CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-734

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-734 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: 1/21/04 **Action Date:** 11/19/04

HFD 570 **Trade and generic names/dosage form:** Children's ElixSure™ - 24 Hour Antihistamine (loratadine oral suspension) 5 mg/5 mL.

Applicant: Taro Pharmaceuticals **Therapeutic Class:**

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): _____

Indication #1: [redacted] **in patients 2 years or older.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

XNo: Please check all that apply: X **Partial Waiver** _____ **Deferred** X **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	_____	**kg**	_____	**mo.** _____	**yr.** 0	**Tanner Stage** _____
Max	_____	**kg**	_____	**mo.** _____	**yr.** L.T. 2	**Tanner Stage** _____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**

XDisease/condition does not exist in children

- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**

- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.** 2 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** Adult **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

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/s/

Anthony Zeccola
11/17/04 02:59:48 PM

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: October 3, 2005

TIME: 4:30 PM

APPLICATION: NDA 21-734

Representative of FDA

Anthony Zeccola, Senior Regulatory Management Officer

Representatives of Taro Pharmaceuticals

Kalpana Rao, Vice President, Regulatory Affairs

Background

This teleconference was held to discuss labeling changes proposed by DMETS in response to Taro's September 2, 2005 label submission. DMETS completed a review of Taro's labeling that was included with their April 1, 2005 submission. This labeling proposed the trade name "Children's [redacted] , but during the review of the NDA, Taro decided not to market this product under the [redacted] trade name and proposed a new name for the product, [redacted] Upon review of the September 2, 2005 submission, Carol Holquist of DMETS said that have the qualifier [redacted] ' is not acceptable as an establishment name and that is should be removed. She also said that the Taro should increase the prominence of the dosage strength on the product labeling.

Discussion

Mr. Zeccola informed Ms. Rao of the DMETS determination. Ms. Rao agreed to both changes and to amend the NDA accordingly.

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/s/

Anthony Zeccola
10/4/2005 11:03:32 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation

FACSIMILE TRANSMITTAL SHEET

DATE: September 14, 2005

To: Kalpana Rao	**From:** Elaine Abraham Project Manager
Company: Taro Pharmaceuticals, USA, Inc.	Division of Nonprescription Clinical Evaluation Office of Nonprescription Products
Fax number: (914) 593-0078	**Fax number:** (301) 827-2315
Phone number: (914) 345-9001	**Phone number:** (301) 827-2276 or (301) 796-0843 after September 16th

Subject: NDA 21-734 additional labeling comments

Total no. of pages including cover: 2

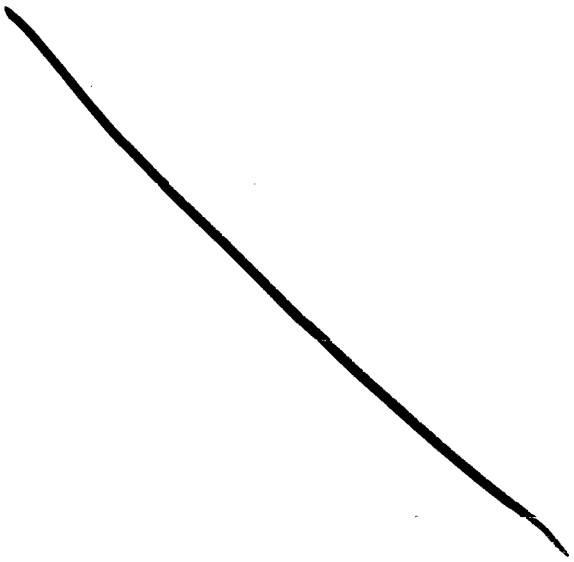
Comments:

Document to be mailed: YES X NO

Please refer to your new drug application NDA 21-734 resubmission dated April 1, 2005, and labeling amendments dated May 5, August 30, and September 2, 2005, for loratadine oral suspension 5mg/5mL, and our faxes of August 15 and September 1, 2005 with labeling comments. We have additional labeling comments in response to your September 2 amendment included in this fax.

