*

Related to recommendation 3 above, the independent third-party data integrity audit plan was communicated to the sponsor on 5/1/12. In the resubmission, sponsor submitted the

report of the third-party audit. Therefore, this review covers the third party audit report and reanalysis of the data after exclusion of subject #5 and subjects #5 and #27 . The third party audit identified that two samples from subject #27 should be considered as high risk and sample swapping or misconduct could not be ruled out. Reanalysis of study M1FT08001 by excluding subject #5 did not affect the conclusion of the study. Therefore, the pharmacokinetic results from the two studies MIFT08001 and MIFT08002 are acceptable.

Table. Comparison of PK Parameters after Single Dose (M1FT08001) Parameters presented as geomean ratio% (90% CI) after Subjects 27 and 5 are excluded.		
Parameter	With subjects 27 and 5	Without subjects 27 and 5
	Fasted ER/Fasted Solution	Fasted ER/Fasted Solution
Cmax (ng/mL)	93.2 (90-97)	93.2 (90-104)
AUC _{0-inf} (ng·h/mL)	100.8 (97-104)	100.6 (97-104)
AUC _t (ng h/mL)	100.8 (98-104)	100.6 (97-104)

Table. Comparison of PK Parameters after Single Dose (M1FT08001) Parameters presented as geomean ratio% (90% CI) after Subjects 5 and 27 are excluded.		
Parameter	With subjects 27 and 5	Without subjects 27 and 5
	Fed ER/Fasted ER	Fed ER/Fasted ER
Cmax (ng/mL)	94 (91-97)	94.7 (92-98)
AUC _{0-inf} (ng·h/mL)	97.9 (95-100)	98.1(95-101)
AUC _t (ng h/mL)	97.5 (95-100)	97.7 (95-101)

Overall, adequate data was provided in this submission demonstrating bioequivalence of the proposed product to the reference product under single dose and multiple dose conditions.

2. QUESTION-BASED REVIEW

2.1. General Attributes

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

The original submission was not approved because of significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b) (4) in (b) (4). See FDA Untitled Letter issued on (b) (4) to (b) (4) regarding the data reliability of studies conducted at the (b) (4) site between (b) (4). To resolve the deficiency, the Agency originally provided three approaches (see Complete Response Letter dated October 7, 2011):

- a. Reanalyze all plasma samples and evaluate the results of the reanalysis data based on regression analysis and Incurred Sample Reanalysis (ISR) approaches if plasma samples for your studies are still available. For the conformational reanalysis endpoint, calculate the % Difference using the corrected repeat value based on the actual plasma stability.
- b. Repeat the clinical pharmacology studies if plasma samples for your studies are not available.
- c. Conduct a clinical development program with clinical efficacy and safety studies to support your carbinoxamine extended release oral suspension product.

On May 3, 2012 FDA notified Tristhe available options the sponsors for bioanalytical studies conducted at (b) (4) between (b) (4) and (b) (4) in support of marketing applications. The Agency will accept studies (conducted between March 1, 2008 and August 31, 2009) for submission and review if the sponsor performs an independent third-party data integrity audit using the Bioanalytical Electronic Raw Data Audit Plan (provided by FDA). Further, studies that were previously submitted as part of an approved or pending application will also need verification of data integrity by an independent third-party audit. The two studies in this application were conducted in April, 2009 and were subjected to third party audit. Sponsor submitted the audit report in the Resubmission.

During this time, an audit of the clinical site was conducted by the Office of Scientific Investigations (OSI). Subject #5 in Study M1FT08001 got pregnant and went through a miscarriage. Subject #5 was administered reference treatment on 1/3/09, test treatment (fast) on 1/17/09, and test treatment (fed) on 1/31/09). She had a positive pregnancy test on 2/3/09 when her 72 hour blood sample (last blood sample for PK in this treatment) was collected. Subsequently, she had a miscarriage on (b) (6). OSI recommended that exclusion of this subject in the analysis be considered.

2.2. General Clinical Pharmacology

2.2.1. What are the PK characteristics of the drug?

2.2.1.1. What are the single dose and multiple dose BE outcomes?

The single dose and multiple dose BE conclusions based on original data not taking into account OSI inspection findings can be found in the clinical pharmacology review by Dr. Ping Ji finalized on Sep 02, 2011.

Based on OSI audit recommendation, the miscarriage for Subject #5 from study M1FT08001 was considered as an adverse event possibly related to drug product dosing or other study activities. The data was reanalyzed excluding this subject. The analysis of the bioequivalence assessment with and without the subject #5 did not affect the BE conclusion (Tables 1 and 2).

Based on the Third Party Audit, two samples from Subject 27 in study M1FT080001 were considered high risk and sample swapping or misconduct could not be excluded. Reanalysis was conducted by excluding Subject 27. The bioequivalence assessment with and without subject #27 did not affect the BE conclusion (Table 3 and 4).

Further, reanalysis was also conducted by excluding Subjects #27 and #5. The bioequivalence assessment with and without subjects #27 and #5 did not affect the results (Tables 5 and 6).

Parameter	With subject 5	Without subject 5
	Fasted ER/Fasted Solution	Fasted ER/Fasted Solution
C _{max} (ng/mL)	93.2 (90-97)	92.3 (89-96)
AUC _{0-inf} (ng-h/mL)	100.8 (97-104)	100.7 (97-104)
AUC _t (ng h/mL)	100.8 (98-104)	100.5 (98-103)

Parameter	With subject 5	Without subject 5
	Fed ER/Fasted ER	Fed ER/Fasted ER
C _{max} (ng/mL)	94 (91-97)	94.3 (91-97)
AUC _{0-inf} (ng-h/mL)	97.9 (95-100)	98.0 (95-101)
AUC _t (ng h/mL)	97.5 (95-100)	97.5 (95-101)

Table 3. Comparison of PK Parameters after Single Dose (M1FT08001) Parameters presented as geomean ratio% (90% CI) after Subject 27 is excluded.

Parameter	With subject 27	Without subject 27
	Fasted ER/Fasted Solution	Fasted ER/Fasted Solution
Cmax (ng/mL)	93.2 (90-97)	93.5 (90-97)
AUC _{0-inf} (ng-h/mL)	100.8 (97-104)	100.9 (98-104)
AUCt (ng h/mL)	100.8 (98-104)	100.9 (97-105)

Table 4. Comparison of PK Parameters after Single Dose (M1FT08001) Parameters presented as geomean ratio% (90% CI) after Subject 27 is excluded.

Parameter	With subject 27	Without subject 27
	Fed ER/Fasted ER	Fed ER/Fasted ER
Cmax (ng/mL)	94 (91-97)	94.3 (91-97)
AUC _{0-inf} (ng-h/mL)	97.9 (95-100)	98.06 (91-101)
AUCt (ng h/mL)	97.5 (95-100)	97.6 (95-101)

Table 5. Comparison of PK Parameters after Single Dose (M1FT08001) Parameters presented as geomean ratio% (90% CI) after Subjects 27 and 5 are excluded.

Parameter	With subjects 27 and 5	Without subjects 27 and 5
	Fasted ER/Fasted Solution	Fasted ER/Fasted Solution
Cmax (ng/mL)	93.2 (90-97)	93.2 (90-104)
AUC _{0-inf} (ng-h/mL)	100.8 (97-104)	100.6 (97-104)
AUCt (ng h/mL)	100.8 (98-104)	100.6 (97-104)

Table 6. Comparison of PK Parameters after Single Dose (M1FT08001) Parameters presented as geomean ratio% (90% CI) after Subjects 5 and 27 are excluded.

Parameter	With subjects 27 and 5	Without subjects 27 and 5
	Fed ER/Fasted ER	Fed ER/Fasted ER
Cmax (ng/mL)	94 (91-97)	94.7 (92-98)
AUC _{0-inf} (ng-h/mL)	97.9 (95-100)	98.1(95-101)
AUCt (ng h/mL)	97.5 (95-100)	97.7 (95-101)

Since this is an age appropriate formulation and appropriate doses corresponding to the immediate release reference product can be figured out and BE of the formulation was established to the immediate release formulation, dosage and administration is extended down to pediatric patients 2 years of age. PERC agreed with this plan on February 20, 2013.

2.3. Analytical Section

2.7.2 How was the assay performed for the analytes?

The studies M1FT08001 and M1FT08002 were audited by third party

(b) (4) The audit included three phases as shown below:

Phase 1 – Review of Documentation: Review of all paper documentation associated with the study, e.g. sample analysis reports, assay validation reports, etc.

Phase 2 – Initial Classification of Daily Work Lists: Assignment of daily assay work lists to low, medium and high risk based on a preliminary assessment.

Phase 3 – In Depth Data Evaluation: In-depth audit of daily medium and high risk runs requiring a more detailed investigation to confirm acceptability of data and resolve issues identified in the Phase 2 audit.

The summary of the analytical samples from both studies are shown in Table 7 and the audited items are summarized in Table 8. The audit results are shown in Table 9. Based on the third-party audit, the study M1FT08002 had no significant deviations, whereas as two samples from Subject #27 in study M1FT08001 were regarded as high risk and therefore unable to rule out sample swapping or misconduct.

Table 7. Summary of analytical samples from Studies M1FT08001 and M1FT08001.

Item	Study M1FT08001	Study M1FT08002
Analytes of Interest	Carbinoxamine	Carbinoxamine
(b) (4) Report Number	0905080.00	0903040.00
Dates of Analysis	April 24, 2009 to May 05, 2009	January 3, 2009 to February 25, 2009
Validation Method Number	Validated method, AP LC/MS/MS LC/MS/MS 365.100	Validated method, AP LC/MS/MS 365.100
Analysis Plan Version	Internal SOPs cited in sample analysis report	AP version NA
Sample Collection Start	March 18, 2009	January 3, 2009
Sample Analysis Completed	May 5, 2009	February 25, 2009
Calculated time from first sample collected to last sample assayed	48 days	53 days
Established LTS at time of report (include	85 days	85 days

Number of samples assayed	2052	3013
Study Design (subjects, periods, # of time	42 subjects with 2 periods 25 time points	39 subjects with 3 periods 26 time points
Calculated number of samples (note	2100 (48 samples received with empty tubes	3042 (29 empty tubes documented in report).
Reported Sample Discrepancies	None reported	Subjects 20, 33 and 41 were noted as study dropouts and not
Issue resolution or investigations	None reported	None reported
ISR Details	1 (b)(4) samples met (b)(4) SOP (u)(4) _SOP_04_LBP_003 requirements. (at least 2/3 of	(b)(4) SOP requirements. (at least 2/3 of the (repeat result and original value

Table 8: A list of items audited.

Item	Audit Items
Audit Company	(b)(4)
Phase 1	Sample Analysis Report
	Complete Validation Report
	Data summary sheet
	Sample/run reconciliation
	Sample matrix
	Stability (long term and extract)
Phase 2	Open the raw data electronic files using Analyst.
	Determine if all Analytical Runs are accounted for
	Determine if there were any PREP runs saved outside of the project system files
	Check chromatograms and determine if there were any unexpected instrument interruptions during sample analysis
	Number of standards & QCs in Prep/Equilibration run
	Number of standards & QCs in Prep/Equilibration run
	Nature of sample IDs in Prep/Equilibration run
	Timing of Final Prep/Equilibration run vs Official run
	Number of Prep/Equilibration runs preceding official run. NB - this is most significant if these runs are immediately preceding the official run (within 8 hours)
	Run sequence.
Phase 3	Assess each yellow color- coded Official Sample Run and associated PREP runs

	Compare the sample ID and injection vial position in the PREP run to that which was run in the official run
	Compare the peak area ratios of PREP run samples to the corresponding samples included in the official run
	Calculate the % difference between the peak area ratios of PREP run samples to their corresponding samples included in the official run
	Number of standards & QCs in Prep/Equilibration run
	Number of subject samples in Prep/Equilibration run
	Nature of sample IDs in Prep/Equilibration run
	Timing of Final Prep/Equilibration run vs Official run
	Number of Prep/Equilibration runs preceding official run. NB - this is most significant if these runs are immediately preceding the official run (within 8 hours)
	Run sequence.

