# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 22-556Orig1s000

# SUMMARY REVIEW

# SUMMARY REVIEW OF REGULATORY ACTION

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|---|---|
| **Date** | March 28, 2013 |
| **From** | Lydia Gilbert-McClain, MD, FCCP |
| **Subject** | Summary Review of Regulatory Action |
| **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™/Carbinoxamine maleate Extended Release oral suspension |
| **Dosage forms/strengths** | Oral suspension/4 mg carbinoxamine maleate/5 mL |
| **Proposed indication (s)** | • Seasonal and perennial allergic rhinitis<br>• Vasomotor rhinitis<br>• Allergic conjunctivitis due to inhalant allergens and foods<br>• Mild, uncomplicated allergic skin manifestations of urticaria and angioedema<br>• Dermatographism<br>• As therapy for anaphylactic reactions *adjunctive* to epinephrine and other standard measures after the acute manifestations have been controlled<br>• Amelioration of the severity of allergic reactions to blood or plasma |
| **Action/Recommended action for NME** | *Approval* |
| **Material Reviewed/Consulted** | **Names of discipline reviewers** |
| Action package including: | |
| Medical officer review | Peter Starke, MD |
| Clinical Pharmacology review | Ping Ji, Ph.D |
| CMC review | Ted Carver, Ph.D., Julia Pinto, Ph.D., Donald Klein, Ph.D., Alan Schroeder, Ph.D., Prasad Peri, Ph.D |
| Biopharmceutics | Sandra Suarez Sharp, PhD |
| CDTL | Suresh Doddapaneni, PhD |
| Microbiology Consult | Jessica G. Cole, Ph.D., Stephen Langille, Ph.D |

## 1. Introduction

This is a 505 (b) (2) new drug application initially submitted on December 7, 2010, (received December 8, 2010) by Tris Pharma, Inc. The application is for an extended release oral suspension of carbinoxamine maleate an anti-histamine originally approved pre-1962 for multiple indications. The application relies on establishing bioequivalence to the immediate

release carbinoxamine product to support efficacy and safety of the extended release product. Although bioequivalence was established, it was unclear whether the Agency could rely on the data from the clinical pharmacology studies because of issues identified during an OSI investigation into bioanalytical studies conducted by (b) (4) the contract organization which completed the studies for carbinoxamine. Therefore, pending resolution of these issues a complete response action was taken on this application on October 7, 2011. The inspection issues have since been resolved and the Applicant submitted a complete response on October 5, 2012.

## 2. Background

Carbinoxamine maleate (originally marketed as Clistin [tablets and Elixir]) was reviewed under DESI (Drug Efficacy Study Implementation) and the Agency's findings were published in the Federal Register March 19, 1973. Clistin is no longer marketed (the products were not withdrawn for reasons of safety or efficacy) and a generic immediate release formulation (oral solution and tablet) is available. As a result of the DESI review process, carbinoxamine (as well as multiple other antihistamines) received multiple 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

The applicant is seeking approval of carbinoxamine extended release (ER) oral suspension for all of the DESI indications which are the same indications as that of the immediate release products.

## 3. CMC

From a CMC standpoint, there are no outstanding drug substance or drug product issues. All facilities involved in the drug substance and drug product manufacturing and microbial testing are found to be acceptable. The submitted stability data support an expiry of 24 months.

## 4. Nonclinical Pharmacology/Toxicology

No non-clinical pharmacology/toxicology studies were required or performed for this application.

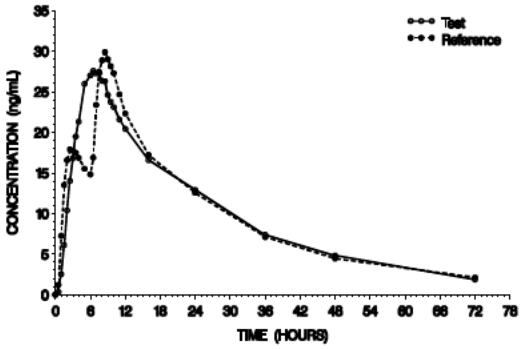
## 5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted two relative bioavailability studies in healthy adults that compared the carbinoxamine extended release oral suspension (Test Product) with a reference product (carbinoxamine maleate oral solution by Mikart). The studies were: 1) a single dose study

(Study MIFT08001)) that evaluated the food effect on the Test Product, and 2) a multiple dose study (Study MIFT08002) that compared the Test and Reference products at steady state under fasted conditions. The results of these two studies show that the Test Product is bioequivalent to the Reference Product after both single dose and multiple dose administration under fasted conditions and that food has no effect on the Test Product. The results for the relative BA and food effect are depicted in the graphs below copied from Dr. Suresh Doddapaneni's CDTL first cycle review.

