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RESEARCH**

APPLICATION NUMBER:

22-556Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 15, 2013
From	Suresh Doddapaneni, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-556
Applicant	Tris Pharma, Inc.
Date of Submission	October 5, 2012
PDUFA Goal Date	April 5, 2013
Proprietary Name / Established (USAN) names	Karbinal ER™/Carbinioxamine Extended Release Oral Suspension
Dosage forms / Strength	4 mg carbinioxamine maleate per 5 mL extended release oral suspension
Proposed Indication(s)	Seasonal & perennial allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, urticaria and angioedema, allergic and anaphylactic reactions
Recommended Action:	Approval

1. Introduction

This memo is for the Resubmission to a Complete Response (CR) to an action taken by the Agency on October 7, 2011 for a 505(b)(2) New Drug Application from Tris Pharma for Carbinioxamine Extended Release (ER) Oral Suspension, 4 mg of carbinioxamine maleate (CM) per 5 mL. The formulation is an extended release formulation of carbinioxamine maleate suspended in a drug-polistirex resin complex. Currently, all approved carbinioxamine products are immediate release products available as either a 4 mg tablet or a 4 mg/5 mL oral solution. As such, if approved, this will be the first extended release dosage form. All the currently available products are generic versions of the innovator products, Clistin 4 mg tablets (NDA 008915) and 4 mg/5 mL elixir (NDA 008955). The innovator, McNeil, discontinued marketing these products and the Orange Book makes the notation that the oral elixir product was not discontinued or withdrawn for safety or efficacy reasons. In the Orange Book, carbinioxamine 4 mg tablets (ANDA 040442) and 4 mg/5 mL solution (ANDA 040458), both marketed under the brand name Palgic by Mikart Inc., are listed as the Reference Listed Products. The immediate release tablet and solution products are approved in patients 2 years or age and older for the following indications:

- 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.

Approval of the proposed Carbinoxamine ER Oral Suspension is sought for all these indications, which are the same as that for the immediate release products.

Approval is sought on the basis of demonstration of bioequivalence (BE) between the proposed product and the reference immediate release Oral Solution product by Mikart in adults in lieu of clinical efficacy and safety studies. As a 505(b)(2) application, which cannot rely on a generic as the reference, the application relies on the no-longer-marketed innovator NDA product (brand name Clistin, manufactured by McNeil) while using the marketed generic immediate release RLD for bridging. This was in agreement between the Agency and Tris in the Pre-IND meeting held on May 15, 2008.

Tris conducted two BE studies to support this NDA submission. The studies were designed to show that the relative bioavailability of the test ER formulation was the same as the reference immediate release carbinoxamine product. The single dose study (M1FT08001) compared test to reference under fasted conditions and also, test to test under fed conditions. The multiple dose study (M1FT08002) compared test to reference at steady state under fasted conditions. These studies demonstrated BE of the test ER formulation to the reference immediate release carbinoxamine product. However, during the first review cycle, Office of Scientific Investigations (OSI) identified significant violations to the bioavailability and bioequivalence requirements of 21 CFR 320 in bioanalytical studies conducted by (b) (4) the center where the studies for this application were conducted. Pending resolution of these issues, a CR action was taken for this NDA since these data were pivotal for approval. Other significant deficiencies cited in the CR letter included Product Quality, Microbiology, and unsatisfactory Facility Inspections issues. The product quality deficiencies were related to non-inclusion of in-process controls for (b) (4) mixing in the manufacturing process, not including a second identity test for release of drug product, and inadequate testing of the drug product in the alternate packaging. The Microbiology deficiencies included not having a test method to recover *Burkholderia cepacia* complex organisms in the final product and not conducting preservative effectiveness testing on three batches of drug product. Since a CR action was taken, labeling negotiations were not carried out during the first cycle. In the Resubmission, sponsor submitted information addressing all the cited deficiencies.

2. Background

Carbinoxamine maleate is a first-generation histamine H₁-receptor blocking agent (antihistamine) of the ethanolamine class. This antihistamine class also includes diphenhydramine, an OTC drug. This class exhibits antihistaminic, anticholinergic, and sedative properties. The NDAs for Clistin date to the 1950s, with the NDA for Clistin 4 mg Tablets and Clistin R-A 8 and 12 mg Tablets (NDA 8-915) approved on June 22, 1953, the NDA for Clistin Elixir 4 mg/5mL (NDA 8-955) approved on June 23, 1953, and the NDA for Clistin Expectorant (NDA 9-248) approved on February 5, 1954.

Carbinoxamine maleate is a pre-1962 drug moiety that was the subject of DESI (Drug Efficacy Study Implementation) review(s) by two panels, the Panel on Drugs Used in Allergy and the Panel on Drugs Used in Dermatology II, and the Agency then published its findings in the

Federal Register (DESI 6303, 38 FR 7265, March 19, 1973). The DESI process evaluated the effectiveness of a drug, with each indication required to be supported by adequate and well-controlled clinical trials. Nevertheless, when taking into consideration the recommendations of the Panels, it is clear that the Agency also took into consideration what was known about other antihistamines in the same or similar classes as it made its determination. This view is supported by the fact that the indications allowed by the Agency were more extensive than those reviewed by the actual DESI Panels. The reason why the panels did not review all of the indications is not known. Nevertheless, the Agency allowed the same [or a very similar] set of indications [as carbinoxamine maleate] for many other prescription antihistamines that were reviewed under the DESI process. Other antihistamines with a similar set of DESI indications include: chlorpheniramine maleate, cyproheptadine hydrochloride, promethazine hydrochloride, diphenhydramine hydrochloride, and tripeleminamine hydrochloride, among others (36 FR 11758, June 18, 1971 and 38 FR 7265, March 19, 1973).

3. CMC

The recommended action from the CMC perspective is Approval.

In the first review cycle, there were several product quality deficiencies related to non-inclusion of in-process controls for content uniformity/dispersion mixing in the manufacturing process, not including a second identity test for release of drug product, inadequate testing of the drug product in the alternate packaging, and unsatisfactory Facilities Inspections issues.