Table 9. Results from analytical audit

	M1FT08002	M1FT08001
Result	None	Two samples in subject 27 are regarded as high risk and therefore unable to rule out sample swapping or misconduct.

3. DETAILED LABELING RECOMMENDATIONS

(Reviewer suggested changes: ~~Strikeout text~~ should be removed from labeling and underlined text should be added to labeling)

7 Drug Interactions

~~Monoamine oxidase inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.~~

~~Carbinoxamine maleate has additive effects with alcohol and other CNS depressants (hypnotics sedatives, tranquilizers, etc.).~~

Avoid use of Karbinal ER with monoamine oxidase inhibitors (MAOIs), which prolong and intensify the anticholinergic (drying) effects of antihistamines.

Avoid use of Karbinal ER with alcohol and other CNS depressants (hypnotics sedatives, tranquilizers, etc.) due to additive effects.

12 Clinical Pharmacology

12.1 Mechanism of Action

(b) (4)

Carbinoxamine is an H₁ receptor antagonist (antihistamine) in the ethanolamine class that also exhibits anticholinergic (drying) and sedative properties.

Antihistamines (b) (4) compete with histamine for receptor sites on effector cells.

12.2 Pharmacodynamics

(b) (4)

12.3 Pharmacokinetics

(b) (4)

Karbinal ER after single-dose administration of 16 mg was bioequivalent to the reference carbinoxamine immediate-release oral solution after the administration of two doses of 8 mg six hours apart under fasting conditions. The carbinoxamine mean (SD) peak plasma concentration (C_{max}) was 28.7 (5.3) ng/mL at 6.7 hours after Karbinal ER administration. The plasma half-life of carbinoxamine was 17.0 hours. There was no effect of food on the pharmacokinetic parameters.

Karbinal ER after multiple-dose administration of 16 mg every 12 hours for 8 days was bioequivalent to the reference carbinoxamine immediate-release oral solution after multiple-dose administration of 8 mg every 6 hours. The mean (SD) steady-state C_{max} was 72.9 (24.4) ng/mL at 5.6 hours after Karbinal ER administration. Carbinoxamine mean (SD) minimum plasma concentration at steady-state was 51.8 (20.3) ng/mL.

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03/05/2013

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03/06/2013

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 22-556	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DPAADP		
Applicant:	Tris Pharma	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	--	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Carbinoxamime ER Oral Suspension	Date Assigned:	Jan 21, 2011
Indication:	Allergic rhinitis	Date of Review:	Sep 1, 2011
Formulation/strengths	Extended Release suspension, 4 mg/5 mL		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Dec 9, 2010 April 19, 2011 June 24, 2011 July 14, 2011	Dec 9, 2010	Jan 21, 2011	Oct 11
Type of Submission:	Original NDA		
Type of Consult:	<ul style="list-style-type: none"> - Dissolution method and acceptance criteria - In vitro alcohol dose-dumping study 		

REVIEW SUMMARY:

The Applicant has developed Carbinoxamine ER Oral Suspension as a 12-hour extended release formulation indicated for treatment of allergic rhinitis. Carbinoxamine Maleate Oral Solution (4mg/5mL), manufactured by Mikart Inc., (Brand Name-Palgic) is being used as the Reference Product for the development and for bioavailability studies. According to the Applicant, the ER properties of this product are controlled by the diffusion of drug through the controlled release polymer (Sodium polystyrene sulfonate).

The Biopharmaceutics review is focused on the acceptability of the dissolution method, dissolution acceptance criteria, and on the evaluation of the in vitro alcohol dose-dumping study.

1) Dissolution Method and Acceptance Criteria

The following dissolution method and acceptance criteria for carbinoxamine ER suspension have been agreed upon with the Applicant (refer to teleconference dated July and submission dated July 14, 2011):

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Carbinoxamine	ER Suspension	USP Paddle	50	900 mL 0.4 M KH ₂ PO ₄	1 hr: (b) (4) 3 hrs: (b) (4) 6hrs: (b) (4) 12 hrs: NLT (b) (4)

The accepted final dissolution acceptance criteria are based on the mean dissolution profiles for the data from registration stability batches, commercial site stability batches.

2) In Vitro Alcohol Dose-Dumping Study

The *in vitro* alcohol dose-dumping study was conducted in the QC medium and 0.1 N HCl under the presence of alcohol at concentrations ranging from 4%, 20%, and 30%. The results in the QC medium showed that more than (b)(4) of the drug is released in two hours in the presence of 30% alcohol, indicating that carbinoxamine ER suspension is susceptible to dose-dumping in the presence of alcohol. The Clinical Pharmacology Review Team/Clinical Review Team should assess the need for in vivo studies evaluating the relevance of alcohol dose-dumping on the efficacy and safety of the product under review.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 22-556 (000) submitted on Dec 9, 2010, April 19, 2011, June 24, 2011, and July 14, 2011. We found this NDA acceptable from the Biopharmaceutics perspective.

The following dissolution method and acceptance criteria have been agreed upon with the Applicant (refer to Submission dated July 14, 2011):

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Carbinoxamine	ER Suspension	USP Paddle	50	900 mL 0.4 M KH ₂ PO ₄	1 hr: (b)(4) 3 hrs: (b)(4) 6hrs: (b)(4) 12 hrs: NLT (b)(4)

Comment to the Clinical Pharmacology/Medical Review Teams

- The *in vitro* alcohol dose-dumping study using the QC medium showed that more than (b)(4) of the drug is released in two hours in the presence of 30% alcohol, indicating that carbinoxamine ER suspension is susceptible to dose-dumping in the presence of alcohol. The Clinical Pharmacology Review Team/Clinical Review Team should assess the need for in vivo studies to evaluate the relevance of alcohol dose-dumping on the efficacy and safety of the product under review.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Lead
Office of New Drug Quality Assessment

c.c. PMarroum, ASchroeder, JPinto, SPatwardhan

INTRODUCTION

The Applicant has developed Carbinoxamine ER Oral Suspension as a 12-hour extended release formulation indicated for treatment of allergic rhinitis. Carbinoxamine Maleate Oral Solution (4mg/5mL), manufactured by Mikart Inc., (Brand Name-Palgic) is being used as the Reference Product for the development and for bioavailability studies. According to the Applicant, the ER properties of this product are controlled by the diffusion of drug through the controlled release polymer (Sodium polystyrene sulfonate).

The clinical development program for (b) (4) ER Oral Suspension included the following relative bioavailability studies:

- a single dose study that compared the Test and Reference Products under fasting conditions
- a single dose food-effect study on the Test Product
- a multiple dose study comparing the Test and Reference Products at steady state under fasting conditions

These studies are being reviewed by the Clinical Pharmacology team. The Biopharmaceutics review is focused on the acceptability of the dissolution method and acceptance criteria and on the *in vitro* alcohol dose-dumping study.

Drug Product

Carbinoxamine ER Oral Suspension is a 12-hour extended release formulation. Each 5 mL (b) (4) of oral suspension contains 4 mg carbinoxamine maleate. The extended release properties of this product are controlled by the diffusion of drug through the controlled release polymer. (b) (4)

(b) (4) major manufacturing steps. (b) (4) were used to produce the final (b) (4) components and composition of the formulation are summarized in Table 1.

Table 1. Components and composition for Carbinoxamine Extended Release Oral Suspension, 4 mg per 5 mL Formulation

Ingredient	%w/v	mg/5mL	Use
Purified Water			(b) (4)
Polysorbate 80			(b) (4)
Sodium Metabisulfile			(b) (4)
Carbinoxamine Maleate			(b) (4)
(b) (4) Polistirex			(b) (4)
Purified Water			(b) (4)
Citric Acid, Anhydrous			(b) (4)
Sucrose			(b) (4)
High Fructose Corn Syrup			(b) (4)
(b) (4)			(b) (4)
Glycerin			(b) (4)
Methylparaben			(b) (4)

Propylparaben	(b) (4)
Xanthan Gum	
Strawberry-Banana flavor	
Purified Water	

Dissolution Method

The following dissolution method was proposed by the Applicant for the carbinoxamine ER Suspension:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium
Carbinoxamine	ER Suspension	USP Paddle	50	900 mL 0.4 M KH ₂ PO ₄

