CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-556Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 22556	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Karbinal ER (pending approval) Established/Proper Name: Carbinoxamine ER Oral Suspension eq. to 4 mg carbinoxamine maleate per 5 mL Dosage Form: Extended Release Oral Suspension Strengths: eq. to 4 mg carbinoxamine maleate per 5 mL		
Applicant: Tris Pharma Inc.		
Date of Receipt: October 5, 2012		
PDUFA Goal Date: April 5, 2013	Action Goal Date (if different): March 28, 2013	
Proposed Indication(s): Treatment of 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		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Reference Product: Clistin Elixir 4 mg per 5 mL (McNeil)	Reference Product listed in Form 356h dated October 5, 2012

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The application relies on the no-longer-marketed innovator NDA product (brand name Clistin, manufactured by McNeil) while using the marketed generic immediate release Carbinoxamine Maleate Oral Solution (marketed under the brand name Palgic, and manufactured by Milkart, Inc.) for bridging. Two pivotal bioavailability studies were conducted, comparing the relative bioavailability of the test ER formulation (Karbinal ER) with immediate release Carbinoxamine Maleate Oral Solution (Palgic),

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Clistin Elixir (Discontinued)	NDA 008955	Yes
Clistin Tablets (Discontinued)	NDA 008915	Yes

Application referred to the listed products and NDA/ANDA #s in an attachment to Form 356h dated December 6, 2010.

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☒ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process: Clistin (DESI 6303)

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Clistin 4 mg Tablets, Clistin R-A 8 mg Tablets, and Clistin Elixir 4mg/5mL.

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

See FR notice of April 10, 2000 in 65 FR 18900.

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in formulation. The NDA 22556 is proposed for an ER Oral Suspension.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period;*

(2) *do not necessarily contain the same inactive ingredients;* ***and*** ***(3)*** *meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be

infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

APPEARS THIS WAY ON ORIGINAL

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

/s/

JESSICA K LEE
03/28/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**Karbinal ER (carbinoxamine) extended-release oral suspension**
Applicant	Tris Pharma, Incorporated
Application/Supplement Number	NDA 22556
Type of Application	Class 2 Resubmission
Indication(s)	Seasonal and perennial allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; dermatographism; therapy for anaphylactic reactions *adjunctive* to epinephrine and other standard measures after the acute manifestations have been controlled; and amelioration of the severity of allergic reactions to blood or plasma
Established Pharmacologic Class[1]	H_1 receptor antagonist
Office/Division	ODEII/DPARP
Division Project Manager	Jessica Lee
Date FDA Received Application	October 5, 2012
Goal Date	April 5, 2013
Date PI Received by SEALD	March 14, 2013
SEALD Review Date	March 19, 2013
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

APPEARS THIS WAY ON ORIGINAL

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *DPARP to grant a waiver of 1/2 page HL limit in approval letter or will edit HL to shorten to 1/2 page.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *Remove established name and dosage form (i.e., "(carbinoxamine) Extended-release Oral suspension") from first sentence of the HL Limitation Statement and remove dosage form (i.e., "Extended-release Oral suspension") from second sentence; only include "KARBINAL ER" in this statement.*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

NO 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *Remove the sponsor's website address "(i.e., "www.trispharma.com") from this statement. Only direct links to a site for AR reporting may be included in this statement. The link included is to a general company website.*

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *Bold revision date and update to reflect correct month of approval.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.
Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.
Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:

N/A

31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

N/A 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information

N/A 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

NO 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *Insert appropriate modification of statement preceding presentation of adverse reactions.*

Patient Counseling Information

N/A 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

DEBRA C BEITZELL
03/19/2013

LAURIE B BURKE
03/20/2013

Division of Pulmonary, Allergy, and Rheumatology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 22556

Name of Drug: Carbinoxamine ER Oral Suspension

Applicant: Tris Pharma Inc.

Labeling Reviewed

Submission Date: October 4, 2012, January 8, 2013

Receipt Date: October 5, 2012, January 9, 2013

Background and Summary Description:

Tris Pharma Inc. submitted a NDA application on December 8, 2010 in which the division took a Complete Response on October 7, 2011. Tris Pharma resubmitted the NDA 22556 application on October 4, 2012 to address the deficiencies in the October 7, 2011 Complete Response. The resubmission is Class 2 with a PDUFA Goal Date of April 5, 2013.