In the Resubmission, sponsor satisfactorily addressed these deficiencies. All facilities involved in the drug substance and drug product manufacturing and microbial testing are recommended as acceptable by Office of Compliance.

There are no other outstanding issues from CMC perspective.

4. Nonclinical Pharmacology/Toxicology

The application is recommended for Approval from a Nonclinical Pharmacology and Toxicology perspective.

In the Pre-IND meeting held on May 18, 2008, it was agreed that no new non-clinical Pharmacology/Toxicology data would be required other than data on any impurities that exceed ICH recommended levels. However, no impurities exceeded ICH Q3 (A) R guidelines for the drug substance and there were no specific inactive ingredient safety issue for the formulation. The recommended nonclinical changes to the sponsor's proposed labeling were to conform to the most current CFR format (Sections 8.1, 8.2, 8.3, 10.1, and 13.1) and to remove extraneous nonclinical information that does not directly relate to human risk (Section

10.1). Dr. Asoke Mukherjee's review in the first cycle contained the recommended labeling changes.

The CR did not contain any Nonclinical Pharmacology/Toxicology deficiencies and Tris did not submit any new data in the Resubmission.

There are no other outstanding nonclinical pharmacology/toxicology review issues.

5. Clinical Pharmacology

The application is recommended for Approval from Clinical Pharmacology and Biopharmaceutics perspective.

In the first review cycle, the recommendation was Complete Response. The approval of this product is dependent on successful demonstration of bioequivalence under single dose (study M1FT08001) and multiple dose (study M1FT08002) conditions of the proposed carbinnoxamine extended release oral suspension (Test) with the Reference carbinnoxamine maleate oral solution (Palgic, manufactured by Mikart) in healthy adults. Although, the data did demonstrate bioequivalence, the data were not accepted due to significant violations in the bioanalytical studies conducted by (b) (4) between the dates of (b) (4), which included the studies for this application. Pending resolution of these issues, a CR action was taken and the Complete Response Letter gave Tris the options of: reanalysis, repeat the studies, or conduct clinical studies. Subsequently, OSI provided to affected NDAs, the option of independent third-party data integrity audit if the studies were conducted between March 1, 2008 to August 31, 2009. Since both these studies were initiated and completed in this time period, Tris followed this approach and had the independent audit conducted by (b) (4). This audit report concluded that except for two samples (subject #28) in study M1FT08001, all other official accepted sample runs in study M1FT08001 and Study M1FT08002 are classified as low-risk for sample manipulation.

In addition, inspection of the clinical component of these bioavailability studies was conducted by Office of Regulatory Affairs in the time period of April 21, 2011 to May 5, 2011. Related to this, in a memo dated September 11, 2012, OSI recommended that miscarriage for Subject #5 in study M1FT08001 should be considered as an adverse event possibly related to drug product dosing or other study activities and should be evaluated whether to exclude this subject from pharmacokinetic evaluations. Reanalysis of study M1FT08001 by excluding subject #5 or both subjects #5 and #27 (shown in tables below) did not affect the conclusion of bioequivalence.

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
C _{max} (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)

There are no pending Clinical Pharmacology and Biopharmaceutics issues.

6. Microbiology

The recommended action from Microbiology is Approval.

In the first review cycle, the recommendation was Complete Response pending resolution of deficiencies related to (a) development of test method and specifications to include the absence of *Burkholderia Cepacia* complex organisms and (b) lack of preservative effectiveness testing on three batches of drug product.

In the Resubmission, Tris developed a test for absence of BCC and included absence of BCC as a release specification and conducted successful preservative effectiveness tests on three lots of drug product.

There are no pending Microbiology issues.

7. Clinical/Statistical- Efficacy

The recommended action from a clinical perspective is Approval.

Since only BA/BE studies were required in support of the application, there were no efficacy data from clinical trials to be reviewed. Instead, clinical review in the first cycle and Resubmission consisted of the assessment of available and relevant reports to determine whether all the sought indications have appropriate supportive data. Statistical review in the first cycle did not have any comments.

Carbinaxamine maleate was the subject of DESI (Drug Efficacy Study Implementation) review(s) by two panels, the Panel on Drugs Used in Allergy and the Panel on Drugs Used in Dermatology II, and the Agency then published its findings in the Federal Register (DESI 6303, 38 FR 7265, March 19, 1973). A wide range of indications were approved for carbinaxamine maleate under the DESI process. In determining these indications, the Agency also took into consideration what was known about other antihistamines in the same or similar

classes. This view is supported by the fact that the indications allowed by the Agency were more extensive than those reviewed by the actual DESI Panels, and the Agency allowed the same set of indications for many other prescription antihistamines under the DESI process.

However, clinical review of the original clinical study publications that were reviewed by the two DESI panels found no support for the current DESI indications for carbinoxamine maleate beyond allergic rhinitis and urticaria. Four published studies served as the basis of the panels' recommendations. Review revealed that only the indications of seasonal and perennial allergic rhinitis (SAR and PAR) are supported by clinical trial data that would be sufficient to meet today's standards for efficacy and safety:

Two of the 4 studies were placebo-controlled, of which 1 used a parallel and 1 used a crossover design. Combined, 3 of the 4 studies give support for the most common indication studied, namely allergic rhinitis, including both SAR and PAR. The results from these studies are considered sufficient to support the indications of SAR and PAR.

Support for the indication of the treatment of urticaria, is based on the results of three studies, 1 placebo-controlled and 2 open-label. The number of patients treated [28] is small and the results are somewhat conflicting. Therefore, the body of evidence for the treatment of urticaria would not be considered adequate by today's standards.

Review revealed that there were insufficient data to support other DESI indications for carbinoxamine maleate. For each of the other indications, either no patients were studied, or the numbers of patients included in studies were too small, or the trial design was not adequate, to make a reasonable conclusion about either the efficacy or safety of carbinoxamine maleate for treatment of that condition.

