CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-734

MEDICAL REVIEW

DIVISION DIRECTOR'S MEMORANDUM

Date: October 4, 2005

To: NDA 21-734

From: Eugene J. Sullivan, MD, FCCP
Deputy Director, Division of Pulmonary and Allergy Products
HFD-570

Through: Badrul A. Chowdhury, MD PhD
Director, Division of Pulmonary and Allergy Products

Product: [redacted] (loratadine oral suspension 5mg/5mL)

Applicant: Taro Pharmaceuticals USA, Inc.

Administrative and Introduction

Taro Pharmaceuticals initially submitted NDA 21-734 for its loratadine oral suspension formulation, then referred to as Children's ElixSure™ 24 hour Antihistamine, on January 19, 2004, under Section 505(b)(2). In a letter dated November 19, 2004, the Division took an Approvable action on the application, based on a determination that the Applicant had failed to demonstrate bioequivalence to the approved reference products. In the current submission (letter date April 1, 2005) the Applicant has submitted a complete response to the Approvable action for the product. The product is proposed for over-the-counter use in patients 2 years of age and older for relief from symptoms due to hay fever or other upper respiratory allergies. The proposed dose is one teaspoon daily for children 2 to under 6 years of age, and two teaspoons once daily in adults and children 6 years of age and older.

As a 505(b)(2) application, approval would rely on the Agency's previous finding of safety and efficacy of loratadine, coupled with information needed to support any change from the approved product. The Office of New Drugs, in consultation with the Office of Regulatory Policy, has reviewed the relevant materials and found that the 505(b)(2) regulatory pathway is appropriate for this application, and that all of the relevant patents have been appropriately certified. Various formulations of loratadine have been approved for marketing in the US, first as prescription products, and more recently as over-the-counter products. Taro's formulation incorporates loratadine into a patented, viscous delivery system ("NonSpil™") that is suggested to be desirable, particularly in children, because it is less likely to spill from the spoon during administration. In order to support this difference in formulation, Taro initially performed two clinical pharmacology studies, comparing the bioavailability/bioequivalence of its formulation with that of two marketed loratadine products, Claritin® Tablets (Schering) and Claritin® Syrup (Schering) (Studies 30218 and 30219). However, although these initial studies demonstrated acceptable bioequivalence for the active metabolite, they failed to

demonstrate bioequivalence for the parent drug, which itself is biologically active. Therefore, the Applicant undertook a larger clinical pharmacology study to compare the bioavailability of its formulation with Claritin Tablets 10mg (Schering), Study R04-1776. The current submission contains the results of this latter study.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The CMC aspects of this application were reviewed by Dr. Kim. The reader is referred to his Chemistry Reviews for detailed discussions. Children's ElixSure™ 24 hour Antihistamine is an oral suspension formulation consisting of 5mg/5mL loratadine and various inactive ingredients. The specific inactive ingredients and their concentrations are consistent with those covered in the FDA Inactive Ingredient database (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm). Due to the presence of the viscosity agent Carbomer 934P, the formulation is quite viscous. The Applicant plans to market this as a "NonSpil" formulation, which will be less likely to spill from a spoon used to administer it. The viscosity of the carbomer gel is pH and temperature dependent. The maximum viscosity occurs at about neutral pH. Increased temperature results in decreased viscosity. The product will be marketed in [redacted] configurations: [redacted] 8 fl. oz. (240mL) bottle [redacted].

The CMC aspects of this product are briefly summarized in the Division Director Memorandum dated November 19, 2004, which describes the rationale for the Approvable action taken at that time. At the time of that action, the CMC team had identified several important deficiencies and had determined that three DMFs for the various components of the drug product were inadequate to support approval. In addition, one of the five sites was not ready for inspection, and therefore the Office of Compliance had recommended that approval of the application be withheld. Based on these findings, the recommendation from the CMC review team at that time was for an Approvable action. After the review of the current submission, including the April 1, 2005, and subsequent submissions, the CMC review team has determined that all of the previously identified deficiencies have been adequately addressed, and the application is adequate to support Approval.