In order to ensure a timely action for this new drug application, we request that you respond to the issues listed below as soon as possible.

We have the following comments on your labeling:



c. *8 fl. oz. immediate container labeling:*

read "*When taken as directed. See Drug Facts panel." This is the standard asterisk text for OTC loratadine-containing drug products.

2. We remind you that if an insert is to be used, a final printed Drug Facts insert (i.e., as submitted in your submission dated May 5, 2005) must be submitted prior to the action due date.

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/s/

Elaine Abraham
9/14/2005 07:22:34 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation

FACSIMILE TRANSMITTAL SHEET

DATE: September 1, 2005

To: Kalpana Rao	**From:** Elaine Abraham Project Manager
Company: Taro Pharmaceuticals, USA, Inc.	Division of Nonprescription Clinical Evaluation Office of Nonprescription Products
Fax number: (914) 593-0078	**Fax number:** (301) 827-2315
Phone number: (914) 345-9001	**Phone number:** (301) 827-2276 or (301) 796-0843 after September 16th

Subject: NDA 21-734 additional labeling comments

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES X NO

Please refer to your new drug application NDA 21-734 resubmission dated April 1, 2005, and labeling amendment dated May 5, 2005, for loratadine oral suspension 5mg/5mL, and our fax of August 15, 2005 with labeling comments. We have additional labeling comments included in this fax.

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

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/s/

Elaine Abraham
9/1/2005 10:59:48 AM
CSO

Appendix B to NDA Regulatory Filing Review
NDA 21-734 Taro Loratadine
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Loaratdine Oral Syrup 20-641

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☒ NO ☐

   (***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))

*If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☒ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***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.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in 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 capsules to solution"). This application provide for a change in dosage form from oral syrup to oral suspension.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ NO ☐

11. 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.)

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

☐ 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):

☐ 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)
Patent number(s): 4,659,716 4,863,931 6,132,758

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 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):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES ☒ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES ☒ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A ☐ YES ☒ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A ☒ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☐ NO ☒

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/s/

Anthony Zeccola
8/29/2005 01:25:06 PM
CSO
Regulatory Filing Review

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation

FACSIMILE TRANSMITTAL SHEET

DATE: August 15, 2005

To: Kalpana Rao	**From:** Elaine Abraham Project Manager
Company: Taro Pharmaceuticals, USA, Inc.	Division of Nonprescription Clinical Evaluation Office of Nonprescription Products
Fax number: (914) 593-0078	**Fax number:** (301) 827-2315
Phone number: (914) 345-9001	**Phone number:** (301) 827-2276

Subject: NDA 21-734 labeling comments

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES X NO

Please refer to your new drug application NDA 21-734 resubmission dated April 1, 2005, and labeling amendment dated May 5, 2005, for [redacted] (loratadine 5mg/5ml) oral suspension.

In order to ensure a timely action for this new drug application, we request that you respond to the issues listed below as soon as possible.

1 Page(s) Withheld

____ Trade Secret / Confidential

✓ Draft Labeling

____ Deliberative Process

Withheld Track Number: Administrative- 2

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/s/

Elaine Abraham
8/15/2005 12:38:33 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: August 17, 2005

To: Kalpana Rao

Fax No.: 914-593-0078

From: Anthony M. Zeccola

Subject: CMC Request for Information
Taro Pharmaceuticals
NDA 21-734 [redacted]

Number of Pages: 3 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

{See appended electronic signature page}

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

We are reviewing your submission to NDA 21-734 dated April 1, 2005, and have the following request for information.