However, both the science and the regulatory environment have advanced since the DESI review process. In current clinical practice, antihistamines are not used for treatment of many of the indications approved under DESI. Practice parameters for treatment of allergic conditions published by accepted authorities, such as the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) and the Joint Council on Allergy, Asthma and Immunology, and others do not provide support for the current DESI indications for carbinoxamine maleate beyond allergic rhinitis and urticaria. First generation antihistamines may be considered for a wide range of indications, although (with the exception of allergic rhinitis, and OTC use under the OTC monograph) their use is infrequent and often as second line or adjunctive therapy, with second generation antihistamines preferred because of concerns for unwanted side effects of sedation, anti-cholinergic effects, and performance impairment with older antihistamines.

Review found no safety concerns about carbinoxamine maleate beyond those already known and labeled, and none that would support limiting the indications in adults. The side effects reported in the clinical pharmacology studies conducted for this application are consistent with the labeling in the current PI for the immediate-release product.

Although, from a scientific perspective, support for all of the proposed indications for carbinoxamine maleate in adults is not present to meet current standards, there is currently no regulatory basis to change or modify the indications for the immediate release product that were allowed under the DESI process (in spite of the identified limitations) in the absence of a safety concern. As such, this product will gain all of the indications that immediate release product has.

8. Safety

Since no new data was submitted, there is no new safety data in the Resubmission.

Safety assessments in the first cycle from the two BA/BE studies M1FT08001 and M1FT08002 showed no deaths or serious adverse events. There were no significant AE findings from the study M1FT08001. During the multiple dose-study M1FT08002, the most frequently reported AEs were constipation and headache with no significant imbalances between test and reference products. These AEs are already listed for carbinoxamine, so no additional labeling is necessary. However, borderline elevations in uric acid noted in study M1FT08002 were added to the Adverse Reactions section of the PI.

9. Advisory Committee Meeting

An Advisory Committee meeting for this product was not needed and not held.

10. Pediatrics

This application triggers PREA because of the new extended-release dosage form, a PREA trigger. [*Note:* The new dosage form also requires a new dosing regimen, also a PREA trigger.] With this submission, the applicant has sought approval for use in children 2 years of age and older, including all of the adult indications and requested waivers for pediatric studies in the following age groups:

1. Pediatric studies birth to <2 years of age, because carbinoxamine carries a Contraindication for use in children under 2 years of age.
2. Pediatric bioequivalence studies in children 2 to <18 years of age. Per guidance, the BA/BE studies were performed in healthy adults; the results of these studies would be applicable to the adolescents and children 2 to <18 years of age.

These waiver requests are appropriate. The pediatric issues for this application were discussed with the Pediatric Review Committee (PeRC) on August 31, 2011 in the first review cycle and again on February 20, 2013 in this cycle, and PeRC agreed with the waiver for children under 2 years of age and transfer of all of the indications and age groups from the immediate release product to the extended release product.

While the Agency may require pediatric studies under PREA to support all the indications considered appropriate for the pediatric age range when data are lacking to support efficacy,

safety, or dosing, since the immediate-release products are already approved for use in children 2 years of age and older and this extended-release product is bioequivalent to the immediate-release product, and lacking a specific known safety risk, this age group is supported by the Agency's previous findings of safety and efficacy for the immediate-release products.

11. Other Relevant Regulatory Issues

OSI audit

Because data from BE studies M1FT08001 and M1FT08002 form the basis for approval of this NDA, an audit of these studies by OSI was requested in the first cycle. These studies were conducted at Cetero Research-Miami, Miami Gardens, FL (clinical site) and (b) (4) (analytical site). On (b) (4), OSI issued an untitled letter to (b) (4) concluding that BA/BE data generated from (b) (4) a (b) (4) facility were unreliable for the following reasons:

Widespread falsification of dates and times in laboratory records for subject sample extractions; The apparent manipulation of equilibrium or "prep" run samples to meet pre-determined acceptance criteria; and the lack of documentation regarding "prep" runs that prevented (b) (4) from conducting an adequate internal investigation to determine the extent and impact of these violations.

As the Analytical data submitted for studies M1FT08001 and M1FT08002 were generated in the identified time interval, OSI concluded that these are unreliable and an inspection is not warranted and recommended that these data be not accepted. In the Complete Response Letter, this issue was cited as a deficiency. To resolve the deficiency, the Agency provided three approaches in the Complete Response Letter:

- 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 Tris the available options the sponsors have for bioanalytical studies conducted at (b) (4) between (b) (4) in support of marketing applications. The option that was relevant to this application was that 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 to Tris). The two studies in this application were conducted in April, 2009 and were eligible for third party audit. Tris

submitted the audit report in the Resubmission. In addition, inspection of the clinical component of these bioavailability studies was conducted by Office of Regulatory Affairs in the time period of April 21, 2011 to May 5, 2011. Related to this, in a memo dated September 11, 2012, OSI recommended that miscarriage for Subject #5 in study M1FT08001 should be considered as an adverse event possibly related to drug product dosing or other study activities and should be evaluated whether to exclude this subject from pharmacokinetic evaluations.

Financial Disclosures:

The Applicant certified that there was no financial arrangement with the clinical investigator whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant further certified no clinical investigator was a recipient of significant payments defined in 21 CFR 54.2(f).

Trade Name:

During the first review cycle, Tris's request for the trade name Karbinal ER was found to be acceptable by Division of Medication Error Prevention and Analysis (DMEPA) and Tris was notified of this decision on November 16, 2011. Previous tradename proposals of (b) (4) were not acceptable. Upon submission of the Complete Response, DMEPA re-reviewed Karbinal ER and found it acceptable and Tris was notified of the same on January 3, 2013.

12. Labeling

Labeling negotiations have been completed with the sponsor and except for some minor editorial changes that are pending, agreement was reached on the final labeling content.

Labeling consults were obtained from the Office of Surveillance and Epidemiology and the Office of Prescription Drug Promotion.