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

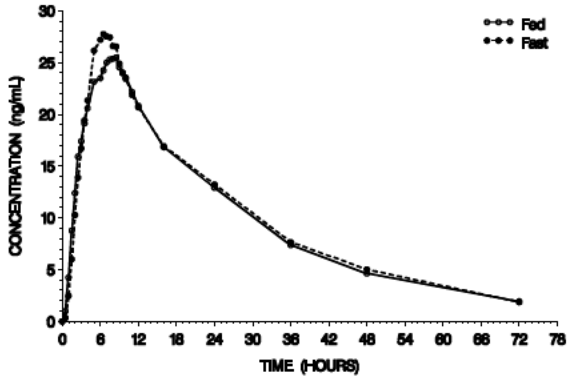
Relative BA




| Parameter | Geometric Least Squares Means | | | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment B | Treatment C | %Ratio | |
| $AUC_{0\ t}$ (ng·h/mL) | 685.7934 | 680.4213 | 100.8 | 97.89 – 103.77 |
| $AUC_{0\ inf}$ (ng·h/mL) | 729.9843 | 724.4320 | 100.8 | 97.45 -104.19 |
| $C_{max}$ (ng/mL) | 28.2150 | 30.2713 | 93.2 | 89.77 – 96.78 |

Reference: Carbinoxamine Maleate Oral Solution (4mg/5 mL) given as an oral dose of 10 mL (8mg) under fasted condition at hour 0 and hour 6.
Test: Carbinoxamine ER Oral Suspension (4mg/5 mL) given as a single oral dose of 20 mL (16 mg) under fasted condition at hour 0.

Food Effect




| Parameter | Geometric Least Squares Means | | | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment A | Treatment B | %Ratio | |
| $AUC_{0\ t}$ (ng·h/mL) | 679.2243 | 696.7027 | 97.5 | 94.69 – 100.38 |
| $AUC_{0\ inf}$ (ng·h/mL) | 726.1847 | 741.7393 | 97.9 | 94.97 – 100.93 |
| $C_{max}$ (ng/mL) | 26.7666 | 28.4788 | 94.0 | 91.06 – 97.01 |

Reference: Carbinoxamine ER Oral Suspension (4mg/5 mL) given under fasted condition.
Test: Carbinoxamine ER Oral Suspension (4mg/5 mL) given as a single oral dose of 20 mL (16 mg) under fed condition at hour 0.

Since this is an extended release (ER) formulation, the potential for dose dumping in the presence of alcohol was evaluated with an *in vitro* dissolution alcohol study. The dissolution profiles for carbinoxamine ER suspension was evaluated in the absence of, and in the presence of 5, 10, 20, 40% alcohol in acidic (0.1 N HCL) conditions and in alkaline (0.4 M phosphate buffer) conditions with 4, 20, and 30% alcohol. In acidic conditions there was little to no dissolution (~ 3%) in the presence of alcohol at all concentrations. In alkaline conditions however, there was ~ (b) (4)% dissolution in 30% alcohol by the 2 hour time point. Given the nature of the formulation, there should not be a clinical concern for dose-dumping *(in vivo)* in the presence of alcohol. The polystyrene sulphonate (b) (4) is insoluble in acidic medium, whereas, the resin ionizes in alkaline medium. Therefore, in the acid medium in the stomach dose dumping should be negligible. Also, the dissolution profile in the alkaline medium is consistent at all alcohol concentrations indicating that there is no immediate formulation failure. Carbinoxamine, like other first generation anti-histamines is sedating and the innovator label already warns against concomitant use with alcohol because of the potential synergistic sedative effect. Taken together, the totality of the data suggests that the extended release carbinoxamine formulation should not have a dose dumping effect

if taken with alcohol. Nevertheless, the product will be labeled to warn against concomitant use with alcohol. For all these reasons I have concluded that an *in vivo* alcohol study is not necessary.