Review

Regulatory Project Manager Physician's Labeling Rule (PLR) review was performed for the NDA 22556, Carbinoxamine ER Oral Suspension, prescribing information. Based upon the PLR review, the following are issues/deficiencies identified in the draft labeling of the October 4, 2012 resubmission:

Highlights

1. Highlight limitation statement is partly bolded and the drug product name is not upper case.
2. The statement under "Indications and Usage" uses the term "effective" for rather than "indicated" for.
3. The revision date is not listed.

Table of Contents

4. No horizontal line to separate the "Table of Contents" (TOC) from the "Full Prescribing Information (FPI)."
5. The subheadings in section 5, "Warnings and Precautions" in TOC does not match FPI, and in section 6, "Adverse Reactions," the subheadings is missing hematologic in TOC that is listed in FPI.

6. In section 6, "Adverse Reactions" subsection is missing hematologic, which is listed in FPI, and altered the numbering.

Full Prescribing Information (FPI)

7. Inconsistent italicized cross-reference statements.

Recommendations

The above deficiencies were communicated to Tris Pharma on January 7, 2013. Tris Pharma submitted a response on January 8, 2013. Tris addressed all the listed comments with the exception of Highlight limitation statement, which remains outstanding. The sponsor did not bold the limitation statement. The outstanding deficiency will be communicated to Tris with comments from other disciplines. Pending agreement from other disciplines, I recommend approval.

Jessica Lee	2/14/13
Regulatory Project Manager	Date
Ladan Jafari	2/14/13
Chief, Project Management Staff	Date

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/s/

JESSICA K LEE
02/19/2013

LADAN JAFARI
02/19/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 22556

Application Type: NDA Class 2 Resubmission

Name of Drug: Carbinoxamine ER Oral Suspension

Applicant: Tri Pharma Inc.

Submission Date: October 4, 2012

Receipt Date: October 5, 2012

1.0 Regulatory History and Applicant's Main Proposals

Tris Pharma Inc. submitted a NDA application on December 8, 2010 in which the division took a Complete Response on October 7, 2011. Tris Pharma resubmitted the NDA 22556 application on October 4, 2012 to address the deficiencies in the October 7, 2011 Complete Response. The resubmission is Class 2 with a PDUFA Goal Date of April 5, 2013.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 10, 2013. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *Longer than one-half page*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *No numerical identifier in the following sections of HL: Dosage Forms and Strengths, Warnings and Precautions*

NO

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *"Revision Date" is not listed*

YES

7. A horizontal line must separate HL and Table of Contents (TOC).
Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *The statement is partly bolded and the drug product name is not UPPER CASE.*

Product Title

YES

10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

NO 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment: *The statement uses "effective" for, rather than "indicated" for*

The pharmacologic class is not listed

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

NO 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *Inserted manufacturer website*

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *No revision date listed.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

NO 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *The subheadings in section 5 Warnings and Precautions in TOC does not match FPI. In section 6 Adverse Reactions, the subheadings is missing hematologic in TOC that is listed in FPI.*

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

NO 34. When a section or subsection is omitted, the numbering does not change.

Comment: *Section 6 Adverse Reactions subsection is missing heamtologic, which is listed in FPI, and altered the numbering.*

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *"See" is not iltalicized in sections 2, 5.1, and 8.4*

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

N/A 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

N/A 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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/s/

JESSICA K LEE
02/19/2013

LADAN JAFARI
02/19/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	February 15, 2013
Reviewer(s):	Lissa C. Owens, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, M.S., PharmD Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	Karbinal ER (Carbinoxamine Maleate) Extended-release Oral Suspension, 4 mg/5 mL
Application Type/Number:	NDA 022556
Applicant/sponsor:	Tris Pharma, Inc.
OSE RCM #:	2012-2430

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed [redacted] (b) (4), container label, carton, and insert labeling for Karbinal ER (Carbinoxamine Maleate) NDA 022556 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Karbinal ER (Carbinoxamine Maleate) Extended-release Oral Suspension is the subject of a 505(b)(2) application. We previously evaluated the [redacted] (b) (4) and labels and labeling in OSE Review # 2011-169 dated August 19, 2011 and provided comments. However, the application received a CR on October 7, 2011. The Applicant has now resubmitted the NDA for the request for review of the labels, and labeling on October 4, 2012.