The following is a highlight of some significant labeling issues pertaining to this product;

- Since this will be the first PLR labeling for a carbinoxamine product, it will be different from the currently approved immediate release products in this respect.
- The Contraindication for children under 2 years of age is maintained. Additionally, since the extent of infant exposure while breast-feeding is unknown, the product was Contraindicated for use in breast-feeding women.
- Since the Warnings section lists warnings hierarchically by importance, the warning with regard to activities requiring mental alertness was elevated to the top of the list, as this is a key warning for use of this drug.
- For accuracy of dosing, the following statement is added to the Dosage and Administration section "Advise patients to measure with an accurate milliliter measuring device. A household teaspoon is not an accurate measuring device and could lead to overdose. A pharmacist can recommend an appropriate measuring device and can provide instructions for measuring the correct dose."

- To reflect the new ONDQA policy that strength and established should match, strength is expressed as “Extended-Release Oral Suspension: 4 mg * per 5 mL (b) (4) (b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is Approval.

- Risk Benefit Assessment

The overall risk-benefit assessment for carbinoxamine maleate extended release suspension based on establishing bioequivalence to the reference immediate release product does not suggest an unfavorable risk benefit in patients 2 years and above.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

14. Recommended Comments to the Sponsor

None

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/s/

SURESH DODDAPANENI
03/18/2013

Cross-Discipline Team Leader Review

Date	August 30, 2011
From	Suresh Doddapaneni, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-556
Applicant	Tris Pharma, Inc.
Date of Submission	December 8, 2010
PDUFA Goal Date	October 8, 2011
Proprietary Name / Established (USAN) names	Under review/carbinoxamine maleate
Dosage forms / Strength	4 mg carbinoxamine maleate per 5 mL extended release oral suspension
Proposed Indication(s)	Seasonal & perennial allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, urticaria and angioedema, allergic and anaphylactic reactions
Recommended:	Complete Response

1. Introduction

This submission is a 505(b)(2) New Drug Application from Tris Pharma for Carbinoxamine Extended Release (ER) Oral Suspension, 4 mg of carbinoxamine maleate (CM) per 5 mL. The formulation is an extended release formulation of carbinoxamine maleate suspended in a drug-polystyrene resin complex. Currently, all approved carbinoxamine products are immediate release products available as either a 4 mg tablet or a 4 mg/5 mL oral solution. As such, if approved, this will be the first extended release dosage form. All the currently available products are generic versions of the innovator products, Clistin 4 mg tablets (NDA 008915) and 4 mg/5 mL elixir (NDA 008955). The innovator, McNeil, discontinued marketing these products and the Orange Book makes the notation that the oral elixir product was not discontinued or withdrawn for safety or efficacy reasons. In the Orange Book, carbinoxamine 4 mg tablets (ANDA 040442) and 4 mg/5 mL solution (ANDA 040458), both marketed under the brand name Palgic by Mikart Inc., are listed as the Reference Listed Products. The immediate release tablet and solution products are approved in patients 2 years or age and older for the following indications:

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- Mild, uncomplicated allergic skin manifestations of urticaria and angioedema
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- Amelioration of the severity of allergic reactions to blood or plasma.

Approval of the proposed Carbinoxamine ER Oral Suspension is sought for all these indications, which are the same as that for the immediate release products.

Approval is sought on the basis of demonstration of bioequivalence (BE) between the proposed product and the reference immediate release Oral Solution product by Mikart in adults in lieu of clinical efficacy and safety studies. As a 505(b)(2) application, which cannot rely on a generic, the application relies on the no-longer-marketed innovator NDA product (brand name Clistin, manufactured by McNeil) while using the marketed generic immediate release RLD for bridging. This was in agreement between the Agency and Tris in the Pre-IND meeting held on May 15, 2008. Tris was also advised to assess alcohol interaction potential through in vitro data followed by in vivo data, if warranted.

Tris conducted two bioavailability (BA)/bioequivalence (BE) studies to support this NDA submission. The studies were designed to show that the relative bioavailability of the test ER formulation was the same as the reference immediate release carbinoxamine product. The single dose study (M1FT08001) compared test to reference under fasted conditions and also, test to test under fed conditions. The multiple dose study (M1FT08002) compared test to reference at steady state under fasted conditions.

2. Background

Carbinoxamine maleate is a first-generation histamine H₁-receptor blocking agent (antihistamine) of the ethanolamine class. This antihistamine class also includes diphenhydramine, an OTC drug. This class exhibits antihistaminic, anticholinergic, and sedative properties.

Carbinoxamine maleate is a pre-1962 drug moiety that was the subject of DESI (Drug Efficacy Study Implementation) review(s) by two panels, the Panel on Drugs Used in Allergy and the Panel on Drugs Used in Dermatology II, and the Agency then published its findings in the Federal Register (DESI 6303, 38 FR 7265, March 19, 1973). The DESI process evaluated the effectiveness of a drug, with each indication required to be supported by adequate and well-controlled clinical trials. Nevertheless, when taking into consideration the recommendations of the Panels, it is clear that the Agency also took into consideration what was known about other antihistamines in the same or similar classes as it made its determination. This view is supported by the fact that the indications allowed by the Agency were more extensive than those reviewed by the actual DESI Panels. The reason why the panels did not review all of the indications is not known. Nevertheless, the Agency allowed the same [or a very similar] set of indications [as carbinoxamine maleate] for many other prescription antihistamines that were reviewed under the DESI process. Other antihistamines with a similar set of DESI indications include: chlorpheniramine maleate, cyproheptadine hydrochloride, promethazine hydrochloride, diphenhydramine hydrochloride, and tripeleminamine hydrochloride, among others (36 FR 11758, June 18, 1971 and 38 FR 7265, March 19, 1973). This indication grouping was understandable, given the prevailing medical view that indications could be based to a large extent on the pharmacologic class of a drug.

3. CMC

The recommended action from the CMC perspective is Complete Response. Several deficiencies and clarifications related to specifications, manufacturing process, control of leachables, updated stability data, control of particle size distribution (PSD) for the final drug product have to be addressed by the sponsor. All drug substance and drug product manufacturing and testing sites will need to have acceptable compliance status prior to approval.