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical- Efficacy

The efficacy of the product is supported by establishing bioequivalence of the proposed drug product to that of the approved immediate release carbinoxamine product as reference. No clinical studies were conducted to support the application.

## 8. Safety

The safety of the product is based on establishing bioequivalence of the product compared to the approved reference product. There were no serious adverse reactions reported in the clinical pharmacology studies. In the multiple dose study, a trend towards increase uric acid levels was seen. The reason for this finding is unclear and this finding will be noted in the product label.

## 9. Advisory Committee Meeting

An advisory committee meeting was not necessary for this application. The active moiety present in this product is not a new molecular entity and there are no issues that need to be discussed at an advisory committee meeting.

## 10. Pediatrics

The original approval for the carbinoxamine immediate release product (Clistin) was for use in children 1 year of age and older. The labeling was revised to contraindicate the use of carbinoxamine in children less than 2 years of age because of safety concerns with the marketed unapproved carbinoxamine-containing products and this labeling change coincided with the Agency's announcement of enforcement action against the marketed unapproved carbinoxamine products (71 FR 33462, June 9, 2006). This application triggers PREA because it is a new dosage form (extended release formulation) and a new dosing regimen (twice daily dosing). The sponsor requested a waiver of pediatric studies in children under 2 years of age (consistent with the labeled contraindication) and a waiver of BE studies in children 2 to 18 years of age. The waiver in children under 2 years of age is appropriate. For the 2 to 18 year old population, BE studies are not performed in the pediatric population and the studies completed in the adult population are acceptable for bioequivalence across the entire age range. The application was presented to 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 less than 2 years of age and transfer of all the indications and age groups from the immediate release product to the extended release product. It is not the Agency's policy to re-visit efficacy if the Agency has already made a determination (in this case via the DESI process. Further, there are no specific safety signals

that would justify requiring new studies in the pediatric population, and 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, all the indications should carry over to the extended release product as well.

**Other Relevant Regulatory Issues**

**Data Quality, Integrity, and Financial Disclosure**

An Office of Scientific Investigations (OSI) inspection was requested during the first review cycle for the two clinical pharmacology studies (M1FT08001 and M1FT08002) submitted to support the NDA. The data from these studies were generated at Cetero Research-Miami, Miami Gardens, FL (clinical site) and (b) (4) (analytical site) during the period January to April 2009. (b) (4) had already been the subject of an ongoing Agency investigation. The Agency had found significant irregularities including widespread falsification of laboratory records at the (b) (4) site resulting in the Agency issuing an Untitled Letter to (b) (4) As a result of the Agency's findings, the OSI concluded that data generated from the (b) (4) site between the period (b) (4), were unreliable and recommended that the Applicant be asked to confirm the validity of the conducted studies. Subsequently, OSI offered the option of independent third-party data integrity audit to NDAs that were affected by the inspection results if the studies supporting those NDAs were conducted between the periods March 1, 2008 to August 31, 2009. Since both studies for this NDA were initiated and completed in this time period, the Applicant followed this approach and had an independent audit conducted by (b) (4). Based on the findings of the independent audit, the data from the two studies M1FT08001, and Study M1FT08002 can be used to support the NDA.

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).

## 11. Labeling

A full labeling review has been completed including reviews by the various OSE divisions, SEALD, and OPDP. The trade name Karbinal ER™ has been reviewed by DMEPA and found to be acceptable. Of note the labeling will include language to alert consumers to use an accurate measuring device to administer the medication.

## 12. Action and Risk Benefit Assessment

**Regulatory action**

The regulatory action on the application will be approval. Tris Pharma Inc. has submitted adequate data to support approval of their extended release carbinoxamine oral suspension

product for use  in children and adults 2 years of age and older. The data from the BA/BE studies demonstrate bioequivalence to the immediate release generic product (currently listed as the RLD in the Orange Book because of withdrawal from the market of the innovator product Clistin).

- Risk Benefit Assessment

The overall risk and benefit assessment of carbinoxamine maleate support approval of this product based on demonstration of bioequivalence to the currently marketed generic.

