

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-556Orig1s000**

**OTHER ACTION LETTERS**



NDA 22556

**COMPLETE RESPONSE**

Tris Pharma  
2033 Route 130  
Suite D  
Monmouth Junction, NJ 08852

Attention: W. Scott Groner  
Director, Regulatory Affairs and Compliance

Dear Mr Groner:

Please refer to your New Drug Application (NDA) dated December 7, 2010, received December 8, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for carbinoxamine ER oral suspension.

We acknowledge receipt of your amendments dated December 30, 2010, January 21, February 28, April 15, June 6, 13, and 27, July 11 and 15, August 15 and 22, and September 22, 2011.

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

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described the actions or information required to resolve these deficiencies in some cases.

**CLINICAL PHARMACOLOGY**

**Deficiency**

1. FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b)(4). The pervasiveness and egregious nature of the violative practices by (b)(4) has led FDA to have significant concerns that the bioanalytical data generated at (b)(4) from (b)(4) (b)(4), as part of studies submitted to FDA in New drug Applications (NDA) and Supplemental New drug Applications (sNDA) are unreliable. The analytical data for your clinical pharmacology studies MIFT08001 and MIFT08002 submitted to support your NDA for carbinoxamine extended release oral suspension were generated in the identified time interval and are unreliable to support your NDA.

Information Needed to Resolve the Deficiency

This deficiency may be addressed by doing the following:

- a. Reanalyze all plasma samples and evaluate the results of the reanalysis data based on regression analysis and Incurred Sample Reanalysis (ISR) approaches if plasma samples for your studies are still available. For the conformational reanalysis endpoint, calculate the % Difference using the corrected repeat value based on the actual plasma stability.

OR

- b. Repeat the clinical pharmacology studies if plasma samples for your studies are not available.

OR

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

**PRODUCT QUALITY**

Deficiency

2. In-process controls for (b) (4) mixing are not included in the manufacturing process.

Information Needed to Resolve the Deficiency

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

Deficiency

3. There is only one identity test used for the release of the drug product.

Information Needed to Resolve the Deficiency

Include a second identity test, in addition to the HPLC identity test, in the release testing of the drug product. Refer to ICH Q6A for guidance.

Deficiency

4. Further testing of the drug product in the alternate packaging (b) (4) (b) (4) should include testing for (b) (4) at the (b) (4)-month stability timepoint.

Information Needed to Resolve the Deficiency

With respect to the drug product in the alternate container (b) (4) (b) (4) used to package test Batch TB-085A, provide test results at the (b) (4) month stability time point for levels of (b) (4) and for levels of the common impurities of (b) (4)

## **MICROBIOLOGY**

### Deficiency

5. There is no test method to recover *Burkholderia cepacia* complex organisms in the final product.

### Information Needed to Resolve the Deficiency

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

### Deficiency

6. Preservative effectiveness testing has not been conducted on three batches of drug product.

### Information Needed to Resolve the Deficiency

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

## **LABELING**

7. Submit draft carton and container labeling revised as follows:

- a. Container Label

1. Revise the established name to read as follows:  
(Carbinoxamine maleate) Extended-release Oral Suspension
2. Revise the font color of the statement “Strawberry Banana Flavored” from (b) (4) black. As currently presented, the statement competes with the prominence of the proprietary name and the established name.
3. Revise the company logo and company name so they do not compete with the prominence of the proprietary name and the established name. This may be achieved by relocating the company logo and name to below the manufacturer statement on the side panel, or by reducing the size of the company name and logo.
4. Relocate the statement “SHAKE WELL BEFORE USE” to the principal display panel and display with adequate white space. This may be achieved by relocating the “Rx Only” statement or the “Strawberry Banana Flavored” statement to the side panel.
5. Revise the statement “Each 5 mL (b) (4) contains 4 mg of Carbinoxamine Maleate, (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.



### **FACILITY INSPECTIONS**

During a recent inspection of the Tris Pharma manufacturing facility, located at 2033 Route 130, Suite D, Monmouth Junction, NJ 08852, for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

### **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary, Allergy, and Rheumatology Products regarding the extent and format of your safety update prior to responding to this letter.

### **ADDITIONAL COMMENTS**

1. Revise the stability commitment noted in your original NDA submission to state that stability results will be submitted to NDA annual reports.
2. Regarding the environmental assessment for categorical exclusion, provide a statement regarding knowledge of any extraordinary circumstances.
3. Information on any overages used in the manufacture of the drug product is not provided in the NDA submission. Clarify if any overages were used in the manufacture of the drug product.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Miranda Raggio, Senior Regulatory Project Manager, at (301) 796-2109.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

/s/  
-----

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