- General product quality considerations

Manufacture and control of the drug substance, Carbinoxamine maleate, is referenced to DMF (b) (4) and was deemed to be adequate in support of the drug product. The drug product is a 12 hour extended release formulation containing 4 mg/5 mL carbinoxamine maleate. It is supplied as light beige to tan viscous suspension with strawberry banana flavor in bottles of fl oz (b) (4). It contains the following inactive ingredients; citric acid anhydrous, flavor, glycerin, high fructose corn syrup, methylparaben, modified food starch, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sulfonate, sucrose, triacetin, and xanthan gum. Formulation uses the (b) (4)

(b) (4) rug product is controlled by testing for Description, Color, Identification (HPLC and UV), pH, Deliverable Volume, Microbial Limits, Preservative Assay, Dissolution, Impurities, and (b) (4). The drug product is packaged in (b) (4) bottles and to be stored under recommended conditions of 25° C with excursions permitted from 15° to 30° C and an expiry of 24 months. Agreement was reached between the Agency and Tris regarding the dissolution method and associated acceptance criteria. ONDQA Biopharmaceutics review assessment of in vitro alcohol dose dumping data identified a potential for dose dumping in light of the increased release in quality control medium containing alcohol. The need for a follow up in vivo study was assessed by Clinical Pharmacology.

Overall, CMC evaluation identified the following deficiencies: No statement regarding overages in the drug product was included in this submission; No justification for a lack of in-process controls for (b) (4) during mixing of (b) (4) was given; In addition to HPLC identity test, a second test for identity is needed; With respect to the alternate container (b) (4) test Batch TB-085A at the 24 month time point results for (b) (4) and for the common impurities of (b) (4) have to be reported to the Agency; The stability commitment needs to be revised to state that the stability results will be submitted to NDA annual reports.

These deficiencies by themselves would have been otherwise been acceptable as post approval commitments or agreements from ONDQA perspective. However, since the application is not being approved sponsor should address these deficiencies in the Complete Response.

- Facilities review/inspection

The drug substance is manufactured, tested, and released, under DMF (b) (4), by (b) (4) (b) (4). The facility has not been given a satisfactory recommendation by Office of Compliance (OC). The manufacturer, testing, packager, and releaser of the drug product is: Tris Pharma, Inc, Monmouth Junction, NJ. OC recommended this site as withhold. In addition, (b) (4) performs microbial testing for the drug product. This facility has not been given a satisfactory recommendation by OC. A final recommendation for the NDA is still pending.

4. Nonclinical Pharmacology/Toxicology

The application is recommended for Approval from a Nonclinical Pharmacology and Toxicology perspective.

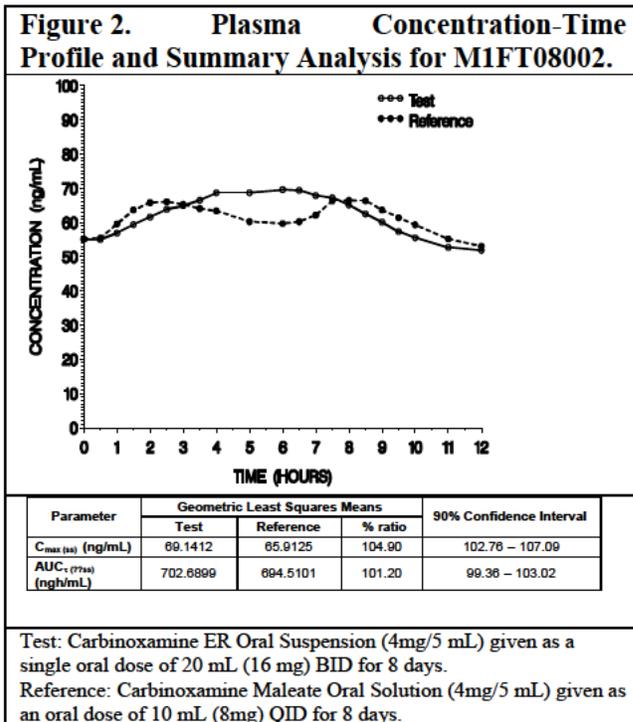
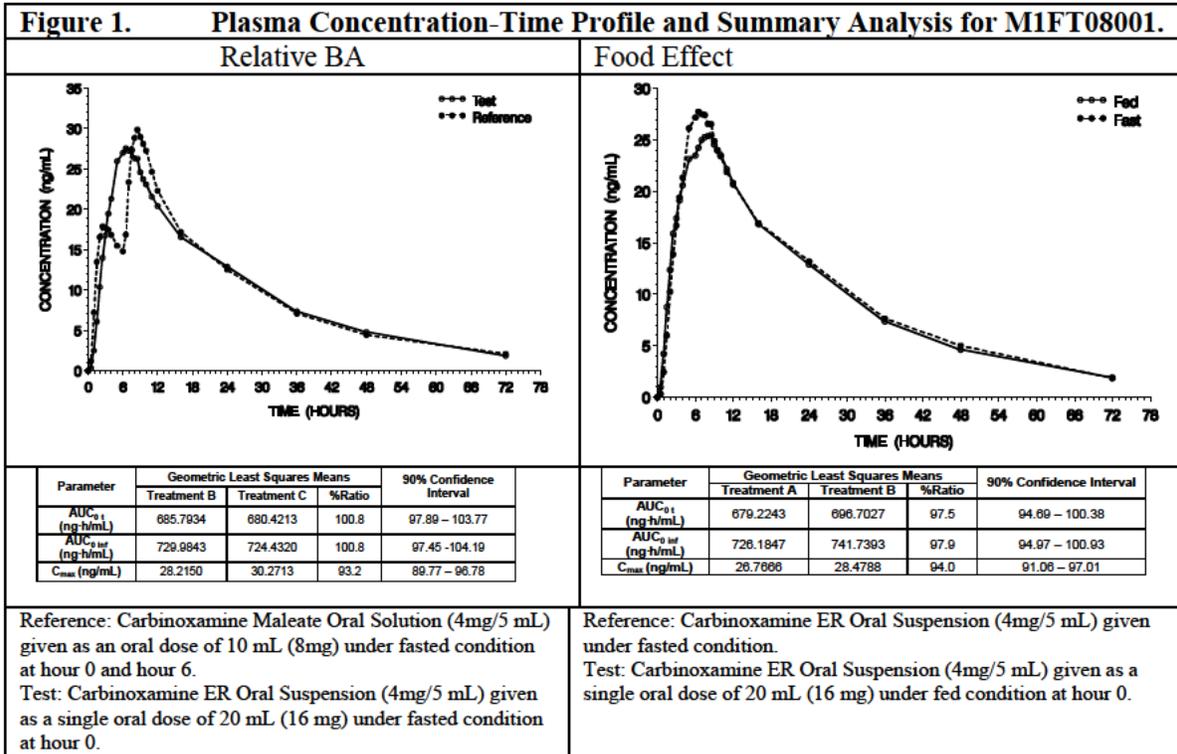
In the Pre-IND meeting held on May 18, 2008, it was agreed that no new non-clinical Pharmacology/Toxicology data would be required other than data on any impurities that exceed ICH recommended levels. However, no impurities exceeded ICH Q3 (A) R guidelines for the drug substance and there were no specific inactive ingredient safety issue for the formulation. The recommended nonclinical changes to the sponsor's proposed labeling were to conform to the most current CFR format (Sections 8.1, 8.2, 8.3, 10.1, and 13.1) and to remove extraneous nonclinical information that does not directly relate to human risk (Section 10.1).