1. [redacted] Tighten the viscosity acceptance criterion so that it is based on and reflective of all of the relevant data. [Response 7 to the November 19, 2004 Approvable letter]

2. It appears that you have now full term data. Provide updated stability data as part of your response.

3. Provide three copies of an updated Methods Validation Package.

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/s/

Anthony Zeccola
8/17/2005 11:45:09 AM
CSO

3 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 3

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: July 20, 2005

TIME: 11:00 AM

APPLICATION: NDA 21-734

Representative of FDA

Anthony Zeccola, Senior Regulatory Management Officer

Representatives of Taro Pharmaceuticals

Kalpana Rao, Vice President, Regulatory Affairs
Abraham Yacobi, Ph.D., Senior Vice President, Research and Development

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Background

This teleconference was held as follow-up to a telephone conversation between Mr. Zeccola, Kalpana Rao and Dr. Yacobi, which took place on July 11, 2005, and a letter from Taro Pharmaceuticals dated July 12, 2005. During the July 11th discussion Mr. Zeccola informed Taro that the Agency was actively reviewing NDA 21-734, but that it would not be possible to take action on the application by July 15th as discussed in previous conversations between Mr. Zeccola and Ms. Rao. During the July 11th discussion, Mr. Zeccola said that the Agency was aware of Taro's request and would make every effort to complete the review prior to the PDUFA due date, but could not make any promises as to the actual action date beyond what is required under PDUFA. Dr. Yacobi asked if Taro could make the request for "expedited review" again, Mr. Zeccola responded that it was up to Taro, but it was unlikely that the Agency's position would change

Discussion

Mr. Zeccola informed Ms. Roa and Dr. Yacobi that their July 12, 2005 letter had been received by the Agency and discussed with Drs. Chowdhury and Ganley. The two Division Directors reiterated their previous comments, the Agency will do what it can to complete the review of this application as quickly as possible, but cannot commit to completion of the review prior to what is required under PDUFA. Furthermore, there is no basis for a priority review, which requires that applications granted this status meet an unmet public health need, "A priority review designation is intended to direct overall attention and resources to the evaluation of applications for products that have the potential for providing a significant treatment, preventative or diagnostic therapeutic advance, as compared to standard applications." (Source: Guidance for Industry – Available Therapy, July 2004). Currently there are several loratadine products available over-the-counter, included formulations specifically intended for pediatric use. Dr. Yacobi inquired as to an anticipated action date and outcome of the NDA review and whether there would be any comments or information requests from

the individual reviewers. Mr. Zeccola declined to comment, stating that if and when comments/information requests become available they will be provided to Taro, and that it would not be appropriate to comment on an anticipated action date (beyond the PDUFA goal date) or the anticipated action at this time.

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/s/

Anthony Zeccola
7/21/05 05:40:55 AM
CSO

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

NDA Labeling Amendment Review

NDA # 21-734

Submission Date : 4/01/05 and 5/5/05
Review Date : 5/25/04

Applicant: Taro Pharmaceuticals U.S.A., Inc.

Applicant's Representative: Kalpana Rao
Vice President, Regulatory Affairs (Global)

Drug: Claritin Allergy
Loratadine Oral Suspension - 5 mg/5 mL

Pharmacological Category: Antihistamine

Submitted: Final printed labeling:

[redacted]

2. 8 fl. oz. (240 mL) carton and immediate container label

[redacted]

Background:

Taro Pharmaceuticals Inc., is seeking approval under a 505(b)(2) application (NDA 21-734) to market over-the-counte[redacted]8 fl. oz, [redacted] (loratadine oral suspension - 5 mg/5 mL) drug products for the relief [redacted]

The sponsor has indicated that it has changed the initial NDA proposed trade name "Children' ElixSure – 24 hr. Antihistamine" to [redacted]

The sponsor's initial resubmission of April 1, 2005, included draft labeling for the above-mentioned SKUs in response to the labeling comments included in FDA's Approvable letter dated November 19, 2004. The April 1, 2005 revised draft labeling appeared acceptable with the exception of the following:

[redacted]

[redacted]

Reviewer Comments:

In the most recent submission of May 5, 2005, Taro Pharmaceuticals resubmitted final printed labeling for the [redacted]' 8 fl. oz. SKUs. The sponsor chose to return to the format originally approved for the Claritin product line at the time of the Rx-to-OTC switch.