Clinical Pharmacology and Biopharmaceutics, and Clinical

As mentioned above, the two clinical pharmacology studies that were submitted with the original NDA failed to demonstrate bioequivalence with the approved reference products. The Applicant has now conducted a third, larger clinical pharmacology study intended to establish the necessary bioequivalence (Study R04-1776). This study is reviewed in depth in the Clinical Pharmacology and Biopharmaceutics Review (Dr. Shinja Kim) and the Medical Officer Review (Dr. Sally Seymour). Briefly, this study was a single-dose, randomized, crossover study performed in 72 healthy subjects in the fasting state. The two treatments were the test drug and Claritin Tablets 10mg. The Cmax and AUC data for the parent drug, loratadine, and the active metabolite, desloratadine from Study R04-1776 are shown in Table 1. The accepted threshold for determining bioequivalence is that the 90% confidence interval (CI) around the ratio of the means of the AUC and Cmax of the test to the reference product must fall within 0.8 and 1.25. The loratadine and desloratadine exposures fell within the accepted bioequivalence limits for both AUC

and C_{max}. On the basis of this finding, the Office of Clinical Pharmacology and Biopharmaceutics review team has recommended Approval.

Table 1. Summary of pharmacokinetic parameters of loratadine and desloratadine from Study R04-1776

	Parameter	Treatment*	Mean (%CV)	Pair	Ratio	90% CI
Loratadine						
	AUC_t (ng*h/mL)	A B	3.76 (135) 3.45 (132)	A/B	108.9	99.9 – 118.7
	AUC_{inf} (ng*h/mL)	A B	3.93 (136) 3.63 (138)	A/B	108.2	99.5 – 117.6
	C_{max} (ng/mL)	A B	1.41 (130) 1.43 (120)	A/B	98.9	88.8 – 110.2
Desloratadine						
	AUC_t (ng*h/mL)	A B	37.7 (32) 35.9 (36)	A/B	105.2	101.4 – 109.1
	AUC_{inf} (ng*h/mL)	A B	40.1 (37) 38.6 (50)	A/B	104.1	99.7 – 108.7
	C_{max} (ng/mL)	A B	28.3 (44) 27.5 (36)	A/B	102.8	97.8 – 108.1

* Treatment Groups: A= Taro loratadine (test), B= Claritin Tablet 10mg (reference)

Pharmacology and Toxicology

The Applicant did not conduct any new preclinical studies for this application. None are considered necessary for this 505(b)(2) application. The recommendation from the Pharm/Tox review team is for an Approval action.

Data Quality, Integrity, and Financial Disclosure

The Agency's Division of Scientific Investigation performed an inspection of the analytical site and reported no findings of concern.

Pediatric Considerations

The applicant is proposing an indication down to the age of 2 years and is not proposing to seek approval in patients below 2 years of age. This is acceptable because this formulation would not be suitable for children younger than 2 years of age.

Product Name

The initial NDA submission included reference to three distinct trade names. The proposed proprietary name in the April 1, 2005, submission was Children's [redacted] The Division consulted the Division of Medication Errors and Technical Support (DMETS) for input on this proposed proprietary name. DMETS determined that the name Children's [redacted] was acceptable. In a submission dated August 30, 2005, the Applicant proposed two new proprietary names, [redacted] In a submission dated September 2, 2005, the Applicant stated that its agreement with

[redacted] had been terminated and therefore the name [redacted] will not be used. Labeling included in that submission indicates the proposed proprietary name is [redacted] Loratadine. A submission dated September 14, 2005 also indicated that the proposed proprietary name is [redacted] Loratadine. DMETS objected to the inclusion of the word [redacted] in the name, and the Applicant has agreed to remove this. The Office of Nonprescription Drugs has reviewed labeling contained in the September 14, 2005, submission and recommends approval.