The name is being evaluated in a separate OSE Review # 2012-2487.

1.2 PRODUCT INFORMATION

The following product information is provided in the October 16, 2012 proprietary name submission.

- Active Ingredient: Carbinoxamine Maleate
- Indication of Use: For symptomatic treatment of, 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 reaction adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled, and Amelioration of the severity of allergic reaction to blood or plasma
- Route of Administration: Oral
- Dosage Form: Extended-release oral suspension
- Strength: 4 mg/5 mL
- Dose and Frequency: adult: 7.5 mL to 20 mL (6 to 16 mg) administered orally every 12 hours. Children: (0.2 to 0.4 mg/kg/day) 3.75 mL to 15 mL (3 to 12 mg) administered orally every 12 hours
- How Supplied: 1 oz professional samples, 10 oz, 16 oz bottles with a [redacted] (b) (4)
- Storage: Room Temperature

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Carbinoxamine Maleate medication error reports. We also reviewed the Karbinal ER labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1. The date of our search was limited from our last search date of August 9, 2011 (OSE RCM # 2011-169). This FAERS database search identified no cases.

Table 1: FAERS Search Strategy	
Date	August 10, 2011 to December 4, 2012 (the search was limited to the date of our last search on August 9, 2011 in OSE RCM # 2011-169)
Drug Names	(Carbinoxamine%)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted October 4, 2012 (Appendix B)
- Professional Sample Carton Labeling submitted October 4, 2012 (Appendix C)
- Professional Sample Container Label submitted October 4, 2012 (Appendix D)
- (b) (4) (Appendix E)
- Insert Labeling submitted October 4, 2012 (no image)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA referenced previous reviews to ensure all previous recommendations were implemented. We note that all of our recommendations have been implemented.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3. INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

Karbinal ER is the first extended-release product for Carbinoxamine Maleate. A (b) (4)

The currently marketed formulations of immediate-release Carbinoxamine Maleate Oral Solution and the proposed Karbinal ER Extended-release Oral Suspension are available in the same single strength, 4 mg/5 mL. Therefore, the overlapping product characteristics (i.e. same active ingredient, strength, liquid dosage forms, and oral route of administration) and that liquid dosage forms are often prescribed in "# mL" pose a risk of confusion and wrong drug medication errors between the immediate-release product and this extended-release product.

In addition, the proposed Karbinal ER has a dosing frequency of every 12 hours, while immediate-release Carbinoxamine Maleate Oral Solution products have a dosing frequency of three to four times daily (every 6 to 8 hours). Because of the different frequency of administration, confusion between the immediate-release product and this extended-release product may lead to underdose or overdose medication errors. This concern was also outlined in our previous review (OSE # 2011-3192).

Ideally, a different strength for the extended-release formulation would help differentiate it from the immediate release formulations and reduce the risk for wrong drug dispensing errors. However, since both formulations are single strength products, the strength may be omitted from prescriptions and the risk of product confusion due to the overlapping product characteristics may still occur. Especially since both products can be administered in mL amounts.

We will attempt to mitigate these potential medication errors through labeling and post-marketing monitoring.

4. RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Comments to the Applicant

All Labels and Labeling

1. Include the frequency of administration ('Dosed every 12 hours') under 'shake well before use' on the principle display panel of all labels and labeling to help decrease confusion between the immediate-release product and the extended-release product.
2. Increase the prominence and font of the established name. As presented the established name is less prominent in comparison to that of the dosage form.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

LISSA C OWENS
02/15/2013

LUBNA A MERCHANT
02/15/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 12, 2013

To: Jessica Lee, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP), Division of Professional Drug Promotion (DPDP)

CC: Lisa Hubbard, Acting Deputy Division Director, DPDP
Matthew Falter, Regulatory Review Officer, OPDP, Division of Consumer Drug Promotion (DCDP)
Twyla Thompson, Group Leader, DCDP

Subject: NDA # 022556
OPDP labeling comments for KARBINAL™ ER (carbinoxamine maleate) Extended-release Oral Suspension

---

OPDP has reviewed the proposed Package Insert (PI) and Carton and Container Labeling for NDA 022556 submitted for consult on October 16, 2012.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled "N22556 TrisLabel EDAccept.doc" that was sent via email from DPARP to OPDP on February 1, 2013. OPDP's comments on the PI are provided directly in the marked-up document attached (see below).