- Recommendations for Postmarketing Risk Management Activities

None

- Recommendations for other Postmarketing Study Commitments

None

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/s/

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LYDIA I GILBERT MCCLAIN
03/28/2013

# SUMMARY REVIEW OF REGULATORY ACTION

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|---|---|
| **Date** | October 7, 2011 |
| **From** | Lydia Gilbert-McClain, MD, FCCP |
| **Subject** | Summary Review of Regulatory Action |
| **NDA/BLA#** | NDA 22-556 |
| **Applicant** | Tris Pharma, Inc. |
| **Date of Submission** | December 7, 2010 |
| **PDUFA Goal Date** | October 8, 2011 |
| **Proprietary Name/Established (USAN) Names** | Under review/Carbinoxamine maleate ER |
| **Dosage forms/strengths** | Oral suspension/4 mg carbinoxamine maleaate/5 mL |
| **Proposed indication (s)** | • Seasonal and perennial allergic rhinitis<br>• Vasomotor rhinitis<br>• Allergic conjunctivitis due to inhalant allergens and foods<br>• Mild, uncomplicated allergic skin manifestations of urticaria and angioedema<br>• Dermatographism<br>• As therapy for anaphylactic reactions *adjunctive* to epinephrine and other standard measures after the acute manifestations have been controlled<br>• Amelioration of the severity of allergic reactions to blood or plasma |
| **Action/Recommended action for NME** | *Complete Response* |
| **Material Reviewed/Consulted** | **Names of discipline reviewers** |
| Action package including: | |
| Medical officer review | Peter Starke, MD |
| Clinical Pharmacology review | Ping Ji, Ph.D |
| CMC review | Ted Carver, Ph.D., Julia Pinto, Ph.D., Donald Klein, Ph.D., Alan Schroeder, Ph.D., Prasad Peri, Ph.D |
| Biopharmceutics | Sandra Suarez Sharp, PhD |
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## 1. Introduction

This is a 505 (b) (2) new drug application submitted on December 7, 2010, (received December 8, 2010) by Tris Pharma, Inc. The application is for an extended release oral suspension of carbinoxamine maleate an anti-histamine originally approved pre-1962 for multiple indications. The application relies on establishing bioequivalence to the immediate

release carbinoxamine product to support efficacy and safety of the extended release product. This review summarizes the salient findings of the review and the basis for the regulatory decision.

## 2. Background

Carbinoxamine maleate (originally marketed as Clistin [tablets and Elixir]) was reviewed under DESI (Drug Efficacy Study Implementation) and the Agency's findings were published in the Federal Register March 19, 1973. Clistin is no longer marketed (the products were not withdrawn for reasons of safety or efficacy) and a generic immediate release formulation (oral solution and tablet) is available. Based on the DESI review, carbinoxamine was determined to be effective for the symptomatic relief of multiple 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

The applicant is seeking approval of carbinoxamine extended release (ER) oral suspension for all of the DESI indications which are the same indications as that of the immediate release products.

## 3. CMC/Device

The proposed product is for an aqueous extended release suspension of carbinoxamine maleate. The extended release properties of the formulation are afforded by a drug- polistirex complex formed with the active ingredient (carbinoxamine maleate, USP) and sodium polystyrene sulfonate, USP. The polistirex drug delivery technology involves (b) (4) . The drug is displaced from (b) (4) in the GI tract when counter ions penetrate the complex causing the drug to slowly diffuse from the complex and then subsequently absorb over a longer period of time. From a CMC standpoint, there are no outstanding drug substance issues. The drug product contains 4 mg carbinoxamine maleate per 5 mL and is supplied as light beige to tan viscous suspension in (b) (4) bottles. The product is strawberry-banana flavored and there are no issues with the inactive ingredients. The drug product is manufactured by Tris Pharma, Inc, Monmouth Junction, NJ and the office of compliance has provided a WITHHOLD recommendation for this site. This is an approvability issue that will need to be resolved before the product can be approved. There are other CMC deficiencies related to specifications, the manufacturing process, control of leachables, and updated stability data that are not necessarily approvability issues but will be conveyed to the applicant in the action letter. Additionally, although this is a non-sterile (b) (4) acceptable microbial limits are still required. There is no testing and acceptance criterion established to demonstrate that the product is free of the objectionable microorganism *Burkholderia*

*cepacia* an organism that could be present in the raw materials and the final product. This deficiency will also be communicated to the applicant in the action letter.