Labeling

The Division reviewed the proposed labeling and conveyed its recommendations to the Office of Nonprescription Products (ONP). ONP also reviewed the proposed labeling and interacted with the Applicant during the review cycle to arrive at acceptable labeling. In a Review dated September 21, 2005, ONP has recommended approval of the agreed upon labeling, which was submitted by the Applicant on September 14, 2005.

Action

As recommended by the CMC, OCPB, Pharm/Tox, and Clinical teams, as well as the reviewers in the Office of Nonprescription Drugs, the regulatory action on this application will be APPROVAL. Because the product will be a nonprescription drug, this will be a joint action taken with the Office of Nonprescription Drugs.

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

/s/

Eugene Sullivan
10/4/2005 12:45:15 PM
MEDICAL OFFICER

Badrul Chowdhury
10/4/2005 12:50:28 PM
MEDICAL OFFICER
I concur

CLINICAL REVIEW

Application Type	NDA
Submission Number	21734
Submission Code	N000 B2
Letter Date	April 1, 2005
Stamp Date	April 4, 2005
PDUFA Goal Date	October 1, 2005
Reviewer Name	Sally Seymour, M.D.
Review Completion Date	September 2, 2005
Established Name	Loratadine
(Proposed) Trade Name	[redacted] (loratadine suspension 5mg/mL)
Therapeutic Class	Antihistamine
Applicant	Taro Phamaceuticals
Priority Designation	S
Formulation	Oral Suspension
Dosing Regimen	Adults and children 6 years and older -2 teaspoons daily (10mg); Children 2 to under 6 year of age - 1 teaspoonful daily (5mg)
Indication	Temporary relief of these symptoms due to hay fever or other upper respiratory allergies- runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat
Intended Population	Children 2 years and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

In this response to approvable submission, Taro Pharmaceuticals demonstrated that [redacted] (loratadine suspension 5mg/5mL) is bioequivalent to the reference listed drug, Claritin® Tablet 10mg (loratadine 10mg). In this application, the Applicant proposes a new suspension formulation of loratadine. This 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 drug, coupled with the information needed to support the change from the approved product. The Agency has previously determined the safety and efficacy of Claritin® Tablet 10mg. Study R04-1776 demonstrated that the key pharmacokinetic parameters for loratadine suspension 5mg/5mL and Claritin® Tablet 10mg were bioequivalent. Under Section 505(b)(2), the Applicant can support approval of a change in dosage form by a comparison of the bioavailability and bioequivalence of the proposed new drug to that of a reference listed drug. The bioequivalence between [redacted] (loratadine suspension 5mg/5mL) and Claritin Tablet 10mg is established by the Applicant's clinical pharmacology studies; therefore, from a clinical perspective, the recommendation is for Approval.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical program for NDA # 21-734 consists of three clinical pharmacology studies, which assess the bioequivalence between [redacted] (loratadine suspension 5mg/5mL) and the reference listed drug, Claritin Tablet 10mg. The original NDA application consisted of two clinical pharmacology studies, 30218 (fasting) and 30219 (fed). However, the two clinical pharmacology studies in the original application failed to demonstrate that the loratadine suspension 5mg/mL was bioequivalent to the reference standards of Claritin Tablets and Claritin Syrup. A key pharmacokinetic parameter (C_{max}) for loratadine suspension 5mg/mL fell below the bioequivalence range; therefore, the original NDA application was given an Approvable action.

In this response to Approvable action, the Applicant conducted a larger clinical pharmacology study to assess the bioequivalence and bioavailability between loratadine suspension 5mg/5mL and the reference listed drug, Claritin Tablets 10mg.