OPDP has reviewed the proposed container labels submitted by the applicant and available in the EDR at:

- \\cdsesub5\EVSPROD\NDA022556\\0000\m1\us\draft-container-label.pdf
- \\cdsesub5\EVSPROD\NDA022556\\0003\m1\us\draft-container-label.pdf
- \\cdsesub5\EVSPROD\NDA022556\\0005\m1\us\container-label.pdf
- \\cdsesub5\EVSPROD\NDA022556\\0012\m1\us\karbinal-er-label.pdf
- \\cdsesub5\EVSPROD\NDA022556\\0017\m1\us\label-1-oz.pdf

- \\cdsesub5\EVSPROD\NDA022556\\0017\m1\us\label-10-oz.pdf
- \\cdsesub5\EVSPROD\NDA022556\\0017\m1\us\label-16-oz.pdf
- \\cdsesub5\EVSPROD\NDA022556\\0017\m1\us\carton-ps.pdf

We note that some of the proposed container labeling located in the EDR refers to the product by earlier proposed trade names. Please ensure when all labeling is finalized that it consistently refers to the product by the approved trade name.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
02/12/2013

M E M O R A N D U M

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

DATE: September 14, 2011

TO: Badrul Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Chandrahas Sahajwalla, Ph.D.
Director,
Division of Clinical Pharmacology II (DCPII)

FROM: Arindam Dasgupta, Ph.D.
Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Audit Request for studies M1FT08001 and M1FT08002 conducted for NDA 22-556

The Office of Scientific Investigation (OSI), Division of Bioequivalence and GLP Compliance (DBGC) received a request for audit of studies M1FT08001 and M1FT08002, conducted at Cetero Research-Miami, Miami Gardens, FL (clinical site) and (b) (4) (analytical site), for NDA 22-556, Carbinoxamine ER oral suspension.

On (b) (4) OSI issued an Untitled Letter to (b) (4) In the letter, FDA concluded that BE/BA data generated from (b) (4) (b) (4) at (b) (4) facility were unreliable for the following reasons:

- The widespread falsification of dates and times in laboratory records for subject sample extractions;
- The apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria; and

- The lack of documentation regarding "prep" runs that prevented [redacted] from conducting an adequate internal investigation to determine the extent and impact of these violations

Analytical data submitted for studies M1FT08001 and M1FT08002 were generated in the interval between [redacted] at [redacted] facility. Hence, the data are unreliable and the requested inspections are not warranted. DBGC declines to conduct the inspections.

DBGC recommends that DPARP contact sponsors of approved and pending NDAs and inform them of the issues in the Untitled Letter and ask them to confirm the validity of studies conducted at [redacted] between [redacted] and [redacted] as provided in the guidance prepared by the Office of Clinical Pharmacology.

Arindam Dasgupta, Ph.D.,
Staff Fellow

cc:
CDER OSI/PM TRACK
CDER/OND/DPARP/Chowdhury/Raggio Miranda
OCP/DCPII/Sahajwalla/Ping Ji
OC/Moreno
DBGC/Salewski/Haidar/Skelly/Dasgupta/Dejernett/CF
Draft: AD 09/13/2011
Edit: MFS 9/14/2011; SHH 9/15/2011
OSI: 6177; O:\BE\MEMOS\22556car.doc

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

/s/

ARINDAM DASGUPTA
09/19/2011

SAM H HAIDAR
09/20/2011

M E M O R A N D U M

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

DATE: September 10, 2012

TO: Badrul Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Chandrahas Sahajwalla, Ph.D.
Director, Division of Clinical Pharmacology II (DCPII)

FROM: Xikui Chen, Ph.D.
Pharmacologist, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering NDA 22-556, Carbinoxamine ER Oral Suspension, sponsored by Tris Pharma, Inc.