There are no other outstanding nonclinical pharmacology/toxicology review issues.

5. Clinical Pharmacology

The application is recommended for Complete Response from Clinical Pharmacology and Biopharmaceutics perspective.

This application is supported with data from two relative bioavailability studies in healthy subjects: a single dose study that compared the Test and Reference Products under fasted conditions and assessed 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.



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.

Per the recommendation of Office of Scientific Investigations (OSI)/Division of Bioequivalence and GLP Compliance (DBGC) related to data integrity issues, current data from studies M1FT08001 and M1FT08002 are not acceptable for decision making. Before the application can be approved, Tris should correct this deficiency by doing the following: (a) re-assay of samples if available and supported by stability data and (b) or repeat the study(s).

6. Microbiology

The recommended action from Microbiology is Complete Response pending resolution of deficiencies related to (a) development of test method and specifications to include the absence of Burkholderia Cepacia complex organisms and (b) preservative effectiveness testing on three batches of drug product.

This is a non-sterile drug product with a complex manufacturing process. The microbiological quality of the precursors is adequately controlled. Product contains [REDACTED] (b) (4) [REDACTED] as preservatives. Product has a pH of [REDACTED] (u) (s) which will likely contribute to the anti-microbial nature of the drug product. Preservative effectiveness studies were conducted on a single batch (lot RD0132-157) and the results met the compendial requirements of NLT (b) (4) log reduction in bacteria from the initial count at 14 days and no increase from 14-28 days. There was no increase in yeast and molds from the initial count at 14 or 28 days. However, these data are required from three batches of drug product. Sponsor was informed in an information request dated 07/15/2011 to provide test methods and acceptance criteria to demonstrate the drug product is free of the Burkholderia Cepacia complex of organisms. Sponsor is developing a test method and the proposed development plan is reasonable. These deficiencies by themselves would have been otherwise been acceptable as post approval commitments or agreements. However, since the product is not being approved, these should be submitted in the Complete Response.

7. Clinical/Statistical- Efficacy

Since only BA/BE studies were required in support of the application, there were no efficacy data from clinical trials to be reviewed. Instead, clinical review consisted of the assessment of available and relevant reports to determine whether all the sought indications have appropriate supportive data. Statistical review did not have any comments. The recommended action from a clinical perspective is Complete Response since the submitted BA/BE data are not acceptable to support the application.

Carbinoxamine maleate was the subject of DESI (Drug Efficacy Study Implementation) review(s) by two panels, the Panel on Drugs Used in Allergy and the Panel on Drugs Used in Dermatology II, and the Agency then published its findings in the Federal Register (DESI 6303, 38 FR 7265, March 19, 1973). A wide range of indications were approved for carbinoxamine maleate under the DESI process. In determining these indications, the Agency also took into consideration what was known about other antihistamines in the same or similar classes. This view is supported by the fact that the indications allowed by the Agency were

more extensive than those reviewed by the actual DESI Panels, and the Agency allowed the same set of indications for many other prescription antihistamines under the DESI process.

However, clinical review of the original clinical study publications that were reviewed by the two DESI panels found no support for the current DESI indications for carbinoxamine maleate beyond allergic rhinitis and urticaria. Four published studies served as the basis of the panels' recommendations. Review revealed that only the indications of seasonal and perennial allergic rhinitis (SAR and PAR) are supported by clinical trial data that would be sufficient to meet today's standards for efficacy and safety:

Two of the 4 studies were placebo-controlled, of which 1 used a parallel (Beale) and 1 used a crossover (MacLaren) design. Combined, 3 of the 4 studies give support for the most common indication studied, namely allergic rhinitis, including both SAR and PAR. The results from these studies are considered sufficient to support the indications of SAR and PAR.

Support for the indication of the treatment of urticaria, is based on the results of three studies, 1 placebo-controlled and 2 open-label. The number of patients treated [28] is small and the results are somewhat conflicting. Therefore, the body of evidence for the treatment of urticaria would not be considered adequate by today's standards.

Review revealed that there were insufficient data to support other DESI indications for carbinoxamine maleate. For each of the other indications, either no patients were studied, or the numbers of patients included in studies were too small, or the trial design was not adequate, to make a reasonable conclusion about either the efficacy or safety of carbinoxamine maleate for treatment of that condition.