1.3.2 Efficacy

In this application, the Applicant proposes a new suspension formulation of loratadine. This NDA 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 drug, coupled with the information needed to support the change from the approved product. The Agency has previously determined the safety and efficacy of Claritin® Tablet 10mg. Study R04-1776 demonstrated that the key pharmacokinetic parameters for loratadine suspension 5mg/5mL and Claritin® Tablet 10mg were bioequivalent. Under Section 505(b)(2), the Applicant can support approval of a change in dosage form by a comparison of the bioavailability and bioequivalence of the proposed new drug to that of a reference listed drug. The bioequivalence between [redacted] (loratadine suspension 5mg/5mL) and Claritin Tablet 10mg is established by the Applicant's clinical pharmacology studies. Since bioequivalence has been established between loratadine suspension 5mg/5mL and Claritin Tablet 10mg, no clinical studies of the efficacy of loratadine suspension 5mg/5mL were required.

1.3.3 Safety

As stated above, this NDA 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 drug and a comparison of the bioavailability and bioequivalence of the proposed new drug to that of a reference listed drug, coupled with the information needed to support the change from the approved product. The safety of loratadine has previously been established by the Agency. In addition, the safety data from the clinical pharmacology studies does not suggest a new safety signal for loratadine suspension 5mg/5mL.

1.3.4 Dosing Regimen and Administration

The proposed dosing for [redacted] is the same as the dosing for the approved product, Claritin. The following proposed dosing regimen is similar to other Claritin products and is acceptable:

- Adults and children 6 years and older
  - 2 teaspoons daily (10mg); do not take more than 2 teaspoonfuls daily
- Children 2 to under 6 year of age
  - 1 teaspoonful daily (5mg); do not take more than 1 teaspoonful daily
- Children under 2 years of age
  - Ask a doctor
- Consumers with liver or kidney disease
  - Ask a doctor.

2 INTRODUCTION AND BACKGROUND

Taro Pharmaceuticals originally submitted NDA# 21-734 on January 21, 2004, for loratadine oral suspension 5mg/5mL. The Applicant incorporated loratadine into a patented NonSpil™ delivery system as an over-the-counter (OTC) antihistamine. The NDA is a 505(b)(2) application, which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved drug and a comparison of the bioavailability and bioequivalence of the

proposed new drug to that of a reference listed drug, coupled with the information needed to support the change from the approved product.

The Applicant originally submitted two clinical pharmacology studies to support NDA# 21-734. The two clinical pharmacology studies showed that compared to the approved products, Claritin® Tablets and Claritin® Syrup, a key pharmacokinetic parameter (C_{max}) for loratadine oral suspension 5mg/5mL fell below the bioequivalence range, which raised the question of the efficacy of loratadine oral suspension 5mg/5mL. Although the safety of loratadine oral suspension 5mg/5mL was established, the efficacy of loratadine oral suspension 5mg/5mL was not established. Thus, the Application received an Approvable action on November 19, 2004.

In this response to Approvable action, the Applicant conducted a larger clinical pharmacology study to assess the bioequivalence and bioavailability between loratadine suspension 5mg/5mL and the reference listed drug, Claritin Tablets 10mg.

5 CLINICAL PHARMACOLOGY

The Applicant conducted three clinical pharmacology studies to support this application. Studies 30218 and 30219 were reviewed in detail in the original NDA review. The third PK study, Study R04-1776, is reviewed in detail in Section 10.1.1, but is briefly discussed here.

Briefly, Study R04-1776 was a randomized, single-dose, two-way crossover study under fasting conditions in 72 non-smoking male and female healthy subjects, 18 years of age and older. Subjects were randomized to receive a single oral dose of loratadine nonspil suspension 10mg (treatment A) or Claritin Tablet 10mg (treatment B). After a 14 day washout period, subjects received a single 10mg dose of the other treatment. Serial blood samples were drawn for pharmacokinetic analysis. The following table summarizes the PK results. The data are presented for loratadine and the metabolite, descarboethoxyloratadine (DCL), using geometric means, ln-transformed. The 90% confidence interval for the ratio of the geometric means of the test and reference products was determined.