At the request of the Division of Pulmonary, Allergy and Rheumatology Products (DPARP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted an audit of the following bioequivalence studies:

Study Number: M1FT08001
Study Title: "A Study to Determine the Relative Bioavailability of Carbinoxamine Polistirex 4 mg/5 ml ER Oral Suspension Versus Carbinoxamine Maleate 4 mg/5 ml Oral Solution Under Fasting Conditions, and to Determine the Effect of Food on Carbinoxamine Polistirex 4 mg/5 ml ER Oral Suspension"

Study Number: M1FT08002
Study Title: "A Steady-State, Multi-Dose Study of Carbinoxamine Polistirex 4 mg/5 ml ER Oral Suspension Versus Carbinoxamine Maleate 4 mg/5 ml Oral Solution"

Clinical Site: Cetero Research—Miami
Miami Gardens, Florida

Initially OSI declined to inspect the studies, based on inspectional findings at the (b) (4) bioanalytical site in (b) (4) (see Dr. Dasgupta's Memorandum on 9/20/2011). However, inspection of the clinical component of these bioavailability studies was conducted at Cetero Research-Miami by ORA inspector Teresa I. Navas of FLA-DO. Bioequivalence reserve samples were collected from (b) (4) and forwarded to the (b) (4). Following the inspection (b) (4)), Form FDA 483 was issued. At the time of this review, OSI had not received the firm's response to the Form FDA 483 observations. Our evaluation of the Form FDA 483 observations follows:

1. **An investigation was not conducted in accordance with the signed statement of investigator.**
   Specifically, per forms FDA 1572 dated 11/25/08 for studies under protocols M1FT08001 and M1FT08002 a physician assistant (b) (4) and two physicians (b) (4) listed as sub-investigators. However, my review of the study source documents found more than 10 individuals (the following list is not all inclusive: (b) (4) were delegated tasks in the study, without documentary evidence of proper delegation of authority.

The clinical investigator Dr. Weiner did not document delegation of responsibilities for 19 individuals who conducted subjects' physical examinations, performed ECGs, administered drug products, drew blood samples, assessed subjects for adverse events, and obtained medical histories and laboratory data. The clinical investigator should have defined the roles each person would perform for the specific studies. Since the time of these studies, procedure (b) (4)SOP_03-PRE-001, entitled "Delegation of Authority," effective 02/15/2011, was amended to include individuals' study responsibilities. The observation may not impact most study outcomes, as the clinical staff was individually qualified to perform their roles according to their job descriptions or training.

2. **Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others. Specifically, on 2/3/09, subject #05; reference #44736 obtained a positive pregnancy test result during the 72 Hour visit to the clinic. A re-test performed at your firm on 2/4/09 confirmed this result. On (b) (6), the subject was admitted to the emergency room of a local hospital, the documentation revealed the subject had a miscarriage. Review of your firm's correspondence with the IRB revealed that your firm did not inform this event to the IRB within the 48 hours required time per protocol M1FT08001. In addition review of your Final Study Report submitted to the agency revealed that your firm also failed to include this event in the aforementioned report.**

Subject #05 was administered the reference product in period 1 on 1/3/09, and test product in period 2 (fasted) on 1/17/2009 and in period 3 (fed) on 1/31/2009. Subject #05 had a positive pregnancy test on 2/3/09, and her last menstrual period was 1/10/2009. Subject #05 reported vaginal bleeding and was diagnosed with a miscarriage on (b) (6) The IRB should have been informed of the subject's pregnancy and miscarriage within the required time per protocol M1FT08001. The miscarriage should be considered as an adverse event possibly related to dosing with the drug products or other study-related activities. DPARP and DCPII should evaluate whether to exclude this subject from the pharmacokinetic evaluations.

Bioanalytical samples for Studies M1FT08001 and M1FT08002 were analyzed at (b) (4) from February 12 to 25, 2009, and April 24 to May 5, 2009, respectively. Referencing FDA's Untitled Letter to (b) (4) issued on (b) (4), and to updated information provided on the FDA website, (b) (4):

"FDA is notifying pharmaceutical companies of the current actions that need to be taken pertaining to certain time frames.

- March 1, 2008, to August 31, 2009: The Agency will accept studies for submission and review if the sponsor performs an independent third-party data integrity audit using the Bioanalytical Electronic Raw Data Audit Plan (provided by FDA). Further, studies that were previously submitted as part of an approved or pending application will also need verification of data integrity by an independent third-party audit."

Given that the bioanalytical components of Studies M1FT08001 and M1FT08002 were completed prior to August 31, 2009, but after March 1, 2008, the sponsor needs to perform an independent third-party data integrity audit using the Bioanalytical Electronic Raw Data Audit Plan (provided by FDA).

