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RESEARCH**

APPLICATION NUMBER:

22-556Orig1s000

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: NDA 22-556 (Carbinoxamine Maleate extended release oral suspension)

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Division of Pulmonary, Allergy, and Rheumatology Products
Pharmacology and Toxicology Team Leader

DATE: March 11, 2013

No nonclinical pharmacology or toxicology studies were provided in the resubmission dated October 4, 2012. See the primary review by Dr. Asoke Mukherjee dated September 6, 2011 and the secondary review by Dr. Molly Shea dated September 9, 2011. Dr. Mukherjee's review contains recommendations for labeling of nonclinical sections of the product label. I concur with the earlier recommendations for approval from the nonclinical perspective.

Tris Pharmaceuticals submitted New Drug Application (NDA) 22-556 for carbinoxamine maleate extended release oral (b) (4), an H₁ receptor antagonist, under the 505(b)(2) pathway with reference to ANDA 40-458 carbinoxamine maleate oral solution manufactured by Mikrat and reference to information available in the public literature with respect to the drug substance and inactive ingredients.

As there are no outstanding pharmacology/toxicology issues for this NDA application, the NDA is recommended for approval from the nonclinical perspective.

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/s/

TIMOTHY W ROBISON
03/11/2013

INTEROFFICE MEMO

TO: NDA 22-556
(Carbinoxamine Maleate extended release oral suspension)
Supporting Document 1/Stamp Date December 8, 2010/Tris Pharma

FROM: Molly E. (Shea) Topper, Ph.D.
Nonclinical Supervisor
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: September 9, 2011

I concur with Dr. Asoke Mukherjee's nonclinical pharmacology review for carbinoxamine maleate extended release oral (b) (4) (4 mg/5 mL) with the proposed indication for the treatment of symptoms of seasonal and perennial allergic rhinitis, conjunctivitis, urticaria and other allergic conditions. Additionally, I concur with the recommendation of approval from the nonclinical perspective pending acceptance of the recommended labeling revisions.

Tris Pharmaceuticals submitted New Drug Application (NDA) 22-556 for carbinoxamine maleate extended release oral (b) (4) an H₁ receptor antagonist, under the 505(b)(2) pathway with reference to ANDA 40-458 carbinoxamine maleate oral solution manufactured by Mikrat and reference to information available in the public literature with respect to the drug substance and inactive ingredients. 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). No nonclinical studies were submitted or required to support this submission (refer to Dr. Mukherjee's review for details).

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/s/

MOLLY E TOPPER
09/09/2011

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 22-556
Supporting document/s: SDN1
Applicant's letter date: Dec 7, 2010
CDER stamp date: Dec 8, 2010
Product: Carbinoxamine ER oral suspension
Indication: Seasonal and perennial allergic rhinitis,
vasomotor rhinitis, allergic conjunctivitis,
urticaria and angioedema, allergic and
anaphylactic reactions
Applicant: Tris Pharma Inc.
Review Division: Division of Pulmonary, Allergy and
Rheumatology Drug Products
Reviewer: Asoke Mukherjee, Ph.D
Supervisor/Team Leader: Molly Shea, Ph.D
Division Director: Badrul Chowdhury, MD, Ph.D
Project Manager: Miranda Raggio

Template Version: December 7, 2009

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22556 are owned by Tris Pharma or are data for which Tris Pharma has obtained a written right of reference. Any information or data necessary for approval of NDA 22556 that Tris Pharma does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Tris Pharma does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22556.

TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
1.1 RECOMMENDATIONS:	3
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS:	5
2 DRUG INFORMATION	5
3 INTEGRATED SUMMARY AND SAFETY EVALUATION	9

Executive Summary

1.1 Recommendations:

Carbinoxamine maleate is a H₁ receptor antagonist that blocks the histaminergic effect in H₁ receptors and also contributes to anti-secretory activity due to the inhibition of muscarinic receptors. The NDA for carbinoxamine extended release formulation is recommended for approval from non-clinical perspective for symptoms of allergic rhinitis, conjunctivitis, urticaria and other allergic conditions.