Table 1 Study R04-1776 Summary of Pharmacokinetic Parameters

Mean Loratadine PK Parameters					
Parameter	**TRT[1]**	**Mean[2] (%CV)**	**Pair**	**Ratio**	**90% CI**
AUC_t (ng*h/mL)	A B	3.76 (135) 3.45 (132)	A/B	108.9	99.9 – 118.7
AUC_{inf} (ng*h/mL)	A B	3.93 (136) 3.63 (138)	A/B	108.2	99.5 – 117.6
C_{max} (ng/mL)	A B	1.41 (130) 1.43 (120)	A/B	98.9	88.8-110.2
Mean DCL PK Parameters					
AUC_t (ng*h/mL)	A B	37.7 (32) 35.9 (36)	A/B	105.2	101.4-109.1
AUC_{inf} (ng*h/mL)	A B	40.1 (37) 38.6 (50)	A/B	104.1	99.7-108.7
C_{max} (ng/mL)	A B	28.3 (44) 27.5 (36)	A/B	102.8	97.8-108.1

1 Treatment Groups: A= Taro ElixSure Loratadine (NonSpil). B=Claritin 10mg tablet
2 Geometric mean, ln-transformed
Source [N21734, April 1, 2005, Vol. 2, pg 39, 333. 364, 366. 373]

According to the Agency, bioequivalence is established when the calculated CI falls between 80-125% for the ratio of the product averages (Guidance to Industry – Statistical Approaches to Establishing Bioequivalence). As shown above, Study R04-1776 supports the bioequivalence between the loratadine suspension (5mg/5mL) and Claritin Tablet 10mg.

6 INTEGRATED REVIEW OF EFFICACY

In this application, the Applicant proposes a new suspension formulation of loratadine. This NDA 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 drug, coupled with the information needed to support the change from the approved product. The Agency has previously determined the safety and efficacy of Claritin® Tablet 10mg. Study R04-1776 demonstrated that the key pharmacokinetic parameters for loratadine suspension 5mg/5mL and Claritin® Tablet 10mg were bioequivalent. Under Section 505(b)(2), the Applicant can support approval of a change in dosage form by a comparison of the bioavailability and bioequivalence of the proposed new drug to that of a reference listed drug. The bioequivalence between [redacted] (loratadine suspension 5mg/5mL) and Claritin Tablet 10mg is established by the Applicant's clinical pharmacology studies. Since bioequivalence has been established between loratadine suspension 5mg/5mL and Claritin Tablet 10mg, no clinical studies of the efficacy of loratadine suspension 5mg/5mL were required.

7 INTEGRATED REVIEW OF SAFETY

Because the exposure to loratadine and DCL for loratadine suspension 5mg/5mL is no greater than the exposure to loratadine and DCL for Claritin Tablet 10mg, it is reasonable to extrapolate the Agency's previous determination of the acceptable safety profile of Claritin Tablet 10mg to

loratadine suspension 5mg/5mL. In addition, the Applicant supported the safety of loratadine suspension 5mg/5mL with data from the pivotal clinical pharmacology studies, safety information for loratadine from the clinical literature, and AE reports in the US AERS database.

In the pivotal clinical pharmacology studies, there were no meaningful differences between the Applicant's product and the Claritin products in adverse events (AEs), withdrawals due to AEs, or other safety endpoints. In addition, in the original NDA submission, a review of the AERS database did not provide evidence of new safety concerns and the Applicant's literature search provided no new safety signal for the use of loratadine in the intended population.