## 4. Nonclinical Pharmacology/Toxicology

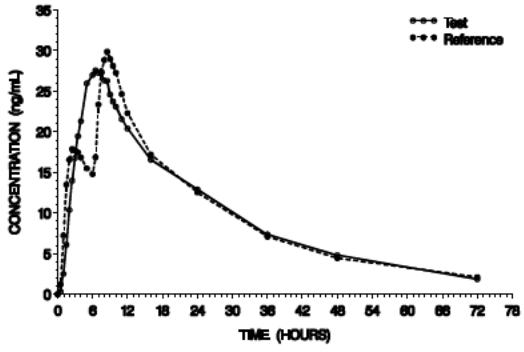
No non-clinical pharmacology/toxicology studies were required or performed for this application.

## 5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted two relative bioavailability studies in healthy adults that compared the carbinoxamine extended release oral suspension (Test Product) with a reference product (carbinoxamine maleate oral solution by Mikart). The studies were a single dose study (Study MIFT08001)) that evaluated the food effect on the Test Product, and a multiple dose study (Study MIFT08002) that compared the Test and Reference products at steady state under fasted conditions. The results of these two studies show that the Test Product is bioequivalent with the Reference Product after both single dose and multiple dose administration under fasted conditions and that food has no effect on the Test Product. The results are depicted in the graphs below (Figure 1 and Figure 2) copied from Dr. Doddapaneni's CDTL review.

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

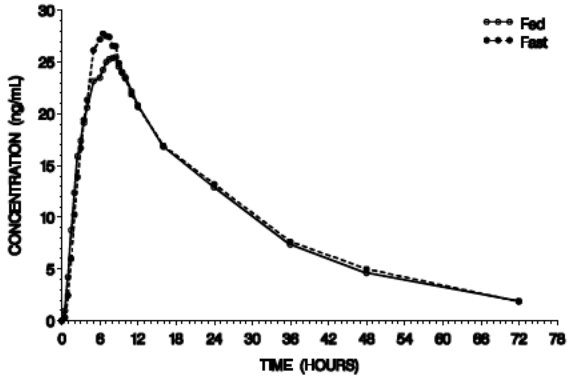
Relative BA




| Parameter | Geometric Least Squares Means | | | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment B | Treatment C | %Ratio | |
| $AUC_{0\,t}$ (ng·h/mL) | 685.7934 | 680.4213 | 100.8 | 97.89 – 103.77 |
| $AUC_{0\,inf}$ (ng·h/mL) | 729.9843 | 724.4320 | 100.8 | 97.45 -104.19 |
| $C_{max}$ (ng/mL) | 28.2150 | 30.2713 | 93.2 | 89.77 – 96.78 |

Reference: Carbinoxamine Maleate Oral Solution (4mg/5 mL) given as an oral dose of 10 mL (8mg) under fasted condition at hour 0 and hour 6.
Test: Carbinoxamine ER Oral Suspension (4mg/5 mL) given as a single oral dose of 20 mL (16 mg) under fasted condition at hour 0.

Food Effect




| Parameter | Geometric Least Squares Means | | | 90% Confidence Interval |
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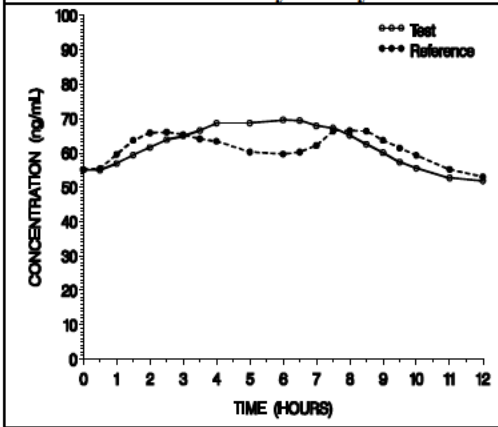
| | Treatment A | Treatment B | %Ratio | |
| $AUC_{0\,t}$ (ng·h/mL) | 679.2243 | 696.7027 | 97.5 | 94.69 – 100.38 |
| $AUC_{0\,inf}$ (ng·h/mL) | 726.1847 | 741.7393 | 97.9 | 94.97 – 100.93 |
| $C_{max}$ (ng/mL) | 26.7666 | 28.4788 | 94.0 | 91.06 – 97.01 |

Reference: Carbinoxamine ER Oral Suspension (4mg/5 mL) given under fasted condition.
Test: Carbinoxamine ER Oral Suspension (4mg/5 mL) given as a single oral dose of 20 mL (16 mg) under fed condition at hour 0.