1.1.1 Approvability

From a non-clinical point of view, the NDA is recommended for approval.

1.1.2 Additional Non-Clinical Recommendations:

No additional non-clinical study is recommended for the 505(b) (2) application.

1.1.3 Labeling:

Recommendations on labeling:

The sponsor submitted proposed labeling in general conformance with 21 CFR Parts 201, 314, and 601 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products and Draft Guidances and Two Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Final Rule and Notices (January 24, 2006). The recommended changes to the labeling are shown as strikeouts and the nonclinical reviewer additions to labeling are presented in color font. The nonclinical changes to labeling are 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). These changes are presented below.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproductive studies have not been conducted with carbinoxamine maleate. It is also not known whether carbinoxamine maleate can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Carbinoxamine Extended Release Oral Suspension-maleate should be given to a pregnant woman only if clearly needed.

8.2 Labor and Delivery

The effect of Carbinoxamine Extended Release Oral Suspension on labor and delivery is not known.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in breast milk and because of the potential risk for serious adverse reactions, (b) (4) with the use of carbinoxamine maleate in infants and young children, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (b) (4)

10.10 OVERDOSAGE

10.1 (b) (4)

Overdosage with carbinoxamine maleate may cause (b) (4) central nervous system depression (b) (4) or stimulation, hallucinations, convulsions, and death. (b) (4) Atropine-like signs and symptoms – dry mouth; fixed, dilated pupils; flushing; and gastrointestinal symptoms may also occur.

13.13 NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to determine the possible effects of carbinoxamine maleate on carcinogenesis, mutagenesis, and fertility.

1.2 Brief Discussion of Nonclinical Findings:

No new non-clinical studies were requested or needed to support this NDA.

2 Drug Information

2.1 Drug:

Carbinoxamine ER oral suspension

2.1.1 CAS Registry Number (Optional)

486-16-8

2.1.2 Generic Name:

Carbinoxamine maleate USP

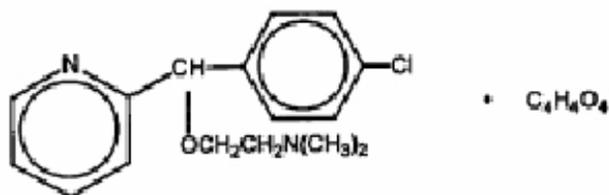
2.1.4 Chemical Name:

2-[(4-chlorophenyl)-2-pyridinyl-methoxy]-N, N-dimethylethanamine
(Z) -2-butenedioate (1:1)

2.1.5 Molecular Formula/Molecular Weight:

$C_{16}H_{19}ClN_2O \cdot C_4H_4O_4$, 406.86

2.1.6 Structure:



2.1.7 Pharmacologic class:

Carbinoxamine is a histamine- H₁ receptor blocker.

2.2 Relevant IND/s, NDA/s, and DMF/s:

IND: 102,091, submitted on Nov 13, 2008 and DMF (b) (4) submitted on Jan 10, 2011

2.3 Clinical Formulation:

The clinical formulation is shown from the sponsor's table below.

Table 1. Clinical formulation per unit dosage form

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

<p>Sucrose NF</p> <p>(b) (4) (Food Starch – Modified)</p> <p>Strawberry Banana Flavor (b) (4) :</p> <p>(b) (4)</p>	<p>(b) (4)</p>
<p>¹ Sodium Polystyrene Sulfonate USP (b) (4)</p> <p>² Amount represents (b) (4)</p> <p>³ Amount represents (b) (4)</p>	<p>(b) (4)</p>

Drug Formulation per unit volume for batches:

Table 2. Drug formulation

Ingredients	Quantity (w/v%)	Amount allowed per IIG (%)
Sodium Polystyrene Sulfonate (b) (4) ¹	(b) (4)	(b) (4)
Povidone USP (b) (4)		
Triacetin USP		
Polyvinyl Acetate (b) (4)		
(b) (4)		
Purified Water USP		
Polysorbate 80 NF (b) (4)		
Sodium Metabisulfite NF (b) (4)		
Glycerin USP		
Methylparaben NF		
Propylparaben NF		
Xanthan Gum NF (b) (4)		
Anhydrous Citric Acid USP		
High Fructose Corn Syrup (b) (4) [®] (b) (4)		
Sucrose NF		
(b) (4) (Food Starch – Modified)		
Strawberry Banana Flavor (b) (4) (includes):		
(b) (4)		

There is no inactive ingredient safety issue for the formulation.