Dissolution Method Development

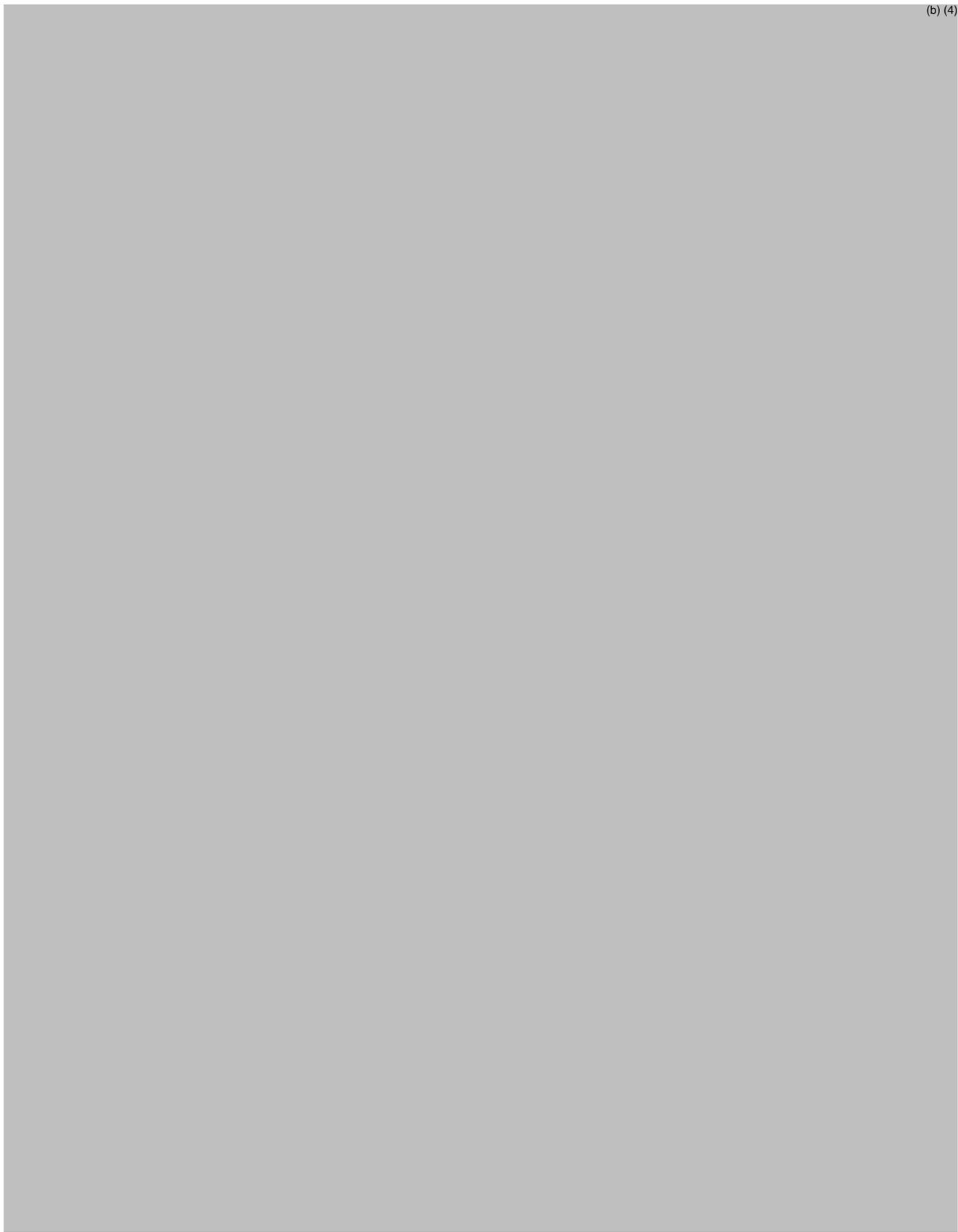


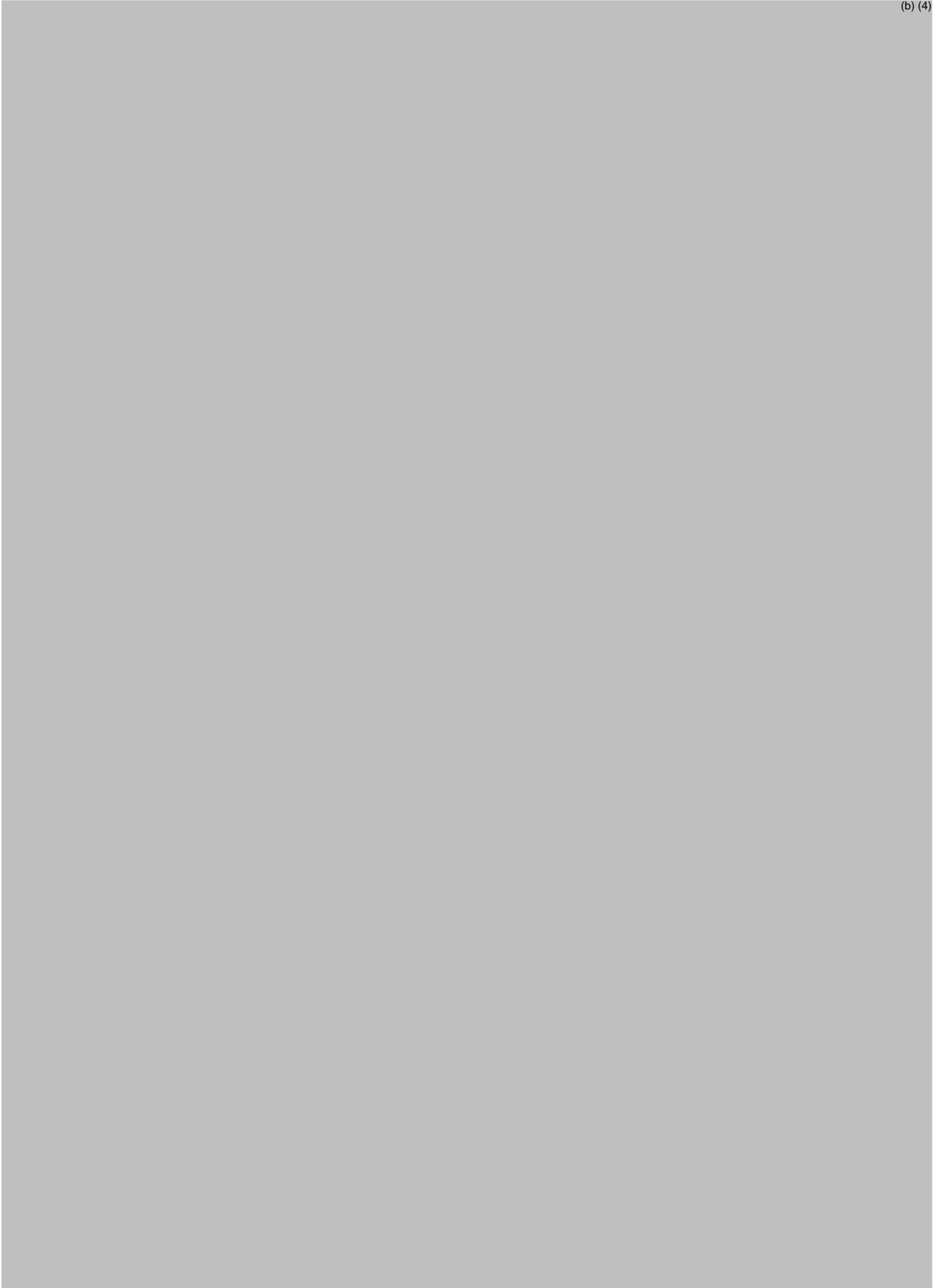
Acceptance Criteria

The following acceptance criteria were originally proposed by the Applicant for the drug product under review:

(b) (4)

(b) (4)









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/s/

SANDRA SUAREZ
09/05/2011

ANGELICA DORANTES
09/05/2011

CLINICAL PHARMACOLOGY REVIEW

<i>NDA</i>	22-556	<i>Submission Date</i>	12/08/2010
<i>Brand Name</i>	TBD		
<i>Generic Name</i>	Carbinoxamine oral suspension		
<i>Reviewer</i>	Ping Ji, Ph.D.		
<i>Team Leader</i>	Suresh Doddapaneni, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology-II		
<i>OND Division</i>	Division of Pulmonary, Allergy, and Rheumatology Products		
<i>Sponsor</i>	Tris Pharmaceuticals		
<i>Relevant IND(s)</i>	102,091		
<i>Submission Type; Code</i>	505 (b) (2)	S	
<i>Formulation; Strength(s)</i>	4 mg carbinoxamine maleate per 5 mL suspension		
<i>Indication</i>	<p>The proposed indications include:</p> <p>Seasonal and perennial allergic rhinitis</p> <p>Vasomotor rhinitis</p> <p>Allergic conjunctivitis due to inhalant allergens and foods</p> <p>Mild, uncomplicated allergic skin manifestations of urticaria and angioedema</p> <p>Dermatographism</p> <p>As therapy for anaphylactic reactions <i>adjunctive</i> to epinephrine and other standard measures after the acute manifestations have been controlled</p> <p>Amelioration of the severity of allergic reactions to blood or plasma</p>		
<i>Proposed Dosing Regimen</i>	<p>Adult Dosage:</p> <p>█^{(b) (4)} (6 to 16 mg) every 12 hours</p> <p>Child's Dosage (approximately 0.2 to 0.4 mg/kg/day):</p> <p>Two to three years – █^{(b) (4)} (3 to 4 mg) every 12 hours</p> <p>█^{(b) (4)} – █^{(b) (4)} (3 to 8 mg) every 12 hours</p> <p>█^{(b) (4)} – █^{(b) (4)} (6 to 12 mg) every 12 hours</p>		

Table of Contents

Table of Contents.....	2
1. Executive Summary.....	3
1.1. Recommendations.....	3
1.2. Phase IV Commitments.....	3
2. Question-Based Review.....	6
2.1. General Attributes.....	6
2.2. General Clinical Pharmacology.....	8
2.3. Intrinsic Factors.....	10
2.4. Extrinsic Factors.....	11
2.5. General Biopharmaceutics.....	13
2.6. Analytical Section.....	13
3. Detailed Labeling Recommendations.....	14
4. Appendixes.....	16
4.1. Proposed Package Insert (Original and Annotated).....	16
4.2. Individual Study Review.....	21
4.3. Clinical Pharmacology and Biopharmaceutics filing form/checklist for NDA 22-450.....	28

1. EXECUTIVE SUMMARY

1.1. Recommendations

The submission is Not Acceptable from a Clinical Pharmacology and Biopharmaceutics perspective because data in the bioanalytical studies conducted during the time period of [REDACTED] (b) (4) by [REDACTED] (b) (4) in [REDACTED] (b) (4) were deemed to be unreliable by FDA as significant violations were identified by FDA investigators. Pivotal BA/BE data supporting this NDA were obtained from this bioanalytical site during the months of January through April of 2009 thus falling within the critical time period identified by FDA.

Sponsor should address this deficiency by doing one of the following: (a) re-assay of samples if available and supported by stability data and (b) repeat the studies. Sponsor should be advised to meet with the Agency for an agreement on the path forward before taking corrective actions.

1.2. Phase IV Commitments

None.

1.2.1. Summary of Clinical Pharmacology and Biopharmaceutics Findings

[REDACTED] (b) (4) ER oral suspension, subject of NDA22556, was developed by Tris Pharmaceuticals for the treatment of allergic symptoms. Currently the marketed carbinoxamine formulations in the US are immediate release oral tablets or solutions that are dosed 3 to 4 times daily. The [REDACTED] (b) (4) ER Oral Suspension is an extended-release formulation that requires twice daily dosing. As agreed upon during the Pre-IND meeting, approval of this product is based on successful demonstration of bioequivalence between [REDACTED] (b) (4) ER Oral Suspension [4 mg/5 mL] by Tris Pharma Inc. (Test Product) with a reference product in lieu of clinical efficacy and safety trials. Carbinoxamine Maleate Oral Solution [4 mg/5 mL] by Mikart was the reference product used by the sponsor in the BA/BE studies. This program is supported with two relative bioavailability studies in healthy subjects: a single dose study that compared the Test and Reference Products under fasted conditions and evaluated the food effect on the Test Product (M1FT08001) and a multiple dose study that compared the Test and Reference Products at steady state under fasted conditions (M1FT08002). The results of these two studies are shown in the Figures 1 and 2, respectively. The Test Product is bioequivalent with the Reference Product after both single dose and multiple doses under fasted condition. Food has no effect on the Test Product.

Figure 1. Plasma Concentration-Time Profile and Summary Analysis for M1FT08001.