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




| Parameter | Geometric Least Squares Means | | | 90% Confidence Interval |
|---|---|---|---|---|
| | Test | Reference | % ratio | |
| $C_{max\ (ss)}$ (ng/mL) | 69.1412 | 65.9125 | 104.90 | 102.76 – 107.09 |
| $AUC_{\tau\ (77hr)}$ (ngh/mL) | 702.6899 | 694.5101 | 101.20 | 99.36 – 103.02 |

Test: Carbinoxamine ER Oral Suspension (4mg/5 mL) given as a single oral dose of 20 mL (16 mg) BID for 8 days.
Reference: Carbinoxamine Maleate Oral Solution (4mg/5 mL) given as an oral dose of 10 mL (8mg) QID for 8 days.

Because of data irregularities discovered during the Office of Scientific Investigations' (OSI) inspection of the (b) (4), facility in (b) (4) the Agency determined that bioanalytical data obtained between the time periods of (b) (4) are unreliable. The data from the clinical pharmacology studies in this NDA were generated during the months of January through April 2009 and thus fall within that objectionable period identified by OSI. Since the NDA is relying on establishing bioequivalence to the immediate release product to support the efficacy and safety of the extended release product, the application cannot be approved at this time.

Since this is an extended release (ER) formulation, the potential for dose dumping in the presence of alcohol was evaluated with an *in vitro* dissolution alcohol study. The dissolution profiles for carbinoxamine ER suspension was evaluated in the absence of, and in the presence of 5, 10, 20, 40% alcohol in acidic (0.1 N HCL) conditions and in alkaline (0.4 M phosphate buffer) conditions with 4, 20, and 30% alcohol. In acidic conditions there was little to no dissolution (~ 3%) in the presence of alcohol at all concentrations. In alkaline conditions however, there was ~ (b) (4)% dissolution in 30% alcohol by the 2 hour time point. Given the nature of the formulation, there should not be a clinical concern for dose-dumping *(in vivo)* in the presence of alcohol. The polystyrene sulphonate (the (b) (4)) is insoluble in acidic medium, whereas, the resin ionizes in alkaline medium. Therefore, in the acid medium in the stomach dose dumping should be negligible. Also, the dissolution profile in the alkaline medium is consistent at all alcohol concentrations indicating that there is no immediate formulation failure. Carbinoxamine, like other first generation anti-histamines is sedating and the innovator label already warns against concomitant use with alcohol because

of the potential synergistic sedative effect. Taken together, the totality of the data suggests that the extended release carbinoxamine formulation should not have a dose dumping effect if taken with alcohol. Nevertheless, the product will be labeled to warn against concomitant use with alcohol. For all these reasons I have concluded that an *in vivo* alcohol study is not necessary.

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical- Efficacy

The efficacy of the product is supported by establishing bioequivalence of the proposed drug product to that of the approved immediate release carbinoxamine product as reference. No clinical studies were conducted to support the application.

## 8. Safety

The safety of the product is based on establishing bioequivalence of the product compared to the approved reference product. There were no serious adverse reactions reported in the clinical pharmacology studies. In the multiple dose study, a trend towards increase uric acid levels was seen. The reason for this finding is unclear and this finding will be noted in the product label.

## 9. Advisory Committee Meeting

An advisory committee meeting was not necessary for this application. The active moiety present in this product is not a new molecular entity and there are no issues that need to be discussed at an advisory committee meeting.

## 10. Pediatrics

The original approval for the carbinoxamine immediate release product (Clistin) was for use in children 1 year of age and older. The labeling was revised to contraindicate the use of carbinoxamine in children less than 2 years of age because of safety concerns with the marketed unapproved carbinoxamine-containing products and this labeling change coincided with the Agency's announcement of enforcement action against the marketed unapproved carbinoxamine products (71 FR 33462, June 9, 2006). This application triggers PREA because it is a new dosage form (extended release formulation) and a new dosing regimen (twice daily dosing). The sponsor requested a waiver of pediatric studies in children under 2 years of age (consistent with the labeled contraindication) and a waiver of BE studies in children 2 to 18 years of age. The waiver in children under 2 years of age is appropriate. For the 2 to 18 year old population, BE studies are not performed in the pediatric population and the studies completed in the adult population are acceptable for bioequivalence across the entire age range. The application was presented to PERC on August 31, 2011 and the committee concurred with the waiver for pediatric patients less than 2 years of age. The medical officer presented arguments in his primary medical officer review and to PERC for requiring clinical studies to support efficacy and safety in the 2 to 18 year old population