The revised labeling and Drug Facts annotated specifications are acceptable. However, the agency notes that on the display tray, the asterisk statement " When taken as directed. See Drug Facts Panel" appears somewhat shaded in color. The agency recommends that this text be made more prominent or appear with the same color intensity as the text declaring the net quantity of contents [redacted]

Recommendation:

1. An approval letter can be issued to the sponsor based on the final printed carton and immediate container labels for the [redacted] 8 fl. oz. SKU, as well as final printed Drug Facts insert and display tray labeling submitted on May 5, 2005.
2. Inform the sponsor of the following:
    a. The word "New" in the phrase "New! NonSpil Technology" must be deleted from the PDP six months after introduction into the market place.

[redacted]

Cazemiro R. Martin
Reg. Review Chemist/IDS

Concur: Marina Chang, R.Ph.
Team Leader

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/s/

Cazemiro Martin
5/25/05 11:49:34 AM
INTERDISCIPLINARY

Marina Chang
5/25/05 12:48:03 PM
INTERDISCIPLINARY

Marina Chang
5/25/05 12:53:47 PM
INTERDISCIPLINARY

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 3, 2004

TIME: 1:45 PM

LOCATION: 10B45 Conference Room

APPLICATION: NDA 21-734 Children's Elixsure 24 hr Antihistamine

FDA Representatives:

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Shinja Kim, Ph.D., Pharmacology and Biopharmaceutics Reviewer
Emmanuel Fadiran, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Sally Seymour, M.D., Medical Officer
Eugene Sullivan, Deputy Division Director
Anthony M. Zeccola, Regulatory Management Officer

Taro Pharmaceuticals Representatives:

Daniel Moros, M.D., Vice Chairman
Kalpana Rao, Vice President, Regulatory Affairs

Background

This teleconference was held at the request of Taro Pharmaceuticals in response to the Approvable Letter to NDA 21-734, dated November 19, 2004. Taro requested the teleconference to seek clarification to our first deficiency comment in that letter.

Discussion

Taro opened the discussion by stating that based on the results of the bioequivalence data that was submitted with this application; it is their belief that their product is bioequivalent to the reference product (Claritin Syrup). In making this argument, Taro stated that their product produced plasma concentrations within the ranges produced by Claritin Syrup and Claritin Tablets. They further stated that Claritin Syrup and Tablets are not bioequivalent and that their product should be viewed in the same light as Claritin Tablets (which achieved lower plasma levels than those seen in Claritin Syrup as discussed in Agency reviews of those to products). Dr. Sullivan pointed out that while their observation regarding the Claritin products is true, the analogy could not be extrapolated to Taro's product. In the case of the Claritin products, efficacy studies were conducted in both the syrup and the tablets. Although the tablets did not achieve the same plasma levels, studies using tablets demonstrated efficacy. Given the different

performance of the Taro product, especially the lower peak plasma concentration levels, efficacy data would be needed demonstrate that the levels achieve were adequate.

Given this situation, Taro requested clarification on their options approval of their product. Dr. Chowdhury said that they have 3 possible options:

1. Reformulate their product and conduct studies that demonstrate acceptable bioequivalence with the reference product.

2. Demonstrate bioequivalence their current product and the reference product.

3. Conduct Clinical trials with their current product to show efficacy.

Taro wanted to know if it would be acceptable to conduct one large, fasted B.E. study against Claritin Tablets. Dr. Fadiran said this would be acceptable, that data should be presented to the Agency using geometric mean and that our review would focus on equivalence with the parent drug (metabolite data is viewed as supportive). Dr. Sullivan added that while this is acceptable, it is the Agency is pessimistic about option 2.