2.3.2 Comments on Novel Excipients:

Polyvinyl Acetate (b) (4) was used as an inactive ingredient at about (b) (4) mg per day for the total daily oral dose of 32 mg carbinoxamine. The amount per day for (b) (4) would be (b) (4)/kg for a 60 kg subject. Based on the toxicity data from the DMF (b) (4) holder, the amount is considered as safe.

The sponsor provided information on sodium polystyrene sulfonate to qualify as an inactive ingredient as reviewed below. Since the inactive ingredient was also used as an approved drug from 15 to 60 g per day and several other drugs containing sodium polystyrene was approved, the total amount of about (b) (4) mg of sodium polystyrene per day from the carbinoxamine formulation was considered safe.

2.3.3 Comments on Impurities/Degradants of Concern

There were no impurities that exceeded ICH Q3 (A) R guidelines for the drug substance.

2.4 Proposed Clinical Population and Dosing Regimen:

Carbinoxamine maleate is proposed for the symptomatic treatment of the following conditions in patients 17 years of age and older:

- 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 usual daily dose for adults is 6 to 16 mg every 12 hours.

2.5 Regulatory Background:

The sponsor submitted this 505(b) (2) application for carbinoxamine maleate with reference to ANDA 40-458 carbinoxamine maleate oral solution manufactured by Mikrat (carbinoxamine 4 mg/5 ml oral solution). The sponsor submitted their original IND 102091 on Nov 12, 2008. A Pre-IND meeting was held on May 15, 2008 to discuss the development and registration of the product. It was agreed during the meeting that no

new non-clinical pharmacology/Toxicology data would be required for the development and registration of the product due to its DESI status and its clinical safety was known from the previous clinical experience. However, the sponsor was asked to provide bioequivalency data. From non-clinical perspectives, the sponsor was also asked provide data on any impurities that exceed ICH recommended levels.

3 Integrated Summary and Safety Evaluation

The sponsor, Tris Pharma, submitted the NDA application for carbinoxamine maleate extended release oral suspension under FDC 505 (b) (2) referencing Carbinoxamine oral solution ANDA 040458. The formulation would contain 4 mg of Carbinoxamine maleate per 5 ml. The sponsor referenced an approved product on Carbinoxamine maleate oral solution and published literature on other antihistamines with similar H₁ antagonistic effects to support the non-clinical safety information needed for approval. No new non-clinical toxicity report was submitted for a review.

Carbinoxamine is an H₁ histamine receptor antagonist for the treatment of several allergic conditions including rhinitis, conjunctivitis, urticaria and anaphylaxis. Carbinoxamine was approved in the US in 1954 as a prescription drug. Since then Carbinoxamine remained a prescription product because there was no application for switching to over the counter uses and carbinoxamine was not a grand-fathered drug to be included in the OTC monographs. Since its first approval, carbinoxamine has been used as an anti-histamine for more than 50 years. However, drugs that were approved before 1962 required safety studies only. Following 1962 an amendment of Food, Drug and Cosmetic Act, all drugs approved before 1962 and not grand-fathered, required establishing their efficacy by a review panel set by FDA under Drug Efficacy Study Implementation (DESI). Carbinoxamine was further reviewed for its efficacy under DESI Program of FDA. Carbinoxamine was granted DESI status as an immediate release form but it was recommended that further approval of its extended release form would require bioequivalency studies. This application for Carbinoxamine extended release formulation provided bioequivalency reports for review and thus qualified as a safe and effective product under DESI. The sponsor had a PIND meeting on May 15, 2008 and the development plan was discussed. The Division agreed that no non-clinical and no clinical efficacy and safety studies would be needed other than bioequivalency studies with the referenced product because safety and efficacy of carbinoxamine as an anti-histamine was established in clinical population and from a previous review under DESI.