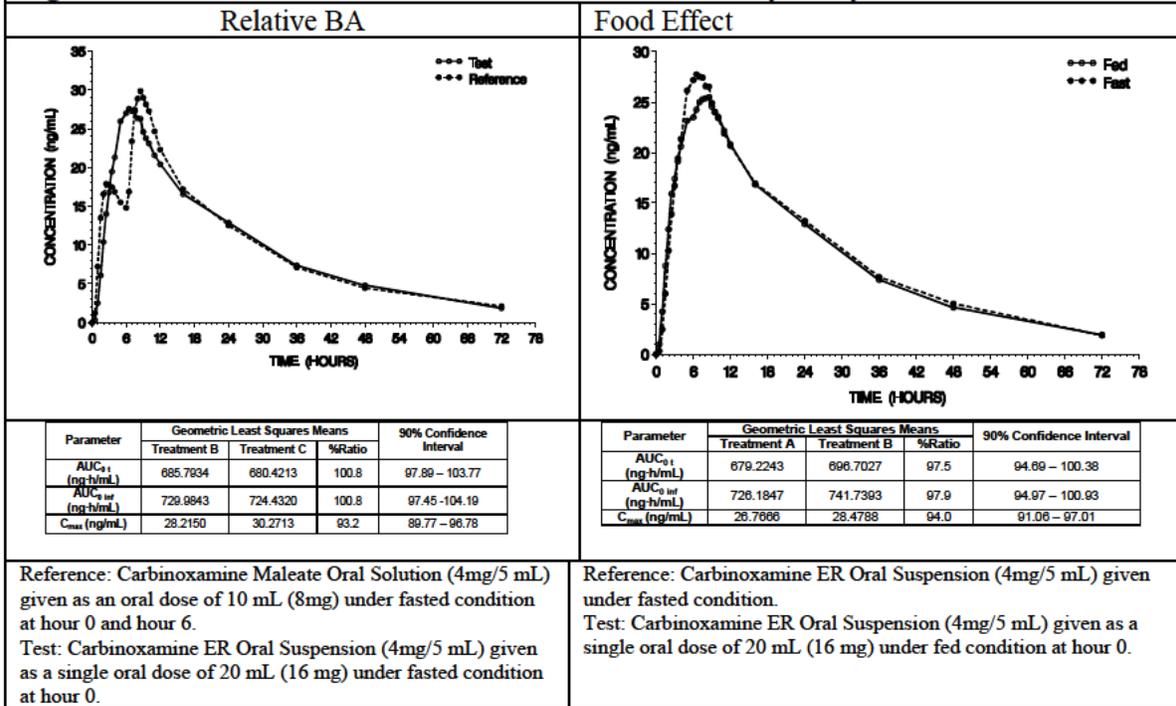
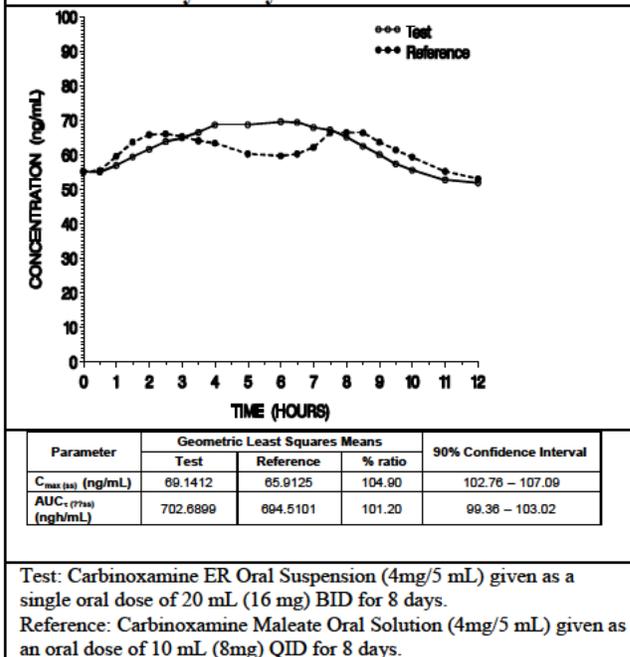


Figure 2. Plasma Concentration-Time Profile and Summary Analysis for M1FT08002.



However, from a Clinical Pharmacology perspective, these data are not acceptable because these pivotal BA/BE data supporting this NDA were obtained from (b) (4) bioanalytical site during the months of January through April of 2009. DSI did not feel the need to inspect these studies as their study conduct fell within the time period of (b) (4) through

(b) (4) during which period data were deemed to be unreliable by FDA as significant violations were identified by FDA investigators.

Related to the alcohol interaction potential of this formulation, totality of evidence in terms of formulation characteristics, dissolution release characteristics, and existing labeling language do not indicate a significant safety concern due to alcohol dose dumping potential and an in vivo study to further characterize the alcohol interaction is not warranted.

2. QUESTION-BASED REVIEW

2.1. General Attributes

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

Carbinoxamine Maleate was marketed as an antihistamine by McNeil Pharmaceuticals, Consumer Division in 1954 under the trade name of CLISTIN[®] under NDA008955. Clinstin was discontinued from marketing by McNeil in 1985. CLISTIN[®] was not withdrawn for safety or efficacy reasons. Since then, several generic versions of CLISTIN[®] were approved. The currently recognized reference list drug (RLD) for carbinoxamine include carbinoxamine maleate 4 mg/5 mL oral solution by Mikart (ANDA040458) and carbinoxamine maleate 4 mg tablet by Mikart (ANDA040442). This is utilizing the 505(b)(2) regulatory pathway for the approval of its proposed Carbinoxamine ER Oral Suspension and is relying on the FDA's safety and efficacy findings for CLISTIN[®] under NDA 008955. At the Pre-IND meeting held on May 15, 2008, Agency agreed that no clinical efficacy and safety studies will be needed for the single ingredient carbinoxamine ER product if bioequivalence is demonstrated between their product and the reference product. As such, this NDA contains two BA/BE studies, study M1FT08001 and M1FT08002, supporting the approval of this NDA in lieu of clinical efficacy and safety studies. Study M1FT08001 assessed single dose BE relative to the reference and effect of food while study M1FT08002 assessed steady state BE relative to the reference.

2.1.2. 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 clinical pharmacology and biopharmaceutics review?

Some attributes of carbinoxamine maleate are shown below:

Molecular Weight:	406.86
Description:	(b) (4)
pKa:	(b) (4)
Polymorphism:	(b) (4)
Solubility:	(b) (4)
Melting Range:	Between 116° and 121°C, determined after drying.
Partition coefficient:	(b) (4)

Formulation composition:

Table 1. Composition of Carbinoxamine ER Suspension.

Ingredients	Function	Quantity (mg/5 mL)
Sodium Polystyrene Sulfonate (b) ¹ (4)		(b) (4)
Povidone USP (b) (4)		
Triacetin USP		
Polyvinyl Acetate (b) (4)		
(b) (4)		
Purified Water USP		
Polysorbate 80 NF (b) (4)		
Sodium Metabisulfite NF (b) (4)		
Carbinoxamine Maleate USP		
Glycerin USP		
Methylparaben NF		
Propylparaben NF		
Xanthan Gum NF (b) (4)		
Anhydrous Citric Acid USP		
High Fructose Corn Syrup (b) (4)		
Sucrose NF		
(b) (4) (Food Starch – Modified)		
Strawberry Banana Flavor (b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		

² Amount represents (b) (4)
³ Amount represents (b) (4)

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

Carbinoxamine Maleate (Ethanolamine, 2-[(4-chlorophenyl)-2pyridineylmethoxy]-N, N-dimthyl-(Z)-butteneddioate) is an antagonist of the histamine H₁-receptor. Carbinoxamine inhibits the effect of histamine at the receptor and reduces or eliminates effects mediated by endogenous histamine which is released during allergic reactions. Carbinoxamine’s anticholinergic action appears to be due to a central antimuscarinic effect which may be responsible for its antiemetic effects, though the exact mechanism is unknown.

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

The proposed dosing regimen is as follows:

Adult Dosage:

(b) (4) (6 to 16 mg) every 12 hours

Child Dosage (approximately 0.2 to 0.4 mg/kg/day):

Two to three years – (b) (4) (3 to 4 mg) every 12 hours

(b) (4) – (b) (4) (3 to 8 mg) every 12 hours

(b) (4) – (b) (4) (6 to 12 mg) every 12 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?

Two *in vivo* relative bioavailability studies were conducted in healthy male and female volunteers:

Study	Objective(s)
M1FT08001	<ul style="list-style-type: none">Assess the relative bioavailability of a single dose of Carbinoxamine ER Oral Suspension versus Carbinoxamine Maleate in healthy adult subjects when administered under fasted conditions.Assess the impact of food on the bioavailability of Carbinoxamine ER Oral Suspension by comparing the pharmacokinetic parameters under fasted and fed conditions following the administration of a single dose
M1FT08002	<ul style="list-style-type: none">Assess the relative bioavailability of Carbinoxamine ER Oral Suspension versus Carbinoxamine Maleate in healthy adult subjects under fasted conditions at steady state.

The Test Product, Carbinoxamine ER Oral Suspension, will be marketed as an extended release dosage form for Carbinoxamine, intended for the same population and therapeutic indication as the Reference Product, Carbinoxamine Maleate Oral Solution.

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

Yes. Please refer to the analytical section for details.

2.2.3. Exposure-response

NA.

2.2.4. What are the PK characteristics of the drug?

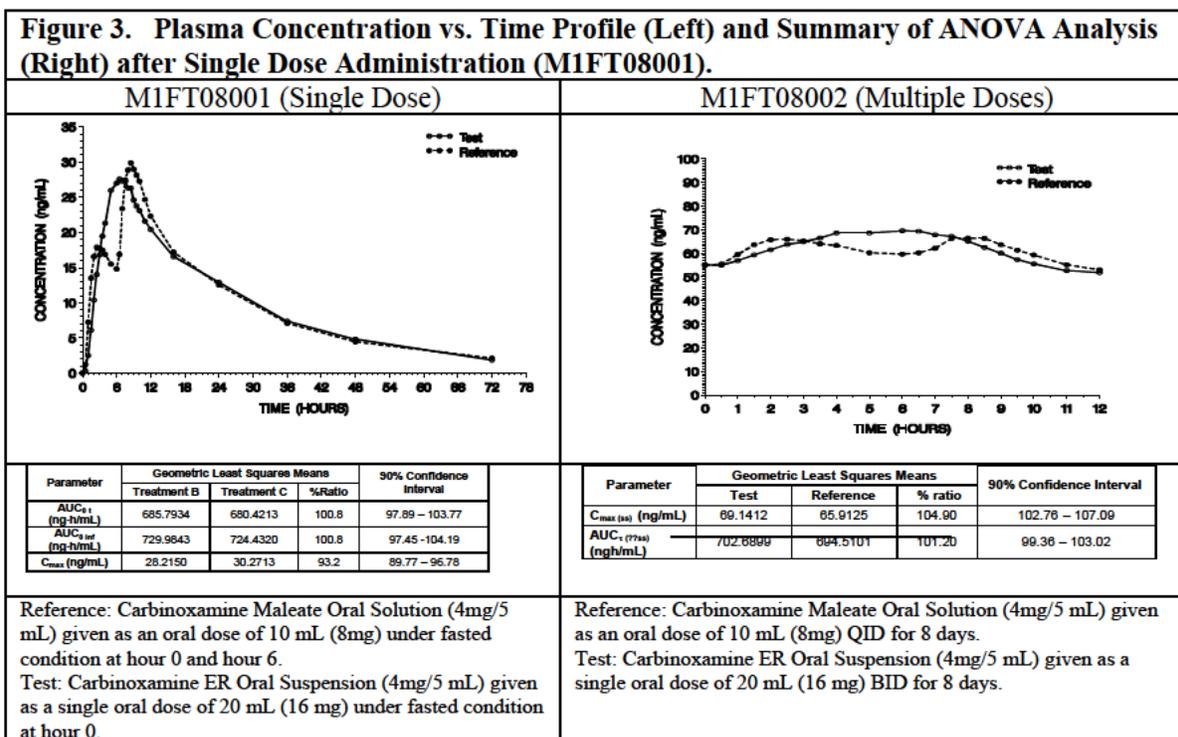
2.2.4.1. What are the single dose and multiple dose PK characteristics?