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/s/

Anthony Zeccola
12/6/2005 10:00:27 AM

Memorandum of Telephone Facsimile Correspondence

Date: November 30, 2004

To: Kalpana Rao
Vice President, Regulatory Affairs

From: Anthony M. Zeccola

Subject: NDA 21-734 Teleconference Request

Total Pages: 3 including this page and electronic signature page

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

{See appended electronic signature page}

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

As discussed during our November 24, 2004 telephone conversation, I have scheduled the teleconference that you requested to take place on Friday December 3, 2004 at 1:45. Please let me know what number we should call you at. The following personnel will represent the Division of Pulmonary and Allergy Drug Products during this discussion:

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Eugene Sullivan, MD, Deputy Division Director
Sally Seymour, M.D., Medical Officer
Shinja Kim, Ph.D., Biopharmaceutics Reviewer
Emmanuel Fadiran, Ph.D., Biopharmaceutics Team Leader
Anthony Zeccola, Regulatory Management Officer

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/s/

Anthony Zeccola
11/30/04 04:25:21 PM

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

NDA Labeling Review - Addendum

NDA # 21-734/BZ

Submission Date : 5/06/04
Review Date : 9/28/04

Applicant: Taro Pharmaceuticals U.S.A., Inc.

Applicant's Representative: Kalpana Rao
Vice President, Regulatory Affairs

Drug: Children's ElixSure - 24 hr Antihistamine
Loratadine Oral Suspension - 5 mg/5 mL

Pharmacological Category: Antihistamine

Submitted: Draft labeling:

[redacted]

2. 8 fl. oz. (240 mL) carton and immediate container label

[redacted]

Background:

Taro Pharmaceuticals Inc., on May 6, 2004, submitted electronically the following draft labeling for its OTC Children's ElixSure - 24 hour antihistamine (loratadine oral suspension; 5 mg/5 mL) drug product:

[redacted]

2. 8 fl. oz. (240 mL) carton and immediate container label

[redacted]

Reviewer Comment:

The draft labeling included in this submission is identical to the labeling submitted on January 19, 2004, and has been reviewed and entered in DFS on August 10, 2004. The labeling recommendations provided in that review (8/10/04) are applicable to this submission.

Recommendation:

See the August 10, 2004 NDA labeling review recommendations.

Cazemiro R. Martin
IDS: Reg. Review Scientist

Concur: Marina Chang, R.Ph.
Team Leader

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/s/

Cazemiro Martin
9/28/04 07:52:48 AM
INTERDISCIPLINARY

Marina Chang
9/28/04 08:41:19 AM
INTERDISCIPLINARY

OTC Drug Labeling Review

Office of Nonprescription Products

Center for Drug Evaluation and Research • Food and Drug Administration

NDA Addendum Labeling Review

NDA # 21-734

Re-submission Date : 9/14/05
Review Date : 9/21/05

Applicant: Taro Pharmaceuticals U.S.A., Inc.

Applicant's Representative: Kalpana Rao
Vice President, Regulatory Affairs (Global)

Drug: Children's Claritin (Allergy)
Loratadine Oral Suspension - 5 mg/5 mL

Pharmacological Category: Antihistamine

Submitted: Draft labeling for:

2. 8 fl. oz. (240 mL) carton and immediate container label

Background:

In response to the Agency's labeling comments (facsimile dated September 14, 2005), the sponsor has submitted revised color mock-up (final printed) carton and container labeling for the 8 fl. oz. SKUs along with annotated specifications.

The sponsor has made the following revisions to the draft labeling:

3. *8 fl. oz. immediate container labeling:*
Directions" has been revised to read "*When taken as directed. See Drug Facts panel."

Recommendation:

An Approval is recommended.