Summary of the study design of CM studies reviewed under DESI

Study	Design	Indications studied	N	Assessments*	Comments
Beale	Placebo-controlled, parallel group	AR, urticaria, asthma, AR and asthma, allergic conjunctivitis	126 113 11 1 26 1	S	Randomization and blinding methodology unstated.
Garat	Open label	PAR, PAR with asthma, asthma, pruritus or urticaria, allergic conjunctivitis, SAR	94 68 12 3 9 1 1	C	Open label study. Provides open-label safety information in patients with PAR.
Johnson	Open label	Acute rhinitis, (common cold) SAR or PAR, asthma, urticaria, poison ivy, pruritus, bronchitis, or	116 77 23 2 8 3	C	Open label study. Most patients had acute rhinitis (common cold). Provides open-label safety information in a limited number of patients with SAR, PAR, and urticaria.

Study	Design	Indications studied	N	Assessments*	Comments
		periorbital edema.	3		
MacLaren	Placebo- and active-controlled, 4-way crossover	AR, AR and asthma, AR and eczema	70 41 26 3	S	Randomization and blinding methodology unstated. Crossover design with no washout.
*Assessments: S=Assessments made by <u>S</u> ubject, C= Assessments made by <u>C</u> aregiver					

However, both the science and the regulatory environment have advanced since the DESI review process. In current clinical practice, antihistamines are not used for treatment of many of the indications approved under DESI. Practice parameters for treatment of allergic conditions published by accepted authorities, such as the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) and the Joint Council on Allergy, Asthma and Immunology, and others do not provide support for the current DESI indications for carbinoxamine maleate beyond allergic rhinitis and urticaria. First generation antihistamines may be considered for a wide range of indications, although (with the exception of allergic rhinitis, and OTC use under the OTC monograph) their use is infrequent and often as second line or adjunctive therapy, with second generation antihistamines preferred because of concerns for unwanted side effects of sedation, anti-cholinergic effects, and performance impairment with older antihistamines. As a result antihistamines are mainly used in current practice to treat the symptoms of allergic rhinitis and chronic idiopathic urticaria, and approval of newer antihistamines (e.g fexofenadine, loratadine, cetirizine) has been limited to these indications based on clinical trials to support each indication.

Although from a scientific perspective support for all of the proposed indications for carbinoxamine maleate in adults is not present, there is currently no regulatory mechanism to limit DESI indications other than rule making. Therefore, if approved, the Agency cannot remove the already-approved DESI indications for this product in adults as there are no overriding safety concerns about this product in adults that would support limiting the indications. As such, even though available information does not support all the sought indications (other than treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR)), this applicant cannot be required to conduct clinical trials to support these additional indications.

8. Safety

Safety assessments from the two BA/BE studies M1FT08001 and M1FT08002 showed no deaths or serious adverse events. There were no significant AE findings from the study M1FT08001. During the multiple dose-study M1FT08002, the most frequently reported AEs were constipation and headache with no significant imbalances between test and reference products. These AEs are already listed for carbinoxamine, so no additional labeling is necessary. However, borderline elevations in uric acid noted in study M1FT08002 should be added to the Adverse Reactions section of the PI.

9. Advisory Committee Meeting

An Advisory Committee meeting for this product was not needed and not held.

10. Pediatrics

The originator, Clistin, was approved for use in children 1 year of age and older. However, the labeling for the RLD, Palgic, now states that it is for use in children 2 years of age and older. The reason for this difference is as follows. Due to safety concerns with use of marketed unapproved carbinoxamine-containing drug products in children under 2 years of age for unapproved indications, the Agency simultaneously announced its intention to take enforcement action against these drug products (71 FR 33462, June 9, 2006) when it issued the Compliance Policy Guide for Marketed Unapproved Drugs in 2006. At the time that this action was taken, the makers of Palgic voluntarily raised the lower age bound for the dosing of their product from 1 year of age to 2 years of age and added a Contraindication for use in patients less than 2 years of age.

This application will trigger PREA because of the new extended-release dosage form, a PREA trigger. [*Note:* The new dosage form also requires a new dosing regimen, also a PREA trigger.] With this submission, the applicant has requested waivers for pediatric studies in the following age groups:

1. Pediatric studies birth to <2 years of age, because carbinoxamine carries a Contraindication for use in children under 2 years of age.
2. Pediatric bioequivalence studies in children 2 to <18 years of age. Per guidance, the BA/BE studies were performed in healthy adults; the results of these studies would be applicable to the adolescents and children 2 to <18 years of age.

These waiver requests are appropriate. The pediatric issues for this application were discussed with the Pediatric Review Committee (PeRC) on August 31, 2011, and PeRC agreed with the waiver for children under 2 years of age.

Dr. Starke's Medical Officer review recommended that pediatric studies be requested under PREA because PK data is not available to support the safety of the proposed dosing recommendations for this extended release product in children 2 through 16 years of age. Therefore, he recommended that pediatric studies be required to support all indications in children 2 through 16 years of age. However, the Agency previously made a determination of the safety of carbinoxamine maleate under DESI, and there is currently no regulatory mechanism to limit the DESI age groups other than by rule making. Therefore, absent a new safety concern in a specific age group, such as the concerns raised at the time when the lower age bound for use of the immediate-release product was changed from 1 to 2 years of age, the Agency cannot request further data for this age group.

11. Other Relevant Regulatory Issues

DSI audit

Because data from BA/BE studies M1FT08001 and M1FT08002 form the basis for approval of this NDA, an audit of these studies by OSI, DBGC was requested. These studies were conducted at Cetero Research-Miami, Miami Gardens, FL (clinical site) and (b) (4) (analytical site). On (b) (4), OSI issued an untitled letter to (b) (4) concluding that BA/BE data generated from (b) (4) a (b) (4) facility were unreliable for the following reasons:

Widespread falsification of dates and times in laboratory records for subject sample extractions; The apparent manipulation of equilibrium or “prep” run samples to meet pre-determined acceptance criteria; and the lack of documentation regarding “prep” runs that prevented (b) (4) from conducting an adequate internal investigation to determine the extent and impact of these violations.