The pharmacokinetic variables of Carbinoxamine from the Test and Reference Products after a single dose and at steady state are presented in Table 2 below. $AUC_{\tau(ss)}$ at steady state was comparable to AUC_{0-inf} after a single dose. The median T_{max} values were about 1-hour earlier at steady state as compared to single dose administration for both Test and Reference products. The half-life of carbinoxamine for Test Product was similar to that for Reference Product.

Parameter	M1FT08001 (single dose)		M1FT08002 (steady state)	
	Test	Reference	Test	Reference
T_{max}^a (h)	6.52 (5.00 – 8.50)	8.50 (7.50 – 10.00)	6.00 (3.00 – 8.50)	7.50 (2.00 – 10.00)
C_{max} (ng/mL)	28.7 ± 5.3	30.8 ± 3.5	73.0 ± 24.4	69.7 ± 23.3
AUC_{0-inf} (ng·h/mL)	756 ± 195	730 ± 179	--	--
$AUC_{\tau(ss)}$ (ng·h/mL)	--	--	745 ± 262	736 ± 259
T_{half} (hr)	17.5 ± 3.2	16.9 ± 2.6	--	--

^a Median (range)

Bioequivalence was demonstrated between the test Carbinoxamine ER suspension and the reference Carbinoxamine solution under both single and multiple dose conditions (Figure 3). However, these data (from studies M1FT08001 and M1FT08002) are not acceptable because the pivotal BA/BE data supporting this NDA were obtained from (b) (4) bioanalytical site during the months of January through April of 2009, which fell within the time period of (b) (4) during which period data were deemed to be unreliable by FDA as significant violations were identified by FDA investigators.



2.2.4.2. How does the PK of the drug in healthy volunteers compare to that in patients?

NA

2.3. Intrinsic Factors

2.3.1. What intrinsic factors (age, gender, weight, etc.) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

2.3.1.1. Pediatric patients

The impact of age on the safety and pharmacokinetics of Carbinoxamine ER Oral Suspension was not evaluated.

Although Carbinoxamine may be administered to patients as young as 2 years of age, the relative bioavailability studies that were conducted included only healthy male and female subjects 18 years of age or older. Sponsor requested the pediatric waiver for the conduct of relative bioavailability studies in pediatrics between the ages of 2 to less than 18 years. At the time of writing this review, discussion is ongoing whether PK, safety, and efficacy studies will be required in children 2 years and above as the prior approval of the immediate release products was made under the DESI review process and that this may have been based on insufficient or no data in pediatric populations to support the indications.

2.3.1.2. Gender

The impact of gender on the safety and pharmacokinetics of Carbinoxamine ER Oral Suspension was not evaluated.

2.3.1.3. Race

The impact of race on the safety and pharmacokinetics of Carbinoxamine ER Oral Suspension was not evaluated.

2.3.1.4. Hepatic impairment

The impact of hepatic function on the safety and pharmacokinetics of Carbinoxamine ER Oral Suspension was not evaluated.

2.3.1.5. Renal impairment

The impact of renal function on the safety and pharmacokinetics of Carbinoxamine ER Oral Suspension was not evaluated.

2.3.2. Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation?

NA.

2.4. Extrinsic Factors

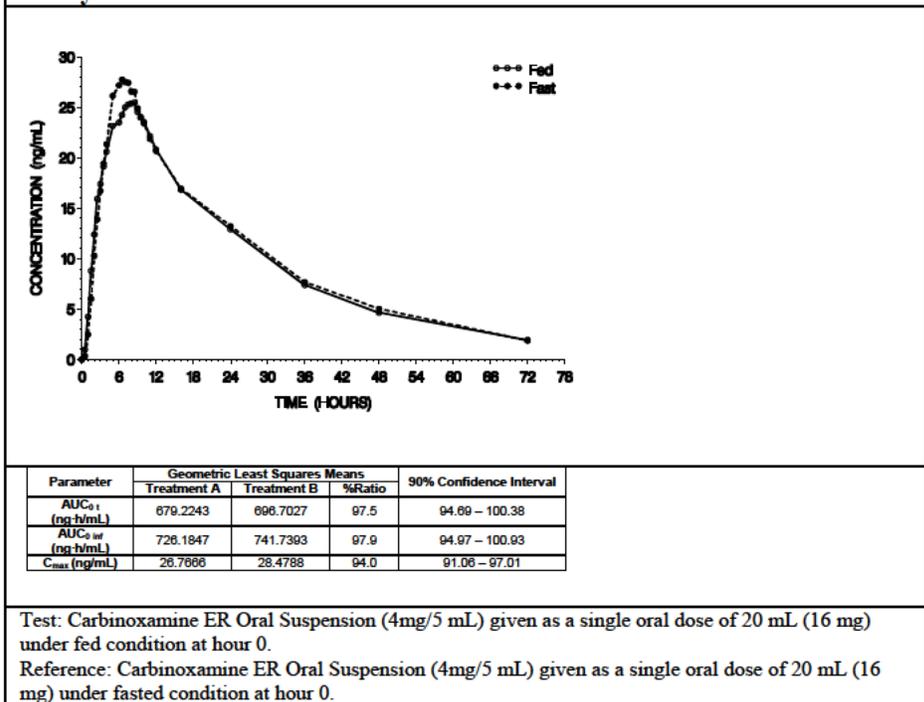
2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Food

Food had no effect on the pharmacokinetics of carbinoxamine for Carbinoxamine ER Oral Suspension.

The effect of food on the pharmacokinetics was evaluated in study MIFT08001. The results are shown in the following figure. The bioavailability of Carbinoxamine ER Oral Suspension was not affected by food, and there was no difference in Tmax under fasted and fed conditions. Both Cmax and AUC met the 90% confidence interval criteria demonstrating no food effect.

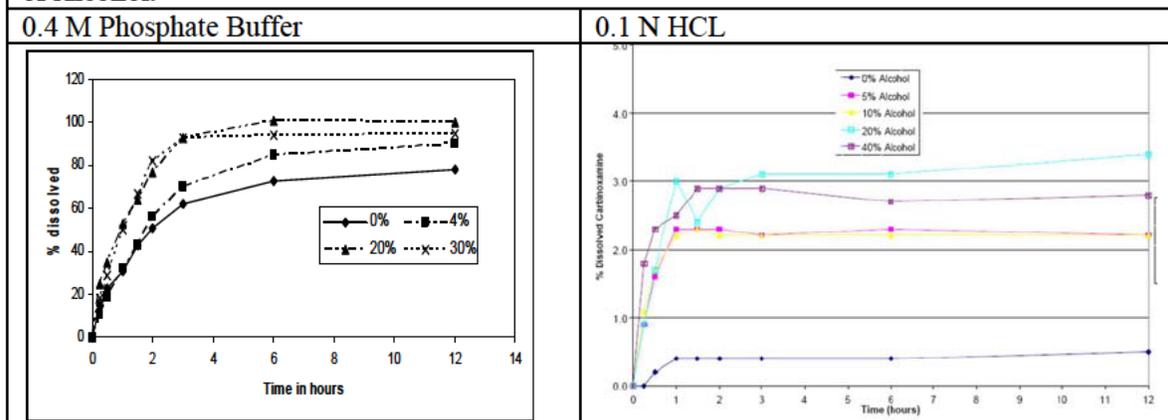
Figure 4. Plasma Concentration vs. Time Profile and Summary Analysis for MIFT08001 for Food Effect.



Alcohol

Per the memorandum of understanding (MOU) between ONDQA and OCP, Dr. Sandra Suarez of the Biopharmaceutics group in ONDQA evaluated the *in vitro* dissolution alcohol dose-dumping data. At the mid-cycle review meeting on May 9, 2011, Dr. Suarez indicated that the dissolution profiles in the presence of alcohol were not similar compared to the profile in the product dissolution medium (Figure 5). In such an instance, per MOU, OCP will be responsible for deciding when an *in vivo* alcohol study is needed. Close examination of the totality of evidence indicates that although the dissolution profiles are not similar, it appears that there is no significant potential for *in vivo* dose dumping warranting an *in vivo* alcohol interaction study. In an *in vivo* alcohol interaction scenario, the time window for interaction is very narrow (about 1 to 2 hours) and the formulation encounters acidic conditions in the stomach first. For this product, the median T_{max} is seen around 8.5 hours after single dose administration. In the medium containing 0.1 N HCL, data shows that dissolution is suppressed with about 3% or less drug release at all alcohol concentrations. This is probably because sodium polystyrene sulphonate ((b) (4)) in the formulation is insoluble in the acidic medium and is blocking the dissolution medium diffusion to leach out the drug from the ER matrix. However, the resin ionizes in the alkaline medium and regulates the drug release by its swelling ability without complete blockage as seen under 0.1 N HCL conditions. Further, in 0.4 M phosphate buffer conditions, the product is maintaining the release profile at all alcohol concentrations (that is, there is no immediate formulation failure). At 1 hour time point, about (b) (4) drug was released in the presence of 0% and 4% alcohol while it increased to about (b) (4) in the presence of 20% and 30% alcohol concentrations. At the two hours time point, drug release was (b) (4) and (b) (4) in the media of 0.4 M phosphate buffer containing 0, 4%, 20%, and 30% alcohol, respectively. It should also be noted the use of carbinoxamine with alcohol is not recommended in the approved package insert of the immediate release products and this product will also carry the same language in the proposed labeling. Use of carbinoxamine with alcohol is not recommended due to potential synergistic drowsiness effect.

Figure 5. Dissolution Profiles for Carbinoxamine ER Suspension in Various Amounts (%) of Alcohol.



2.5. General Biopharmaceutics

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The formulation Carbinoxamine ER Oral Suspension used in study MIFT08001 and MIFT08002 will be the marketed formulation.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma and urine in the clinical pharmacology studies?

The determination of Carbinoxamine in human plasma was validated using an API 3000 LC/MS/MS system with detection in the range of 0.2000 to 100.0 ng/mL.

2.7.2 How was the assay performed for the analytes?

For QC samples, intra-day precision and accuracy were evaluated from the results of the QC samples processed in three (3) separate batch runs. The intra-day precision (%CV) of Carbinoxamine QC samples in three (3) separate batch runs was within the range of 0.6 to 4.0% and the intra-day accuracy (Bias) was within the range of -10.8 to 5.7%. The intra-day precision (%CV) for Carbinoxamine at the ULOQ QC sample was in the range of 1.0 to 1.9% and at the LLOQ QC sample was in the range of 2.2 to 3.8%. The intra-day accuracy (%Bias) at the ULOQ was in the range of 4.9 to 14.2% and at the LLOQ was in the range of -2.1 to 4.6%.

The inter-day precision of the Carbinoxamine QC samples was within the range of 2.8 to 5.3% and the inter-day accuracy (Bias) was within the range of -6.2 to 2.4%. These results indicated that the intra-day and inter-day precision and accuracy were satisfactory. The inter-day precision for Carbinoxamine at the ULOQ QC sample was 4.1% and at the LLOQ QC sample was 4.2%. The inter-day accuracies at the ULOQ and LLOQ were 8.4% and 1.8%, respectively.

3. DETAILED LABELING RECOMMENDATIONS

(Reviewer suggested changes: ~~Strikeout text~~ should be removed from labeling and underlined text should be added to labeling)

7 Drug Interactions

Monoamine oxidase inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.

Carbinoxamine maleate has additive effects with alcohol and other CNS depressants (hypnotics sedatives, tranquilizers, etc.).

12 Clinical Pharmacology

12.1 Mechanism of Action

Carbinoxamine maleate is an antihistamine with anticholinergic (drying) and sedative properties.