Hence, OSI considers the data from these studies to be unreliable, unless a satisfactory independent third-party data integrity audit report is provided to the agency.

Conclusion:

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

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

Final Classification:

VAI – Cetero Research–Miami, Miami Gardens, FL
FEI 3008432144

cc:
OSI/Moreno
OSI/DBGC/Taylor/Haidar/Skelly/Dejernett/Chen/CF
CDER/OND/DPARP/Chowdhury
OCP/DCPII/Sahajwalla/Ping Ji
FLO-DO/Navas
CDER DSI PM TRACK
Draft: XC 9/5/2012,
Edit: MFS 9/5/2012; SHH 9/7/2012, WHT 9/10/2012
DSI: BE 6177; O:\Bioequiv\EIRCover\22556.tri.car.doc
FACTS: 1260578

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

/s/

XIKUI CHEN
09/10/2012

SAM H HAIDAR
09/11/2012

WILLIAM H TAYLOR
09/11/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 22556 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: not yet established Established/Proper Name: Carbinoxamine Dosage Form: ER Oral Suspension Strengths: 4mg/5ml		
Applicant: Tris Pharma Agent for Applicant (if applicable):		
Date of Application: 12-7-10 Date of Receipt: 12-8-10 Date clock started after UN:		
PDUFA Goal Date: October 8, 2011	Action Goal Date (if different):	
Filing Date: 2-2-11	Date of Filing Meeting: 1-19-11	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Systemic treatment of seasonal allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; dermatographism; as a therapy for anaphylactic reactions adjunctive to ephinephrine and other standard measures after the acute manifestations have been controlled; amelioration of the severity of allergic reactions to blood or plasma.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 102091	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	XX			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	XX			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	XX			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		x		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		x		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		x		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		x		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		x		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		x		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		x		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**x**			
Index: Does the submission contain an accurate comprehensive index?	**x**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**x**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	x			
Are all establishments and their registration numbers listed on the form/attached to the form?(*amendment submitted to include this information per the request of CMC)*	x			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	x			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	x			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with	x			

authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			x	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**x**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)[2](done)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	x			PERC date is 9-7-11

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		x		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	x			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	x			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		x		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		x		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		x		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	x			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**		x		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If yes, distribute minutes before filing meeting				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		x		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		x		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 19, 2010

BLA/NDA/Supp #: NDA 22556

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: Carbinoxamine

DOSAGE FORM/STRENGTH: ER Oral Suspension 4mg per 5ml

APPLICANT: Tris Pharma

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Systemic treatment of seasonal allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; dermatographism; as a therapy for anaphylactic reactions adjunctive to ephinephrine and other standard measures after the acute manifestations have been controlled; amelioration of the severity of allergic reactions to blood or plasma.

BACKGROUND: Original NDA

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Miranda Raggio	Yes
	CPMS/TL:	Sandy Barnes	No
Cross-Discipline Team Leader (CDTL)	Lydia Gilbert-McClain		Yes
Clinical	Reviewer:	Peter Starke	Yes
	TL:	Lydia Gilbert-McClain	Yes
Social Scientist Review (*for OTC products*)	Reviewer:	None	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	None	
	TL:		
Clinical Microbiology (*for antimicrobial*	Reviewer:	None	

products)			
	TL:		

Clinical Pharmacology	Reviewer:	Ping Ji	Yes
	TL:	Yun Xu	Yes
Biostatistics	Reviewer:	Joan Buenconsejo	Yes
	TL:	Same	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Asoke Musherjee	Yes
	TL:	Molly Topper	Yes
Statistics (carcinogenicity)	Reviewer:	None	
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	None	
	TL:		
Product Quality (CMC)	Reviewer:	Ted Carver	Yes
	TL:	Alan Schroeder	Yes
Quality Microbiology *(for sterile products)*	Reviewer:	None	
	TL:		
CMC Labeling Review	Reviewer:	None	
	TL:		
Facility Review/Inspection	Reviewer:	None	
	TL:	None	
OSE/DMEPA (proprietary name)	Reviewer:	Nichelle Rashad	Yes
	TL:		
OSE/DRISK (REMS)	Reviewer:	Nichelle Rashad	Yes
	TL:		
OC/DCRMS (REMS)	Reviewer:	None	

	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	None	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	None	
	TL:		
Other reviewers	None		
Other attendees	None		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: Biopharm team will submit clinical pharmacology site inspection request to DSI	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

reason. For example: ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☐ FILE ☒ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**: No stats review required	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: BY CMC	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Division Director, Badrul A. Chowdhury, M.D., Ph.D.

