CLINICAL PHARMACOLOGY REVIEW

NDA	22-556	*Submission Date*	12/08/2010 (SDN0) 10/04/2012 (SDN016)
Brand Name		Karbinal	
Generic Name		Carbinoxamine oral suspension	
Reviewer		Ping Ji, Ph.D.	
Team Leader		Suresh Doddapaneni, Ph.D.	
OCP Division		Division of Clinical Pharmacology-II	
OND Division		Division of Pulmonary, Allergy, and Rheumatology Products	
Sponsor		Tris Pharmaceuticals	
Relevant IND(s)		102,091	
Submission Type; Code		505 (b) (2)	S
Formulation; Strength(s)		4 mg carbinoxamine maleate per 5 mL suspension	
Indication		The proposed indications include: 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 *adjunctive* to epinephrine and other standard measures after the acute manifestations have been controlled Amelioration of the severity of allergic reactions to blood or plasma	
Proposed Dosing Regimen		Adult Dosage: (b) (4) (6 to 16 mg) every 12 hours 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	

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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)
$AUC_{0\text{-}inf}$ (ng·h/mL)	100.8 (97-104)	100.6 (97-104)
AUCt (ng h/mL)	100.8 (98-104)	100.6 (97-104)

Table. 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)
$AUC_{0\text{-}inf}$ (ng·h/mL)	97.9 (95-100)	98.1(95-101)
AUCt (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) 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 exlcuded. 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).

Table 1. Comparison of PK Parameters after Single Dose (M1FT08001) Parameters presented as geomean ratio% (90% CI) after Subject 27 is excluded

Parameter	With subject 5	Without subject 5
	Fasted ER/Fasted Solution	Fasted ER/Fasted Solution
Cmax (ng/mL)	93.2 (90-97)	92.3 (89-96)
$AUC_{0\text{-}inf}$ (ng·h/mL)	100.8 (97-104)	100.7 (97-104)
AUCt (ng h/mL)	100.8 (98-104)	100.5 (98-103)

Table 2. Comparison of PK Parameters after Single Dose (M1FT08001) presented as geomean ratio% (90% CI) after Subject 27 is excluded

Parameter	With subject 5	Without subject 5
	Fed ER/Fasted ER	Fed ER/Fasted ER
Cmax (ng/mL)	94 (91-97)	94.3 (91-97)
$AUC_{0\text{-}inf}$ (ng·h/mL)	97.9 (95-100)	98.0 (95-101)
AUCt (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)
$AUC_{0\text{-}inf}$ (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)
$AUC_{0\text{-}inf}$ (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)
$AUC_{0\text{-}inf}$ (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)
$AUC_{0\text{-}inf}$ (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 [redacted] 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 MIFT08001 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	nples met (b) (4) SOP (b) (4) _SOP_04_LBP_003 requirements. (at least 2/3 of	(b) (4) SOP equirements. (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 H_1 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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/s/

PING JI
03/05/2013

SURESH DODDAPANENI
03/06/2013