Antihistamines appear to compete with histamine for receptor sites on effector cells.



12.3 Pharmacokinetics



The pharmacokinetic properties of carbinoxamine administered as an extended-release oral suspension have been evaluated in healthy adult volunteers.

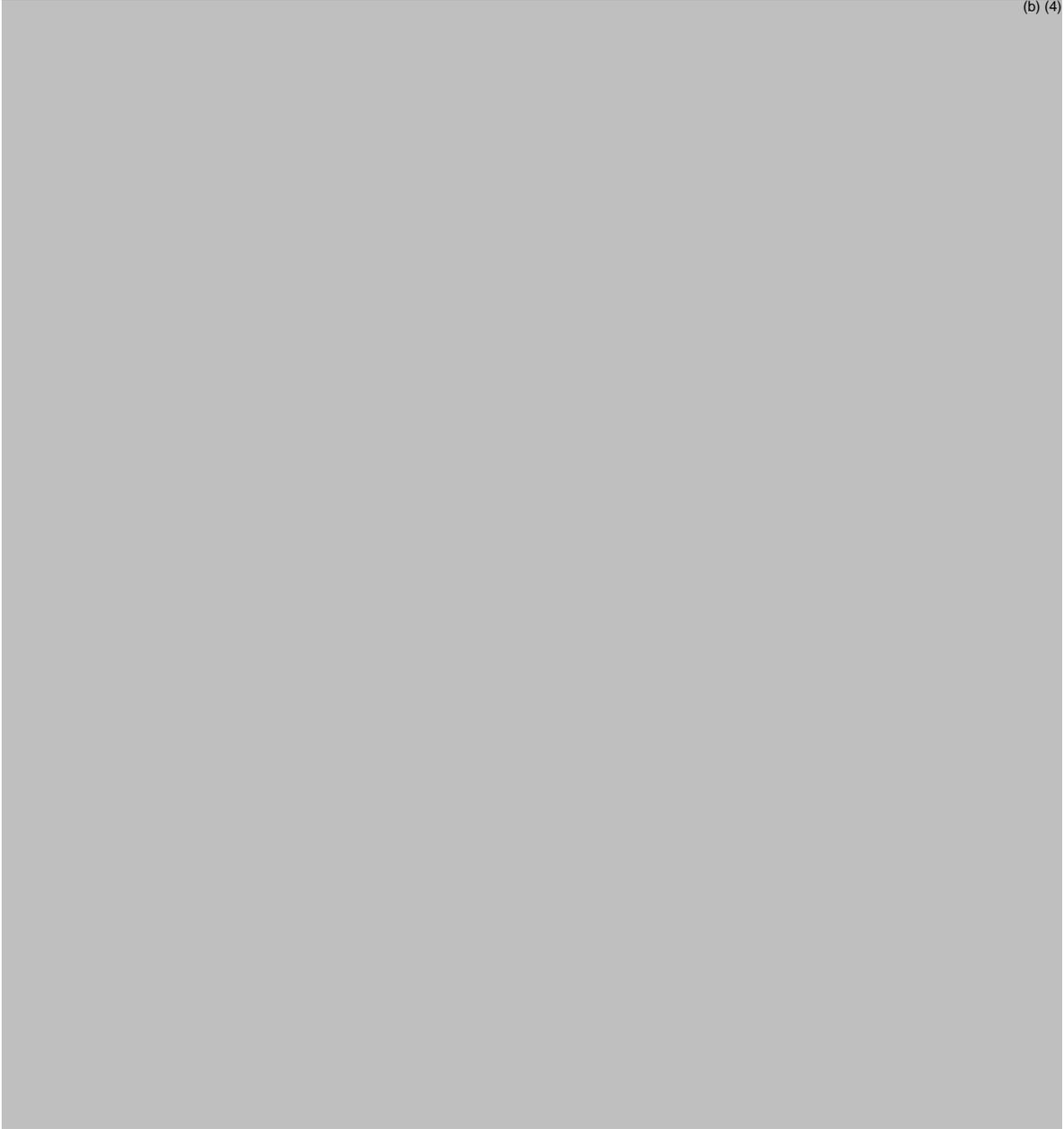
In a single dose crossover study in healthy volunteers, equivalent values for carbinoxamine AUC and C_{max} (total daily exposure) were observed for the extended-release and immediate-release formulations. Following single dosing with 20 mL (16 mg) Carbinoxamine ER Oral Suspension, eq. to 4 mg carbinoxamine maleate per 5 mL under fasting conditions, carbinoxamine mean (S.D.) peak plasma concentrations of 28.7^{(b) (4)} (5.3) ng/mL occurred at 6.67 hours. There was no effect of food on the pharmacokinetic parameters.

Following multiple dosing with Carbinoxamine ER Oral Suspension, pharmacokinetic parameters were assessed on Day 9. Carbinoxamine mean (S.D.) peak plasma concentrations at steady-state was 72.9^{(b) (4)} (24.4) ng/mL, and occurred at 5.6 hours. Carbinoxamine mean (S.D.) minimum plasma concentrations at steady-state was 51.8^{(b) (4)} (20.3) ng/mL. The plasma half-life of carbinoxamine is 17.04 hours.

4. APPENDIXES

4.1. Proposed Package Insert (Original and Annotated)

(b) (4)



4 Pages of draft labeling withheld in full as b(4) following this page.

4.2. Individual Study Review

M1FT08001

Study Title: A Study to Determine the Relative Bioavailability of Carbinoxamine Polistirex 4 mg/5 mL ER Oral Suspension versus Carbinoxamine Maleate 4 mg/5 mL Oral Solution Under Fasted Conditions, and to Determine the Effect of Food on Carbinoxamine Polistirex 4 mg/5 mL ER Oral Suspension

Objectives: This study assessed the relative bioavailability of 4 mg/5 mL ER Carbinoxamine Polistirex Oral Suspension by Tris Pharma, Inc., following a 20 mL single oral dose at Hour 0, compared to that of 4 mg/5 mL Carbinoxamine Maleate Oral Solution by MIKART Inc, following a 10 mL single oral dose at Hour 0 and Hour 6, in healthy adult subjects when administered under fasted conditions. This study also assessed the effect of food on the bioavailability of Carbinoxamine Polistirex 4 mg/5 mL ER oral suspension (Tris Pharma, Inc.) by comparing the pharmacokinetic parameters in healthy subjects under fasted and fed conditions.

Study Design: This is an open label, single-dose, randomized, three-period, three-treatment crossover study, with a 14-day washout between periods. The subjects were randomized to receive each of the following three drug treatments:

- Treatment A: Carbinoxamine ER Oral Suspension (4mg/5 mL) given as a single oral dose of 20 mL (16 mg) at Hour 0 with 8 fl. oz. of room temperature water 30 minutes after initiation of a standardized high fat – high calorie meal preceded by an overnight fast of at least 10 hours.
- Treatment B: Carbinoxamine ER Oral Suspension (4mg/5 mL) given as a single oral dose of 20 mL (16 mg) at Hour 0 with 8 fl. oz. of room temperature water after an overnight fast of at least 10 hours
- Treatment C: Carbinoxamine Maleate Oral Solution (4mg/5 mL) given as an oral dose of 10 mL (8mg) at Hour 0 and at Hour 6 with 8 fl. oz. of room temperature water after an overnight fast of at least 10 hours.

Blood samples (1 x 6 mL) for plasma Carbinoxamine analysis were collected at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 16, 24, 36, 48 and 72 hours post-dose. The Hour 6 sample was taken pre-dose for Treatment C.

Study Population: A total of 42 subjects were enrolled in the study, and 38 subjects completed the study in its entirety.

Data Analysis: The following pharmacokinetic parameters were calculated for Carbinoxamine plasma concentrations: AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , K_{el} , and $T_{1/2}$. Analyses of variance (ANOVA) were performed on ln-transformed AUC_{0-t} , AUC_{0-inf} and C_{max} . The ANOVA model included sequence, treatment and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. As food may have had an impact on the bioavailability of the test formulation, the ANOVA was conducted separately for the fasting analysis and for the food effect analysis. This prevented the potentially different mean estimates from the food effect from increasing the variability, which would have impacted the results of the fasting analysis comparing Treatments B and C. Thus, Treatments A versus B and Treatments B versus C were analyzed in two separate two-way analyses.

For Carbinoxamine ER Oral Suspension (Treatment B) and Carbinoxamine Maleate immediate-release formulation (Treatment C) to meet bioequivalence criteria defined by the FDA, or to conclude that food has no impact on the bioavailability of Carbinoxamine ER Oral Suspension (i.e. Treatment A versus Treatment B), the ratios of geometric LSMs and their 90% confidence intervals were to be within 80.00 to 125.00% for AUC_{0-t} , AUC_{0-inf} and C_{max} .

Pharmacokinetic Results:

Figure 1 Plasma Concentration vs Time Profile for M1FT08001, Treatment B (Test) vs Treatment C (Reference)

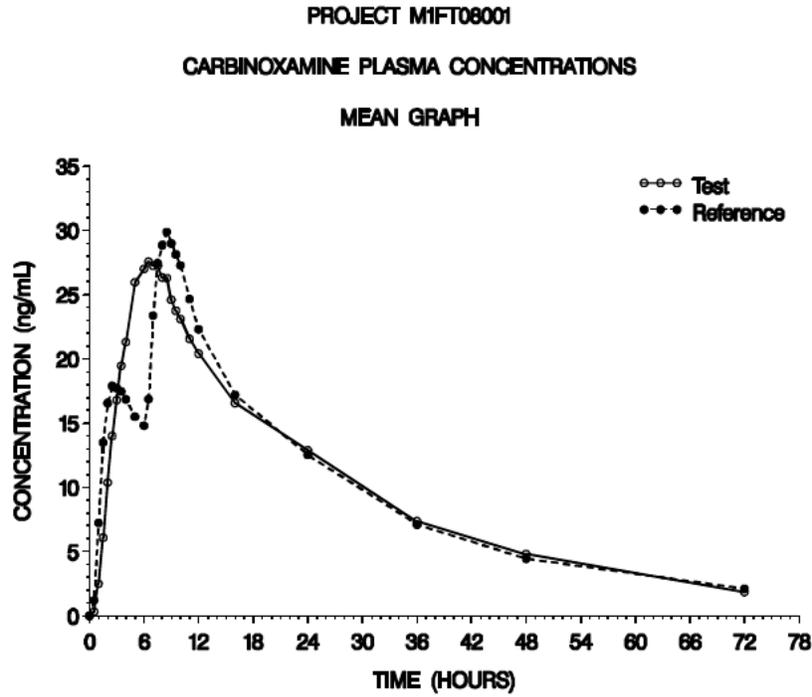


Table 1: Summary of ANOVA results for M1FT08001, Treatment B (Test) vs Treatment C (Reference)

Parameter	Geometric Least Squares Means			90% Confidence Interval
	Treatment B	Treatment C	%Ratio	
AUC _{0-t} (ng·h/mL)	704.2972	698.7477	100.8	97.80 – 103.79
AUC _{0-inf} (ng·h/mL)	753.3516	748.0097	100.7	97.20 – 104.22
C _{max} (ng/mL)	28.6687	30.7841	93.1	89.73 – 96.52
T _{max} (h)	6.67	8.55	78.0	74.35 – 81.70
Kel (h ⁻¹)	0.0419	0.0424	98.9	95.24 – 102.60
t _{1/2} (h)	17.04	16.83	101.3	97.50 – 105.40