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

MIRANDA B RAGGIO
08/30/2011

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary, Allergy, and Rheumatology Products

Application Number: 22556

Name of Drug: Carbinoxamine ER Oral Suspension 4mg/5ml

Applicant: Tris Pharma

Material Reviewed:

Submission Date(s): 12-7-10

Receipt Date(s): 12-8-10

Submission Date of Structure Product Labeling (SPL): 12-7-10

Type of Labeling Reviewed: SPL and WORD

Background and Summary

Tris Pharma submitted an original 505(b)(2) NDA on December 8, 2010, for carbinoxamine ER oral suspension for the treatment of seasonal and perennial allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis dur to inhalant allergens and foods, mild, uncomplicated allergic skin manifestations of urticaria and angioedema, dermatographism, anaphylactic reactions adjunctive to ephinephrine, and ameliorationof the severity of allergic reactions to blood or plasma in patients (b) (4)

Review

The following issues/deficiencies have been identified in the proposed labeling submitted on December 7, 2010:

HIGHLIGHTS

1. RECENT MAJOR CHANGES

   Remove this section. It is not required for original NDAs.

2. INDICATIONS AND USAGE

If the drug is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class as follows: "(Drug) is a (name of class) indicated for (indications(s))." If the drug is not a member of an established pharmacologic class, the statement should be omitted.

For the pharmacological class web page see http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm

.

3. ADVERSE REACTIONS

This section should include not only a list of the most frequently occurring adverse reactions, but also the criteria used to determine inclusion(e.g., incidence rate great than x%).

4. USE IN SPECIFIC POPULATIONS

The pregnancy category designation is not appropriate for inclusion in Highlights because the pregnancy category, in isolation, tends to oversimplify the risks of drugs in pregnancy, and, as a result, may be confusing. Therefore, do not include the pregnancy category in the Highlights section.

TABLE OF CONTENTS

5. USE IN SPECIFIC POPULATIONS

Any required section, subsection, or specific information that is clearly inapplicable may be omitted from the FPI. However, the numbering does not change. This is important to remember for the required subsections in Sections 8 (Use in Specific Populations), 12 (Clinical Pharmacology) and 13 (Nonclinical Toxicology). Subsection 8.2, Labor and Delivery, has been omitted but the following subsections were renumbered. Revise the numbering as 8.1, 8.3, 8.4, 8.5, in the Table of Contents. Revise the corresponding subsections in the FPI accordingly.

FULL PRESCRIBING INFORMATION

6. CONTRAINDICATIONS

For each contraindications, use numbered subsections headings OR bullets.

7. WARNINGS AND PRECAUTIONS

A subheading should be used for each adverse reaction, syndrome, or constellation of reactions prioritized based on relative public health significance. (The subheading should convey the risk.)

Recommendations

These deficiencies will be included in the 74-day letter to Tris Pharma. The updated version of

labeling will be used for further labeling discussions.

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager

Supervisory Comment/Concurrence:
S. Barnes/ January 26, 2011

Sandy Barnes
Chief, Project Management Staff

Drafted: Miranda Raggio/December 21, 2010
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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/s/

MIRANDA B RAGGIO
08/30/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	August 29, 2011
Reviewer:	Chi-Ming (Alice), Tu PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Carlos M. Mena-Grillasca, RPh, Team Leader Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
Drug Name(s):	Karbinal ER (Carbinoxamine Maleate) Extended-release Oral Suspension, 4 mg/5 mL
Application Type/Number:	NDA 022556
Applicant/sponsor:	Tris Pharma
OSE RCM #:	2011-169

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the container label submitted on August 19, 2011 and [redacted] for Karbinal ER (Carbinoxamine Maleate) Extended-release Oral Suspension, 4 mg/5 mL, for areas of vulnerability that can lead to medication errors in response to a request from the Division of Pulmonary, Allergy and Rheumatology Products.