Carbinoxamine belongs to ethylethanamine-substituted compound. Some of the other antihistamines that belong to this class of drugs include bromodiphenhydramine, clemastine, doxylamine, phenyltoxamine, diphenpyralimine and diphenylidrate. These H₁ antagonists have sedative and anticholinergic effects. However, very little published data are available on Carbinoxamine for its non-clinical pharmacology, toxicity and non-clinical pharmacokinetics. The Division agreed during the PIND meeting that no non-clinical data would be required because the safety and

effectiveness of Carbinoxamine was established in the clinical population when given by the same route of administration. However, the sponsor was reminded that they would need to qualify any impurities in the drug substance and drug product that exceeds ICH Q3A and Q3B guidelines. The review of application did not show any impurities of structural alert that exceeds the recommended guidelines. The inactive ingredients used were used previously in approved products for the same proposed routes of administration. Furthermore, the safety of [REDACTED] ^{(b) (4)} used in the formulation was studied and found to be safe.

The sponsor provided a tabulated summary to indicate that other anti-histamines that are used clinically e.g., pyralamine, tripelamine, diphenhydramine, anistine prevents bronchoconstriction, GI smooth muscle contractions, cutaneous permeability induced by histamine in several animal species including guinea-pigs, dogs, rabbits and cats. Based on the information, it is anticipated that pharmacological effects of carbinoxamine would be associated with anti-spasmodic, anti-secretory, and anti-edematous effects. Published literature summarized that of 113 pregnant women exposed to tripolidine, pyrobutamine, cyclizine, dexbrompheniramine, chlorcycline, phenindamine, phenyldiamine, bromodiphenhydramine, cyproheptadine, carbinoxamine, dimethindene and diphenylpyraline 5 delivered malformed children. However, it is not known if these pregnant women were treated with carbinoxamine (Anti nauseants, Anti-histamines and Phenothiazines, pp 322-323, in Birth Defects and Drugs in Pregnancy, Edited by Heinonen, O.P., Slone D, Shapiro, S. Publishing Sciences Group Inc. Littleton, Massachusetts, 1977).

The review recommended changes in the proposed label to conform with the CFR 21 Parts 201, 314, and 601 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products and Draft Guidances and Two Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Final Rule and Notices (January 24, 2006) and inclusion of the trade name for the product. In the proposed label.

Based on the review of the label and inactive ingredients used in the formulation, there is no further non-clinical safety concern for the approval of the product. The NDA can be approved from the non-clinical point of view.

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/s/

ASOKE MUKHERJEE
09/06/2011

MOLLY E TOPPER
09/06/2011
I concur.

NDA Number: 22-556

Applicant: Tris Pharma Inc.

Stamp Date: Dec 8, 2010

Drug Name: Carbinoxamine NDA/BLA Type: 505(b)(2)
oral suspensions

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		No new pharmacology toxicology data were submitted for the 505(b)(2) application
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?		x	No data submitted
3	Is the pharmacology/toxicology section legible so that substantive review can begin?		x	No data submitted
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?		X	Reference product label needs to be submitted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		x	No pharmacology/Toxicology data submitted
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?		X	No pharmacology/Toxicology data submitted
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?		X	No pharmacology/Toxicology data submitted
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X	Safety for leachable and extractable impurities were not provided according to CDER May 1999 guidelines as requested in PreIND meeting minutes

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA 22-556**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		x	No new data submitted
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		
11	Has the applicant addressed any abuse potential issues in the submission?		x	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

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

1. Please provide an approved label of the reference product and data for safety of leachables and extractables of container system following a 74-day filing IR.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/s/

ASOKE MUKHERJEE
01/31/2011

MOLLY E TOPPER
01/31/2011