Figure 2: Plasma Concentration vs Time Profile for M1FT08001, Treatment A (Fed) vs Treatment B (Fasting)

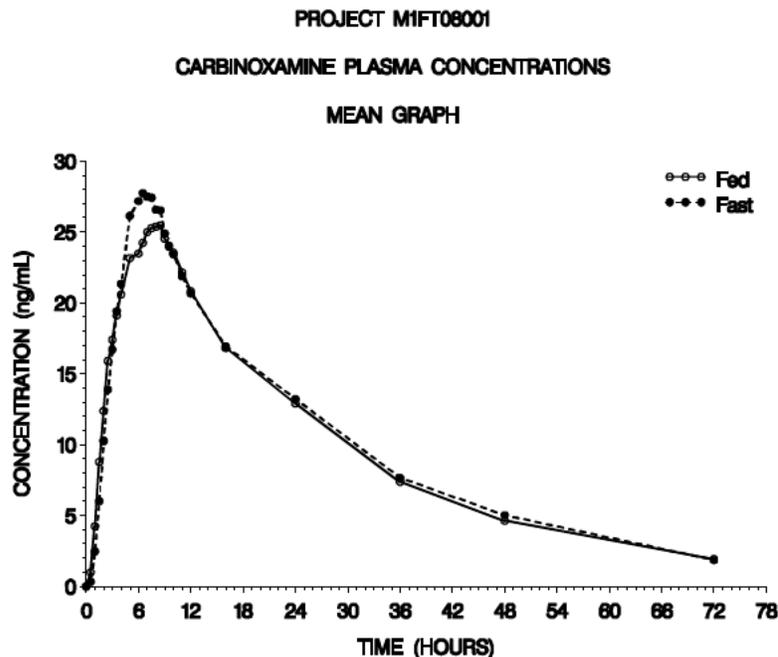


Table 2: Summary of ANOVA Results for M1FT08001, Treatment A (Fed) vs Treatment B (Fasting)

Parameter	Geometric Least Squares Means			90% Confidence Interval
	Treatment A	Treatment B	%Ratio	
AUC _{0-t} (ng·h/mL)	699.3871	719.3494	97.2	94.16 – 100.29
AUC _{0-inf} (ng·h/mL)	752.0027	769.0579	97.8	94.74 – 100.82
C _{max} (ng/mL)	27.2067	28.9597	93.9	90.83 – 97.07
T _{max} (h)	7.18	6.69	107.3	99.42 – 115.22
Kel (h ⁻¹)	0.0408	0.0425	95.9	90.05 – 101.81
t _{1/2} (h)	17.50	16.92	103.4	96.96 – 109.94

Conclusions: Carbinoxamine ER Oral Suspension met the bioequivalence criteria when compared to Carbinoxamine Maleate Oral Solution. In addition, food did not have a significant effect on the bioavailability of Carbinoxamine ER Oral Suspension and therefore it may be administered without regards to meals.

M1FT08002

Study Title: A Steady-State, Multi-Dose Study of Carbinoxamine Polistirex 4 mg / 5 mL ER Oral Suspension Versus Carbinoxamine Maleate 4 mg / 5 mL Oral Solution

Objectives: This was a steady state, multiple dose study that assessed the relative bioavailability of 4 mg / 5 mL Carbinoxamine Polistirex ER oral suspension by Tris Pharma, Inc., as one single dose 20 mL (16 mg) given with 8 fl. oz of room temperature

water at Hours 0 and 12 on Days 1, 2, 3, 4, 5, 6, 7, 8, and at Hour 0 only on Day 9, compared to that of Carbinoxamine Maleate by MIKART, Inc., as one single dose 10 mL (8 mg) given with 8 fl. oz of room temperature water at Hours 0, 6, 12, and 18 on Days 1, 2, 3, 4, 5, 6, 7, 8, and Hours 0 and 6 only on Day 9, in healthy adult subjects when administered under fasted conditions.

Study Design: The study was an open label, randomized, steady-state, two-way crossover study with a 14 day washout between periods. The subjects were randomized to receive the following two drug treatments:

Treatment A: Carbinoxamine ER Oral Suspension (4mg/5 mL) ER oral suspension given as a single oral dose of 20 mL (16 mg) with 8 fl. oz. of room temperature water at Hours 0 and 12 on Days 1, 2, 3, 4, 5, 6, 7, and 8, and Hour 0 only on Day 9.

Treatment B: Carbinoxamine Maleate Oral Solution (4mg/5 mL), given as a single oral dose of 10 mL (8 mg) with 8 fl. oz. of room temperature water at Hours 0, 6, 12, and 18 on Days 1, 2, 3, 4, 5, 6, 7, and 8, and Hours 0 and 6 on Day 9.

Blood samples (1 x 6 mL) for plasma Carbinoxamine analysis were collected at Hour 0 (pre-dose) on Days 1, 6, 7, 8 and 9, and at Hours 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, and 12 on Day 9. The Hour 6 sample was taken pre-dose for Treatment B.

Study Population: A total of 42 subjects were enrolled in the study, and 41 subjects completed the study.

Data Analysis: The following pharmacokinetic parameters were calculated for Carbinoxamine plasma concentrations: $AUC_{\tau (ss)}$, $C_{max (ss)}$, $C_{avg (ss)}$, $C_{min (ss)}$, $T_{max (ss)}$, flux and swing. Analyses of variance (ANOVA) were performed on the ln-transformed pharmacokinetic parameters $AUC_{\tau (ss)}$ and $C_{max (ss)}$. The ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. A 10% level of significance was used to test the sequence effect.

A steady state analysis was performed on the log-transformed pre-dose $C_{min (ss)}$ concentrations (i.e. Hour 0 pre-dose concentrations of Days 6, 7, 8 and 9) using Helmert's Contrasts.

Pharmacokinetic Results:

Figure 3: Plasma Concentration vs Time Profile for M1FT08002 (Day 9)

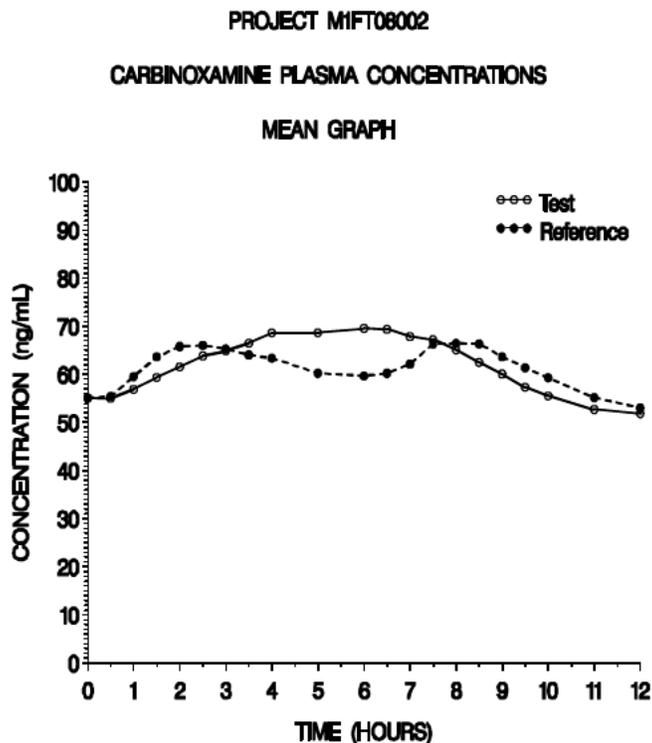


Table 3: Summary of ANOVA Analysis for M1FT08002

Parameter	Geometric Least Squares Means			90% Confidence Interval
	Test	Reference	% ratio	
$C_{max(ss)}$ (ng/mL)	73.0473	69.6773	104.80	102.50 – 107.18
$AUC_{\tau(ss)}$ (ng-h/mL)	746.2903	737.7528	101.20	99.31 – 103.01
$C_{min(ss)}$ (ng/mL)	51.9384	53.1582	97.79	94.82 – 100.59
$C_{avg(ss)}$ (ng/mL)	62.1909	61.4794	101.20	99.31 – 103.01
$T_{max(ss)}$ (h)	5.58	5.92	94.30	82.94 – 105.58
Flux (%)	35.43	27.74	127.20	119.53 – 135.93
Swing (%)	43.60	32.79	132.90	123.11 – 142.79

For Carbinoxamine ER Oral Suspension and Carbinoxamine Maleate Oral Solution to meet bioequivalence criteria defined by the FDA under steady state conditions, the ratios of geometric LSMs and their 90% confidence intervals were to be within 80.00 to 125.00% for $AUC_{\tau(ss)}$ and $C_{max(ss)}$. The ratio of $C_{min(ss)}$ was also to be within the limits of 80.00 to 125.00%. The comparison of the Test and Reference treatments demonstrated that the Test formulation satisfied the requirements for bioequivalence with the Reference formulation.

Conclusions: Carbinoxamine ER Oral Suspension met bioequivalence criteria when compared to Carbinoxamine Maleate immediate-release formulation under fasted conditions at steady state. Furthermore, the ratio and 90% confidence interval of $C_{\min(ss)}$ was also within the range of 80.00 to 125.00%.

4.3. Clinical Pharmacology and Biopharmaceutics filing form/checklist for
NDA 22-450

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	022556	Brand Name	TBD
OCP Division (I, II, III, IV, V)	II	Generic Name	(b) (4) 4 MG/5 ML ER ORAL SUSPENSION
Medical Division	DPARP	Drug Class	Allergy
OCP Reviewer	Ping Ji	Indication(s)	Seasonal and perennial allergic rhinitis Vasomotor rhinitis Allergic conjunctivitis due to inhalant allergens and foods Mild, uncomplicated allergic skin manifestations of urticaria and angioedema Dermatographism As therapy for anaphylactic reactions <i>adjunctive</i> to epinephrine and other standard measures after the acute manifestations have been controlled Amelioration of the severity of allergic reactions to blood or plasma
OCP Team Leader	Suresh Doddapaneni	Dosage Form	ER Oral suspension

Pharmacometrics Reviewer		Dosing Regimen	Usual Adult Dosage: (b) (4) (6 to 16 mg) every 12 hours Usual Child's Dosage (approximately 0.2 to 0.4 mg/kg/day): Two to three years – (b) (4) (3) to 4 mg) every 12 hours (b) (4) (3 to 8 mg) every 12 hours (b) (4) (6 to 12 mg) every 12 hours	
Date of Submission	Dec 9, 2010	Route of Administration	Oral	
Estimated Due Date of OCP Review	Aug 31, 2011	Sponsor	Tris Pharma	
Medical Division Due Date	Sep 10, 2011	Priority Classification	S	
PDUFA Due Date	Oct 8, 2011			
Clin. Pharm. and Biopharm. Information				
	"X" included if filing at	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	x			
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	2		
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	1		
replicate design; single / multi dose:				
Food-drug interaction studies	x	1		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	x	1		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x	1		
Literature References				
Total Number of Studies		6		

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			x	

	effective?				
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? y_____

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.

no

Ping Ji, PhD
 Reviewing Clinical Pharmacologist Date:

Suresh Doddapaneni, PhD
 Team Lead Date:

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/s/

Ping Ji
09/02/2011

SURESH DODDAPANENI
09/02/2011

BIOPHARMACEUTICS REVIEW
Office of New Drugs Quality Assessment

Application No.:	NDA 22-556	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DPAADP		
Sponsor:	Tris Pharma	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	--	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Carbinoxamime ER Oral Suspension	Date Assigned:	Jan 21, 2011
Indication:	Allergic rhinitis	Date of Review:	Feb 07, 2011
Formulation/strengths	Extended Release suspension, 4 mg/5 mL		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Dec 9, 2010	Dec 9, 2010	Jan 21, 2011	Oct 11

Type of Submission:	Original NDA
Type of Consult:	FILING REVIEW Dissolution method and specifications/in vitro alcohol dose-dumping study

REVIEW SUMMARY:

The sponsor has developed Carbinoxamine ER Oral Suspension as a 12-hour extended release formulation indicated for treatment of allergic rhinitis. Carbinoxamine Maleate Oral Solution (4mg/5mL), manufactured by Mikart Inc., (Brand Name-Palgic) is being used as the Reference Product for the development and for bioavailability studies. According to the sponsor, the ER properties of this product is controlled by the diffusion of drug through the controlled release polymer (Sodium polystyrene sulfonate).