Michael L. Koenig, Ph.D.
IDS Reviewer

Concur: Marina Chang, R.Ph.
Team Leader

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/s/

Michael Koenig
9/21/2005 02:07:16 PM
INTERDISCIPLINARY

Marina Chang
9/21/2005 02:46:16 PM
INTERDISCIPLINARY

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

NDA Labeling Review

NDA # 21-734

Submission Date : 1/19/04
Review Date : 8/10/04

Applicant: Taro Pharmaceuticals U.S.A., Inc.

Applicant's Representative: Kalpana Rao
Vice President, Regulatory Affairs

Drug: Children's ElixSure - 24 hr Antihistamine
Loratadine Oral Suspension - 5 mg/5 mL

Pharmacological Category: Antihistamine

Submitted: Draft labeling:

2. 8 fl. oz. (240 mL) carton and immediate container label

Background:

Loratadine was approved for prescription (Rx) use in the United States on April 12, 1993, and was switched from Rx to OTC status on November 27, 2002.

Taro Pharmaceuticals Inc., is seeking approval under a 505(b)(2) application (NDA 21-734) to market over-the-counter 8 fl. oz, Children's ElixSure - 24 hour antihistamine (loratadine oral suspension - 5 mg/5 mL) drug products

Reviewer Comment:
Reviewer recommended additions are identified by "redlining" (shaded text) and deletions are identified by "strike out."

The annotated specifications submitted by the sponsor for the "Drug Facts" graphical features for the 8 fl. oz. proposed draft labeling are acceptable.

1. General comment: Product name - "Children's ElixSure - 24 hr Antihistamine"

*[Reviewer comment: **The sponsor uses three different names for this drug product:***

1. "Children's ElixSure - 24 hr Antihistamine" (In the cover letter dated January 19, 2004, and Form 356h)

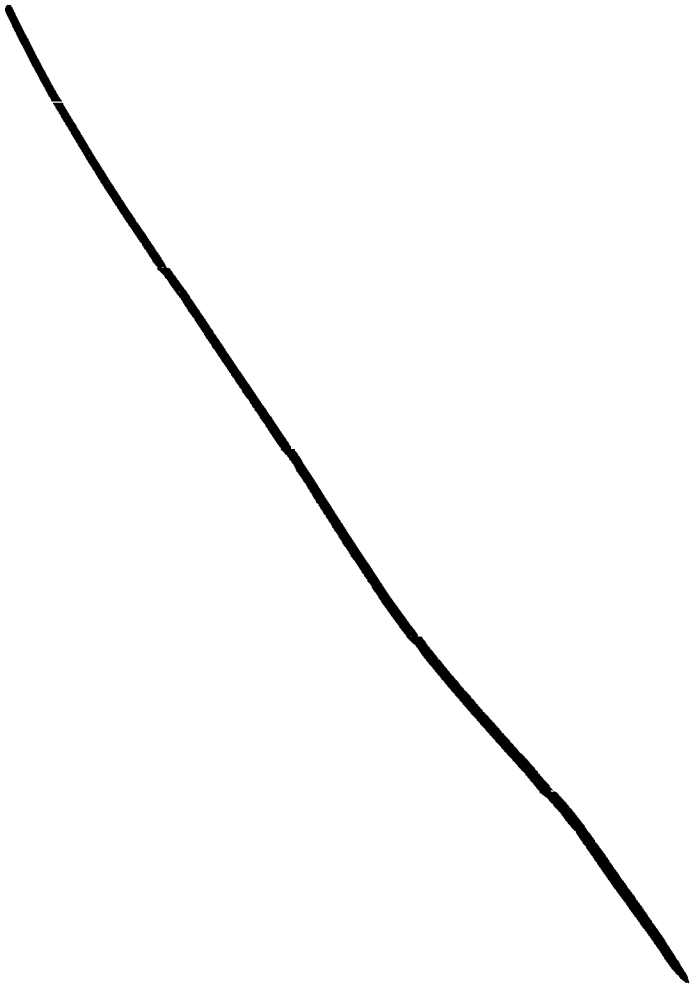
6 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 4



6. **To Project Management Staff**:

(i) In the cover letter, the sponsor indicated that it is seeking approval to market this OTC drug product for the

Please check with the **medical officer(s)** and **other reviewers** on this NDA review team to ensure that there are no additional labeling comments or revisions that need to be forwarded to the sponsor.