1.1 PRODUCT INFORMATION

Karbinal ER (Carbinoxamine maleate) Extended-release Oral Suspension, 4 mg/5 mL, is an antihistamine with anticholinergic and sedative properties. The proposed indication is for the symptomatic treatment of:

- 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 reaction adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled
- Amelioration of the severity of allergic reaction to blood or plasma

The recommended [redacted] dosage is [redacted] (6 to 16 mg) administered orally every 12 hours, and [redacted] (0.2 to 0.4 mg/kg/day) administered orally every 12 hours in [redacted] Karbinal ER will be supplied in [redacted] It should be stored at room temperature (25°C).

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed container label and [redacted] for any vulnerability that can lead to medication errors. We also searched the FDA Adverse Event Reporting System (AERS) Database to determine if any medication errors due to labels and labeling have occurred with the currently marketed immediate release formulations of Carbinoxamine Maleate Oral Solution. We could not determine whether currently marketed Carbinoxamine Maleate Oral Solution is distributed with an accompanying dosing device.

2.1 LABELS AND LABELING

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 19, 2011
- [redacted]

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2.2 ADVERSE EVENT REPORTING SYSTEM (AERS)

DMEPA conducted previous AERS searches on August 9, 2011 for medication errors involving Carbinoxamine Maleate. The search criteria included "clistin%" for trade and verbatim terms, and "carbinoxamine%" for active and verbatim terms with MedDRA High Level Group Term "Medication Errors." The date of the search was limited from our last search date of January 12, 2006 (OSE RCM#06-0064).

Foreign reports were excluded because foreign label and labeling may differ from those marketed in the United States. Duplicate reports were combined into cases. The cases were manually reviewed to determine if a medication error occurred. The cases that described a medication error were further evaluated by the reviewer to identify contributing factors to the error. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review were excluded from further analysis.

3 RESULTS

The following sections summarize our analysis of the container label and (b) (4), as well as the results from our AERS search.

3.1 LABEL AND LABELING

3.1.1 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)

3.2 ADVERSE EVENT REPORTING SYSTEM (AERS)

Our search of the AERS database for Carbinoxamine Maleate retrieved twelve reports. However, after combining duplicate reports and excluding cases for the reasons stated in Section 2.2, no medication error applicable to this review was identified. See Appendix C for ISR numbers of the twelve retrieved reports.

4 CONCLUSIONS AND RECOMMENDATIONS

We conclude that the proposed container label and (b) (4) introduce vulnerability that can lead to medication errors. We provide recommendations to the Applicant in Section 4.1 to mitigate the risk of such errors. We request these recommendations be communicated to the Applicant for revision prior to approval.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

4.1 COMMENTS TO THE APPLICANT

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 red 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 (one (b) (4)) contains 4 mg of Carbinoxamine Maleate, (b) (4)" 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 (b) (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.

B. [redacted] (b) (4)

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/s/

CHI-MING TU
08/29/2011

CARLOS M MENA-GRILLASCA
08/29/2011

CAROL A HOLQUIST
08/29/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: August 11, 2011

To: Miranda Raggio, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Robyn Tyler, DTC Group Leader
Matthew Falter, Regulatory Review Officer
Olga Salis, Regulatory Health Project Manager
Michael Wade, Regulatory Health Project Manager
(DDMAC)

Subject: NDA # 022556
DDMAC labeling comments for Carbinoxamine (carbinoxamine maleate) Extended Release Oral Suspension

---

DDMAC has reviewed the proposed Prescribing Information (PI) and Carton and Container Labeling for NDA 022556 submitted for consult on January 21, 2011.

DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled "SCPINDA 22556 draft-labeling8-4-11.doc" that was sent via email from DPARP to DDMAC on August 4, 2011. DDMAC's comments on the PI are provided directly in the marked-up document attached (see below).

DDMAC has reviewed the proposed container labels submitted by the applicant and available in the EDR at:

- \\cdsesub1\EVSPROD\NDA022556\\0000\m1\us\draft-container-label.pdf
- \\cdsesub1\EVSPROD\NDA022556\\0003\m1\us\draft-container-label.pdf
- \\cdsesub1\EVSPROD\NDA022556\\0005\m1\us\container-label.pdf

We have no comments at this time on the proposed container labeling.

Thank you for the opportunity to comment on these materials.

If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
08/11/2011