because of the paucity of data available from the DESI review for the originator product for the pediatric population. [redacted] was discussed with [redacted] Of note, the extended release product is relying on establishing bioequivalence to the immediate release generic product (which in turn relied on the Agency's finding of efficacy and safety of the innovator product – Clistin). Therefore, [redacted] Although the label lists multiple indications, in reality the product is generally mainly used for relief of symptoms of allergic rhinitis, and the other indications are listed simply because the innovator product carries these indications.

## 11. Other Relevant Regulatory Issues

**Data Quality, Integrity, and Financial Disclosure**

An Office of Scientific Investigations (OSI) inspection was requested for the two clinical pharmacology studies (M1FT08001 and M1FT08002) submitted to support the NDA. The data from these studies were generated at Cetero Research-Miami, Miami Gardens, FL (clinical site) and [redacted] analytical site) during the period January to April 2009. [redacted] had already been the subject of an ongoing Agency investigation. The Agency found significant irregularities including widespread falsification of laboratory records at the [redacted] site resulting in the Agency issuing an Untitled Letter to [redacted] As a result of the Agency's findings, the OSI concluded that data generated from the [redacted] site between the period [redacted], were unreliable and recommended that the Applicant be asked to confirm the validity of the conducted studies as provided in the guidance prepared by the office of Clinical Pharmacology. Since the studies submitted in this NDA were conducted during the time period that the irregularities were found at [redacted] a separate inspection was not warranted for these studies. The Office of Scientific Investigations issued an Untitled Letter to [redacted] on [redacted], advising them that BA/BE data generated from [redacted], [redacted], at [redacted] facility were unreliable. On the recommendation of the Division of Bioequivalence and GLP Compliance (DBGC) in the Office of Scientific Investigations (OSI), the Applicant was informed on September 13, 2011, of the issues in the Untitled Letter that was issued to [redacted]

## 12. Labeling

A preliminary labeling review was conducted during the review cycle but given that the clinical pharmacology data are not acceptable to support the application, a marked up

proposed package insert will not be sent to the sponsor with the action letter. The applicant proposed trade name Karbinal ER is currently under review.

## 13. Action and Risk Benefit Assessment

**Regulatory action**

The regulatory action on the application will be a complete response. Tris Pharma Inc. has not submitted adequate data to support approval of their extended release carbinoxamine oral suspension product for use in children and adults 2 years of age and older. The data from the BA/BE studies conducted cannot be relied upon to support approval because of the data integrity findings by the Division of Scientific Investigations (DSI) in the Office of Compliance.

The comments below are for the Complete Response action letter

FDA investigators have identified 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) The pervasiveness and egregious nature of the violative practices by (b) (4) has led FDA to have significant concerns that the bioanalytical data generated at (b) (4) from (b) (4) (b) (4), as part of studies submitted to FDA in New drug Applications (NDA) and Supplemental New drug Applications (sNDA) are unreliable. The analytical data for your clinical pharmacology studies M1FT08001 and M1FT08002 submitted to support your NDA for carbinoxamine extended release oral suspension were generated in the identified time interval and are unreliable to support your NDA.

This deficiency may be addressed by doing the following:

1) 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.

OR

2) Repeat the clinical pharmacology studies if plasma samples for your studies are not available.

OR

3) Conduct a clinical development program with clinical efficacy and safety studies to support your carbinoxamine extended release oral suspension product.

- Risk Benefit Assessment

The overall risk and benefit assessment of carbinoxamine maleate does not support approval of this product because the clinical pharmacology data upon which the application relies to support efficacy and safety are unreliable.

- Recommendations for Postmarketing Risk Management Activities

Not applicable since the action is a Complete Response

- Recommendations for other Postmarketing Study Commitments

Not applicable since the action is a Complete Response.

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/s/

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LYDIA I GILBERT MCCLAIN
10/07/2011
Deputy Division Director