Cazemiro R. Martin
IDS: Reg. Review Scientist

Concur: Marina Chang, R.Ph.
Team Leader

Attachment:
Agency's recommended prototype labeling:

1 Page(s) Withheld

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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 5

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/s/

Cazemiro Martin
8/10/04 01:33:36 PM
INTERDISCIPLINARY

Marina Chang
8/10/04 01:46:07 PM
INTERDISCIPLINARY

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: April 16, 2004

To: Kalpana Rao	**From:** Anthony Zeccola
Company: Taro Pharmaceuticals	Division of Pulmonary and Allergy Drug Products
Fax number:	**Fax number:** 301-827-1271
Phone number:	**Phone number:** 301-827-1058

Subject: NDA 21-734

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES xNO

Your submission dated January 19, 2004, to NDA 21-734, is currently under review and we have the following request(s):

1. Clarify the address for the clinical site for Study #30218.
   In Module 2: 2.7.1.2, the address for the clinical site for Study #30218 is

   [redacted]

   In Module 5: 5.3.1.2.1 pg VII, the address for the clinical site for Study #30218 is

   [redacted]

2. Clarify the adverse events for Study #30219. In Module 5: 5.3.1.2.2, the Adverse Events section (2.1.14) of the Methodology and Summary of Study #30219 reports 27 post-dose adverse events and refers to Table C4 (Post-Dose Adverse Events) for a summary of the post dose adverse events. Table C4 only lists 21 adverse events.

If there are any questions, please contact Anthony Zeccola, Regulatory Management Officer, at 301-827-1058.

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/s/

Anthony Zeccola
4/16/04 11:05:49 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-734

Taro Pharmaceuticals, U.S.A., Inc.
Five Skyline Drive
Hawthorne, NY 10532

Attention: Kalpana Rao

Dear Ms. Rao,

Please refer to your January 19, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Children's ElixSure™ – 24 Hour Antihistamine (Loratadine Oral Suspension) 5mg/5ml.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on March 19, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Your application was submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved reference product (Claritin®) and a comparison of the bioavailability and bioequivalence of the proposed new drug (Children's ElixSure™ – 24 Hour Antihistamine) to those reference products. Therefore, in the absence of clinical studies establishing the safety and efficacy of your product, demonstrating bioequivalence is an important element of your application. A preliminary review of the two bioavailability studies revealed that some of the key pharmacokinetic parameters important for establishing bioequivalence with the reference product were outside the bioequivalence range. No justification for the pharmacokinetic difference between Claritin® and Children's ElixSure™ – 24 Hour Antihistamine was provided. During the review process, we will need to consider the clinical implication of the difference in pharmacokinetics between Claritin® and Children's ElixSure™ – 24 Hour Antihistamine.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Drug master files (DMFs) referenced in support of NDA 21-734 should be in adequate status.

2. The 9 months stability data should be provided as soon as feasible.

3. All the facilities involved in the manufacturing and controls should be in compliance with cGMP.

4. You have provided executed batch records for three biobatches. Your commercial batch size cannot exceed [redacted].

5. Composition of the masking agent should be provided in detail.

6. You have provided a CDROM of the AERS/ADR data for Claritin. You should provide a tabular summary of the frequencies of these adverse events and a narrative analysis and conclusions based upon this summary.

7. Your cover letter states that the indication for this OTC drug product will be for the relief [redacted]

8. Submit all draft labeling in WORD format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
4/2/04 02:56:22 PM