The clinical development program for (b) (4) ER Oral Suspension included the following relative bioavailability studies:

- A single dose study that compared the Test and Reference Products under fasting conditions
- A single dose food-effect study on the Test Product
- A multiple dose study comparing the Test and Reference Products at steady state under fasting conditions

These studies will be reviewed by the Clinical Pharmacology team. The Biopharmaceutics review will focus on the acceptability of the dissolution method, specifications and on the in vitro alcohol dose-dumping study.

The following dissolution method and specifications are proposed for carbinoxamine ER suspension:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Carbinoxamine	ER Suspension	USP Paddle	50	900 mL 0.4 M KH ₂ PO ₄	1 hr: (b) (4) 3 hrs: (b) (4) 6hrs: (b) (4) 12 hrs: (b) (4)

It is noted that the information provided on the in vitro alcohol interaction study for carbinoxamine ER suspension used only the proposed QC method an up to 30 % alcohol. According to the sponsor, 40% alcohol showed drug precipitation. In order to rule out a possible dose-dumping (DD) effect in the presence of alcohol in the acidic environment of the stomach, we recommend that the sponsor conduct an additional drug-alcohol interaction study in 0.1 N HCl.

The NDA is filable from biopharmaceutics perspective. The acceptability of in vitro alcohol interaction study, and dissolution method and specifications will be a review issue.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 22-556 (000) for filing purposes. We found this NDA filable from the biopharmaceutics perspective. The following comments should be conveyed to the sponsor as part of the 74-day letter:

1. *Submit the complete dissolution profile data (raw data, mean values, and SD) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values) for your proposed extended release (ER) product.*
2. *Submit the dissolution method report including the complete dissolution profile (individual, mean, SD, profiles) data for your proposed ER suspension collected during the development of the proposed dissolution method.*
3. *You have provided information on the in vitro alcohol interaction study for carbinoxamine ER suspension using the proposed QC method. However, in order to rule out a possible dose-dumping (DD) effect in the presence of alcohol in the acidic environment of the stomach, we recommend that you conduct an additional drug-alcohol interaction study in 0.1 N HCl with the following alcohol concentrations; 0 %, 5 %, 10 %, 20 %, and 40 % as the dissolution media. Dissolution testing should be conducted using the same apparatus and paddle speed as the QC method. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.*

Please include the following information as part of your study report:

- *The comparison dissolution profile data to determine if the modified release characteristics are maintained, especially in the first 2 hours.*
- *The similarity f_2 values to assess the similarity (or lack thereof) in the dissolution profiles.*

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

c.c. ADorantes, ASchroeder, TCarver, Mraggio, SPatwardhan

INTRODUCTION

The sponsor has developed Carbinoxamine ER Oral Suspension as a 12-hour extended release formulation indicated for treatment of allergic rhinitis. Carbinoxamine Maleate Oral Solution (4mg/5mL), manufactured by Mikart Inc., (Brand Name-Palgic) is being used as the Reference Product for the development and for bioavailability studies. According to the sponsor, the ER properties of this product is controlled by the diffusion of drug through the controlled release polymer (Sodium polystyrene sulfonate).

The clinical development program for (b) (4) ER Oral Suspension included the following relative bioavailability studies:

- a single dose study that compared the Test and Reference Products under fasting conditions
- a single dose food-effect study on the Test Product
- a multiple dose study comparing the Test and Reference Products at steady state under fasting conditions

These studies will be reviewed by the Clinical Pharmacology team. The Biopharmaceutics review will focus on the acceptability of the dissolution method and specification and on the in vitro alcohol dose-dumping study.

Drug Product

Carbinoxamine ER Oral Suspension is a 12-hour extended release formulation. Each 5 mL (b) (4) of oral suspension contains 4 mg carbinoxamine maleate. The extended release properties of this product is controlled by the diffusion of drug through the controlled release polymer. (b) (4)

(b) (4) major manufacturing steps. (b) (4) were used to produce the final (b) (4)

(b) (4) The components and composition of the formulation are summarized in Table 1.

Table 1. Components and composition for Carbinoxamine Extended Release Oral Suspension, 4 mg per 5 mL Formulation

Ingredient	%w/v	mg/5mL	Use
Purified Water			(b) (4)
Polysorbate 80			(b) (4)
Sodium Metabisulfile			(b) (4)
Carbinoxamine Maleate			(b) (4)
(b) (4) Polistirex			(b) (4)
Purified Water			(b) (4)
Citric Acid, Anhydrous			(b) (4)
Sucrose			(b) (4)
High Fructose Corn Syrup			(b) (4)
(b) (4)			(b) (4)
Glycerin			(b) (4)

Methylparaben	(b) (4)
Propylparaben	
Xanthan Gum	
Strawberry-Banana flavor	
Purified Water	

Dissolution Method and Specifications

The following dissolution method and specification are proposed for the carbinoxamine ER Suspension:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Carbinoxamine	ER Suspension	USP Paddle	50	900 mL 0.4 M KH ₂ PO ₄	1 hr: (b) (4) 3 hrs: (b) (4) 6hrs: (b) (4) 12 hrs: (b) (4)

Figure 1 shows a typical dissolution profile for carbinoxamine ER suspension.

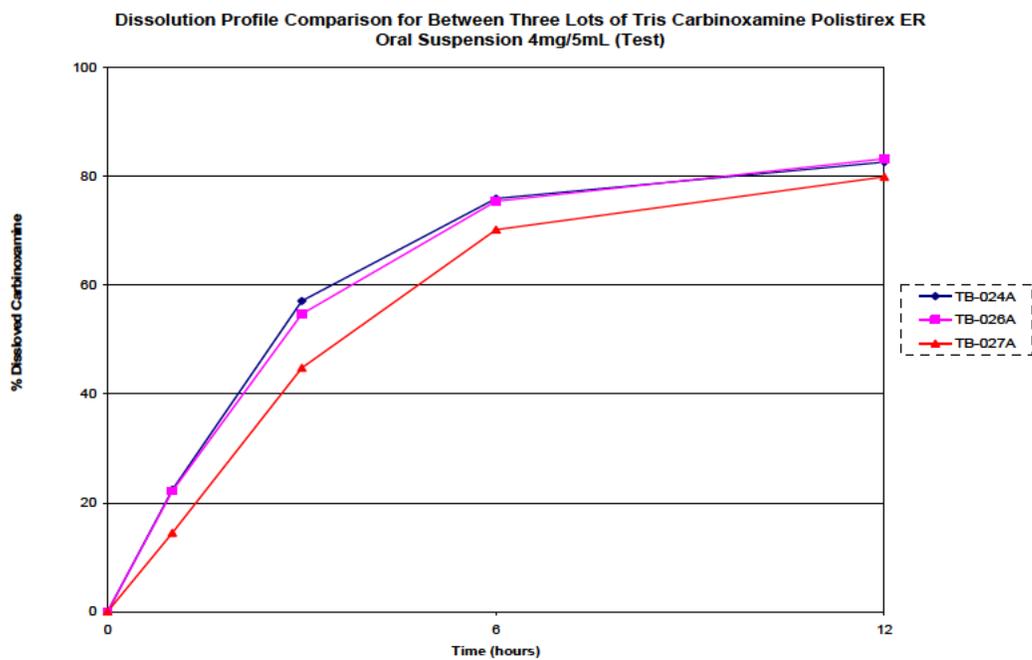


Figure 1. Dissolution profiles for batches used in the pivotal PK studies

Dissolution Method Development



(b) (4)



Alcohol Interaction Study

The influence of an alcoholic medium containing 4%, 20%, and 30% ethanol on the in vitro dissolution behavior of Carbinoxamine ER suspension was investigated. The dissolution conditions were identical to those proposed for routine quality control testing of the drug product. Figure 3 summarized the results of the study.

Figure 2. Dissolution Profile Plot Comparison of 0.4M Phosphate Buffer with Alcohol Concentrations of 0%, 4%, 20%, and 30% Alcohol of Tris' Carbinoxamine Polistirex ER Oral Suspension 4mg/5mL TB-026A (Test)

Conclusion

The NDA is filable from the biopharmaceutics perspective. The in vitro alcohol interaction study, and dissolution method and specifications will be a review issue.

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/s/

SANDRA SUAREZ
02/10/2011

PATRICK J MARROUM
02/10/2011

Clinical Pharmacology and Biopharmaceutics filing form/checklist for NDA 22556

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	022556	Brand Name	
OCP Division (I, II, III, IV, V)	II	Generic Name	(b) (4) 4 MG/5 ML ER ORAL SUSPENSION
Medical Division	DPARP	Drug Class	Allergy
OCP Reviewer	Ping Ji	Indication(s)	Seasonal and perennial allergic rhinitis Vasomotor rhinitis Allergic conjunctivitis due to inhalant allergens and foods Mild, uncomplicated allergic skin manifestations of urticaria and angioedema Dermatographism As therapy for anaphylactic reactions <i>adjunctive</i> to epinephrine and other standard measures after the acute manifestations have been controlled Amelioration of the severity of allergic reactions to blood or plasma
OCP Team Leader	Yun, Xu	Dosage Form	ER Oral suspension
Pharmacometrics Reviewer	Ping Ji	Dosing Regimen	Usual Adult Dosage: (b) (4) (6 to 16 mg) every 12 hours Usual Child's Dosage (approximately 0.2 to 0.4 mg/kg/day): Two to three years – (b) (4) (3 to 4 mg) every 12 hours (b) (4) – (b) (4) (3 to 8 mg) every 12 hours (b) (4) – (b) (4) (6 to 12 mg) every 12 hours
Date of Submission	Dec 9, 2010	Route of Administration	Oral
Estimated Due Date of OCP Review	Aug 31, 2011	Sponsor	Tris Pharma
Medical Division Due Date	Sep 10, 2011	Priority Classification	S

PDUFA Due Date	Oct 8, 2011			
Clin. Pharm. and Biopharm. Information				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	x			
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	2		
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	1		
replicate design; single / multi dose:				
Food-drug interaction studies	x	1		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	x	1		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5		

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,			x	

	as described in the WR?				
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? y_____

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.

no

Ping Ji, PhD

Reviewing Clinical Pharmacologist

Date: Jan 31, 2011

Yun Xu, PhD

Team Lead

Date: Jan 31, 2011

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

/s/

Ping Ji
01/31/2011

YUN XU
02/01/2011