As the Analytical data submitted for studies M1FT08001 and M1FT08002 were generated in the identified time interval, DBGC concluded that these are unreliable and an inspection is not warranted. DBGC recommended that the sponsor be contacted and inform them of the issues in the Untitled Letter and ask them to confirm the validity of the studies. To this effect, Correspondence dated 09/13/2011 was sent to Tris. With respect to the affected studies, the Letter stated that the sponsor will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted. Tris is aware of these issues and in submission dated 09/09/2011, informed their plans to address these issues as follows; Plasma samples for Study M1FT08001 were discarded and no longer available. However, the plasma samples from Study M1FT08002 are still available and since they feel that the steady-state multi-dose study forms the primary basis for approval, all plasma samples (approximately 2052 samples) from Study M1FT08002 would be reanalyzed and that the results of the reanalysis data will be evaluated based on regression analysis and Incurred Sample Reanalysis (ISR) approaches. Regarding the conformational reanalysis endpoint, %Difference will be calculated using the corrected repeat value calculated based on the actual plasma stability.

TradeName:

On 08/19/2011, Tris requested the tradename Karbinal ER which is currently under review by Division of Medication Error Prevention and Analysis. Previous tradename proposals of (b) (4) and (b) (4) were not acceptable.

12. Labeling

Labeling negotiations with the sponsor will not be done during this cycle. However, when approved this will be the first PLR labeling for a carbinoxamine product and will be different

from currently products in this respect. Review team has gone through preliminary labeling edits of the proposed label prior to the information related to data integrity issues of the BA/BE studies was known. Division of Medication Error Prevention and Analysis in the Office of Medical Error Prevention and Risk Management provided following assessment on the container label and ^{(b) (4)}

Container Label : The established name should state “Carbinoxamine maleate” instead of only “Carbinoxamine” because each 5 mL oral suspension contains 4 mg of Carbinoxamine maleate; the company name, logo and flavoring statements compete with the prominence of the proprietary and established names.

(b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is Complete Response.

- Risk Benefit Assessment

The risk-benefit assessment for carbinoxamine maleate extended release suspension does not favor approval of the product. The key BA/BE data required for approval submitted in this application have data integrity issues and cannot be relied upon for making a regulatory decision making. Acceptable BA/BE data should be submitted from new studies, or reanalysis of samples from existing studies, or through a combination of both approaches before the application can be approved. Aside from these Clinical Pharmacology deficiencies, all drug substance and drug product manufacturing and testing sites will need to have acceptable compliance status prior to an approval. In addition, sponsor has also to resolve several ONDQA and Microbiology deficiencies.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management strategies are recommended as the product is not approved in this cycle

- Recommendation for other Postmarketing Requirements and Commitments

No postmarketing requirements and commitments are recommended as the product is not approved in this cycle.

14. Recommended Comments to the Sponsor

Clinical Pharmacology:

1. Data from studies M1FT08001 and M1FT08002 submitted in the NDA are not acceptable because of data integrity issues identified in the (b) (4) bioanalytical site.

Data from both studies M1FT08001 and M1FT08002 form the basis of approval. If plasma samples for study M1FT08001 are no longer available, you should repeat that study and submit the new data. For the sample reanalysis in the multiple dose study M1FT08002, the analytical run acceptance criteria for the calibration standards and quality control samples appear reasonable. However, we remind you that the adequate sample stability should exist to allow for sample reanalysis approach. Regarding the conformational reanalysis endpoint, %Difference should be calculated based on the original repeat value and not based on corrected repeat value calculation based on the actual plasma stability.

CMC

1. Clarify if any overages were used in the manufacture of the drug product.

2. Include in-process controls for (b) (4) during mixing of the (b) (4)

3. Update the NDA specifications to include testing for particle size distribution of the drug product at release and stability. Also include a test and acceptance criteria for (b) (4) carbinoxamine at release. Clarify if the labeled strength is based upon the carbinoxamine (b) (4) or the carbinoxamine (b) (4). Clarify if the maleate salt is (b) (4). Revise the drug product specifications accordingly.

4. We also acknowledge receipt of your amendment dated September 21, 2011, related to the finished product analysis for (b) (4) and impurities, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

5. With respect to the alternate container (b) (4) used to package test Batch TB-085A, provide test results at the 24 month time point for (b) (4) and for the common impurities of (b) (4)

6. Revise the stability commitment to state that stability results will be submitted to NDA annual reports.

Microbiology:

1. The applicant should continue to develop a test method to recover *Burkholderia cepacia* complex organisms potentially present in raw materials and the final product. The test method and revised specification should be submitted in the complete response.

2. Preservative effectiveness testing should be conducted on three batches of drug product.

Division of Medical Error Prevention and Analysis:

A. Container Label

1. Revise the established name to read as follows:

(Carbinoxamine maleate) Extended-release Oral Suspension

2. Revise the font color of the statement “Strawberry Banana Flavored” from (b) (4) to black. As currently presented, the statement competes with the prominence of the proprietary name and the established name.

3. Revise the company logo and company name so they do not compete with the prominence of the proprietary name and the established name. This may be achieved by relocating the company logo and name to below the manufacturer statement on the side panel, or by reducing the size of the company name and logo.

4. Relocate the statement “SHAKE WELL BEFORE USE” to the principal display panel and display with adequate white space. This may be achieved by relocating the “Rx Only” statement or the “Strawberry Banana Flavored” statement to the side panel.

5. Revise the statement “Each 5 mL (b) (4) contains 4 mg of Carbinoxamine Maleate, USP” to read “Each 5 mL contains 4 mg of Carbinoxamine Maleate.” A household teaspoon is not an accurate measuring device and could lead to under or overdose. Reference to (b) (4) should be removed and patients should measure your product in milliliters. Reference to (w) (4) should also be removed because the established name of this product is only Carbinoxamine maleate Extended Release Oral Suspension.

6. Revise the dosage statement to read “Usual Dosage: see prescribing information.”

7. Unbold the statement “[See USP controlled room temperature].” The specific temperature range for storage is already provided in the storage statement, thus it is unnecessary to emphasize the reference to USP controlled room temperature.



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/s/

SURESH DODDAPANENI
09/28/2011