CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-734

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-734

Taro Pharmaceuticals, U.S.A., Inc,
5 Skyline Drive
Hawthorne, N.Y., 10532

Attention: Kalpana Rao
Vice President, Regulatory Affairs

Dear Ms. Rao:

Please refer to your new drug application (NDA) dated January 19, 2004, received January 21, 2004, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Children's ElixSure™ - 24 Hour Antihistamine (loratadine oral suspension) 5 mg/5 mL.

We also refer to your amendments dated April 20, and 23, May 6, August 4, and 26, and September 2 and 16, 2004.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to adequately resolve the following deficiencies.

1. You have not succeeded in demonstrating that Children's ElixSure™-24 hr Antihistamine (Loratadine Oral Suspension) 5mg/5mL is bioequivalent to the reference standards of Claritin® 10mg Tablets or Claritin® Syrup. Pharmacokinetic studies show that compared to the reference standards of Claritin® Tablets and Claritin® Syrup, a key pharmacokinetic parameter (Cmax) for Children's ElixSure™-24 hr Antihistamine fell below the bioequivalence range, which raises the question of the efficacy of Children's ElixSure™-24 hr Antihistamine. Because the Cmax and AUC for your Children's Elixsure™-24 hr did not exceed the upper bioequivalence limits, the safety of your product has been established. Additional clinical studies with Children's ElixSure™-24 hr Antihistamine will be necessary to demonstrate efficacy. If you choose to reformulate the suspension and repeat the BA/BE studies, the safety and efficacy of the new formulation will need to be established.

2. The following comments pertain to the [redacted] drug substance specifications and test methods that were submitted in your application.

   a. '[redacted]' is too vague as an appearance specification. Describe the color in a quantitative way (e.g., [redacted] color index).

b. Limit unknown individual impurities to less than [redacted] each.

c. Provide your detailed method for particle size analysis.

3. The following comments pertain to the release specification of the drug product.

"Homogeneity" testing and acceptance criteria has been listed on the specifications sheet. However, batch analysis data do not show any homogeneity testing as being performed on the batch. Provide "homogeneity" data for batch release.

4. The following comment pertains to the analytical procedure SOP # A-1134.

a. Resolution sample chromatogram (Figure 2) shows [redacted] The second peak interferes with the loratadine peak. Identify the two peaks and calculate the resolution between loratadine peak and [redacted] peak two.

b. Provide appropriately expanded versions of chromatograms (Figures 2, 4, and 8).

5. The following comments pertain to the container closure systems.

a. The following drug master files, [redacted] are deficient and the DMF holders have been notified.

b. Provide extractables /leachables data for the snap top closure [redacted]

c. Provide extractables/leachables data [redacted]

6. The following comments pertain to the [redacted] bulk sample bag:

a. Provide components and quantitative composition of the sample bag and the screw cap.

b. Provide extractables/leachables data [redacted] including the screw cap.

c. Provide appropriate references to the indirect food additive regulations.

d. Provide pertinent data for protection from light exposure, reactive gases, solvent loss, and moisture permeation.

7. The following comment pertains to the drug product stability.

You have proposed the acceptance criterion for viscosity to not less than [redacted] 8 oz packages. Modify the acceptance criterion for viscosity e.g., to not less than [redacted] or justify your proposal with data.

8. Our field investigator could not complete inspection of your manufacturing facility at [redacted] because the facility was not ready for inspection. Satisfactory inspection is required before this application may be approved.

9. In addition, it will be necessary for you to submit draft labeling revised as follows:

a. In this submission, you use three different trade names for this drug product:

- "Children's ElixSure - 24 hr Antihistamine" (in the cover letter dated January 19, 2004, and Form 356h)
- [redacted]
- [redacted]

Indicate which tradename you propose to use and revise the labels accordingly. After you indicate the tradename you intend to use for your drug product, we will need to consult with the Division of Medication Errors and Technical Support for comments on the proposed name.

b. [redacted]

c. Revise the [redacted] 8 fl. oz. carton and immediate container labels as follows and resubmit new proposed labeling for our review and comment:

(1) **Immediate Container Labels:**

(a) **[[redacted] 8 fl. oz.]:**

(i) Add the potency of the formulation (i.e., "5 mg/5 mL") as part of the established name.

(ii) Add the pharmacological category (i.e., "Antihistamine") of the product immediately following the established name (see 21 CFR 201.61) (i.e., Loratadine Suspension - 5 mg/5 mL Antihistamine).

(iii) "*Directions*" section:

i) Add the population group, "children under 2 years of age", followed by the text "ask a doctor" to the dosing table. This population group must be included in the "*Directions*" section for complete dosing information.

ii) For labeling consistency, we recommend that the presentation of dosing information for the four population groups appear in the following order: adults and children 6 years and over; children 2 to under 6 years of age;

children under 2 years of age; and lastly, consumers with liver or kidney disease.

(b) [redacted]

(c) [[redacted] 8 fl. oz.]:

(i [redacted]

(ii) Under the heading "*Other information*", revise the bulleted storage temperature statement to reflect the USP controlled room temperature range (i.e., "store between 20 - 25° C (68 - 77° F)"), unless data can be provided to support a wider temperature range.

(d) Tamper-evident packaging statement:

(i) [redacted]

(ii) [[redacted] 8 fl. oz.]: Relocate the tamper-evident packaging statement (i.e., "Do not use if [redacted] safety band is torn or missing") on the side panel to appear more prominently and conspicuously as described in 21 CFR 211.132.

(2) **Carton Labels ([redacted] 8 fl. oz.):**

(a) PDP:

(i) Include the potency of the formulation (i.e., 5 mg/5 mL) as part of the established name.

(ii) Add the pharmacological category (i.e., "Antihistamine") immediately following the established name (see 21 CFR 201.61).

(iii) Add an asterisk immediately after the statement "Non-Drowsy" and a statement to define the "*". The asterisk refers consumers to the following statement: "*When taken as directed. See Drug Facts Panel." This statement must appear at the bottom of the PDP in conspicuous print.

(b) [redacted]

(c) **Drug Facts panels:**

(i) [redacted]

(ii) **[8 fl. oz.]**:

i) The information following "Distribution by" and the information following "Subject to some * * * " should not appear in this location. This information must appear outside of the "Drug Facts" information (see 21 CFR 201.66(c)(7)).

ii) "*Questions or comments?*" section: If this heading and subsequent information is included in the drug products' label, it must not appear as a separate boxed area. For labeling consistency, this information must appear within the Drug Facts box (see 21 CFR 201.66(d)(7) and (d)(8)) and as the last section within the Drug Facts enclosure (see 21 CFR 201.66(c)).

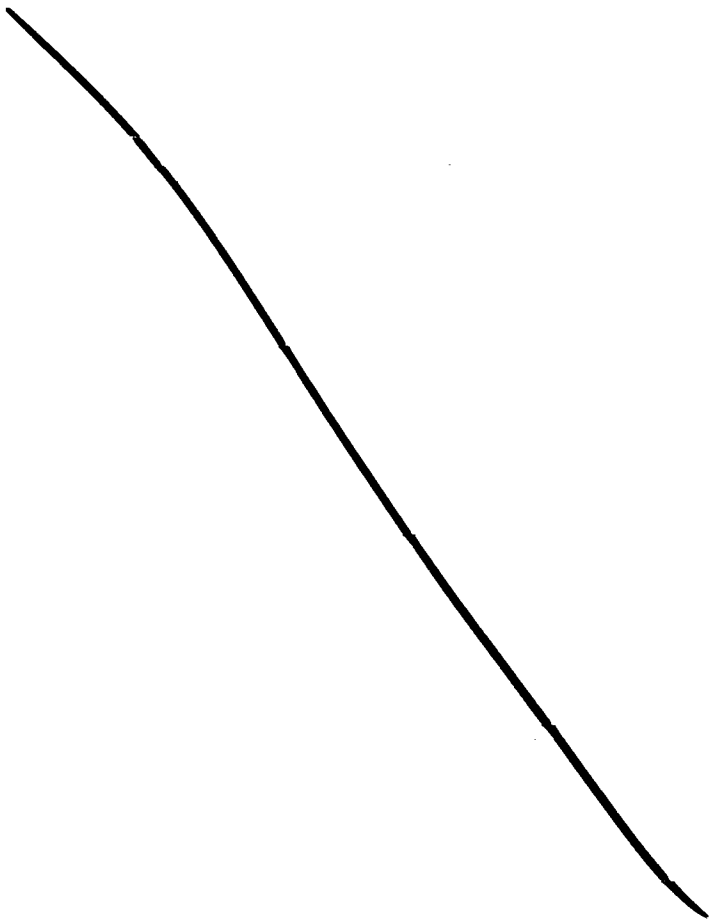
(iii) [redacted] **8 fl. oz.]**

i) "*Directions*" section:
   (a) Add the population group, "children under 2 years of age", followed by the text "ask a doctor" to the dosing table. This population group must be included in the "*Directions*" section for complete dosing information.

(b) For labeling consistency, we recommend that the presentation of dosing information for the four population groups appear in the following order: adults and children 6 years and over; children 2 to under 6 years of age; children under 2 years of age; and lastly, consumers with liver or kidney disease.

ii) "*Other information*" section: Revise the storage temperature to read: "store between 20 - 25°C (68 to 77 °F)". The USP controlled room temperature range should appear here, unless data are provided to support a wider temperature range.

iii) "*Inactive ingredients*" section: List the inactive ingredients in alphabetical order (see 21 CFR 201.66(c)(8)).



If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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 and Allergy Drug Products regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

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

If you have any questions, call Anthony M. Zeccola, Regulatory Management Officer, at (301) 827-1058.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
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/

Charles Ganley
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