9 OVERALL ASSESSMENT

9.1 Conclusions

In this response to approvable submission, Taro Pharmaceuticals demonstrated that [redacted] (loratadine suspension 5mg/5mL) is bioequivalent to the reference listed drug, Claritin® Tablet 10mg. In this application, the Applicant proposes a new suspension formulation of loratadine. This 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 drug, coupled with the information needed to support the change from the approved product. The Agency has previously determined the safety and efficacy of Claritin® Tablet 10mg. Study R04-1776 demonstrated that the key pharmacokinetic parameters for loratadine suspension 5mg/5mL and Claritin® Tablet 10mg were bioequivalent. Under Section 505(b)(2), the Applicant can support approval of a change in dosage form by a comparison of the bioavailability and bioequivalence of the proposed new drug to that of a reference listed drug. The bioequivalence between [redacted] (loratadine suspension 5mg/5mL) and Claritin Tablet 10mg is established by the Applicant's clinical pharmacology studies.

9.2 Recommendation on Regulatory Action

From a clinical perspective, this application is recommended for Approval.

9.3 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions.

9.4 Labeling Review

The product labels and packages for the [redacted] 8 ounce products were reviewed in detail by the Division of Nonprescription Products. The Division of Pulmonary and Allergy Drug Products raised the following concerns about the proposed package label to the Division of Nonprescription Products.

- Carton side panel contains claims regarding the NonSpil Technology. It is unclear if these claims are supported.
- [redacted]
- The statements "spill resistant' [redacted] would not typically be allowed on prescription drug products.
- The [redacted] 'Peach [redacted] ' claim with picture of a peach would not typically be allowed on a prescription drug product.

The final product label is deferred to the Division of Nonprescription Products.

9.5 Comments to Applicant

There are no clinical comments to be conveyed to the Applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study R04-1776

Title: A Relative Bioavailability Study of Loratadine NonSpil Oral Suspension (1mg/mL) versus Tablets (10mg) Following the Administration of 10mg Oral Dose Under Fasting Conditions

10.1.1.1 Protocol

Study R04-1776 was a randomized, single-dose, two-way crossover study under fasting conditions in 72 non-smoking male and female healthy subjects, 18 years of age and older. Females of childbearing potential were required to practice an acceptable method of birth control for the duration of the study. Pertinent exclusion criteria included clinically significant medical illness, clinically significant abnormal laboratory tests, drug, tobacco or alcohol use, Hepatitis B or C positive, HIV positive, recent use of prescription medications (14 days), OTC medications (3 days), or medications which affect hepatic drug metabolism (28 days) [N21734, April 1, 2005, Vol. 2, pg 56].

Informed consent was obtained from all subjects prior to initiation of study procedures. Screening procedures were performed within 28 days prior to administration of study medication. Screening procedures included: history and physical exam, ECG, chemistry, hematology, HIV screening, hepatitis screening, urinalysis, serum pregnancy screen, and urine drug screen [N21734, April 1, 2005, Vol. 2, pg 55].

Subjects were instructed to abstain from xanthine or caffeine containing food or beverages or energy drinks, alcohol, or grapefruit products for 48 hours prior to study drug administration.

Eligible subjects were admitted to the study center approximately 10 hours prior to dosing with study medication. A serum pregnancy screen was collected and eligibility was reconfirmed. Subjects were served a light snack then fasted. Fluids were allowed during the fasting period, but restricted about one hour prior to dosing. Meals were standardized [N21734, April 1, 2005, Vol. 2, pg 63].

On study day 1 after the overnight fast, subjects were randomized to receive a single oral dose of loratadine nonspil suspension 10mg (treatment A) or Claritin Tablet 10mg (treatment B). Study medication was administered at 8AM with 240mL of room temperature water. After dosing, subjects were to remain in an upright position for 4 hours. Two hours post-dosing subjects drank 240mL of water [N21734, April 1, 2005, Vol. 2, pg 58].

Blood samples for pharmacokinetic measurements were collected before dosing (0 hour) and at 0:15, 0:30, 0:40, 0:50, 1:00, 1:15, 1:30, 1:45, 2:00, 2:30, 3:00, 3:30, 4:00, 6:00, 8:00, 12:00, 24:00, 48:00, and 72:00 hours post-dose. Subjects were allowed to leave the study center after the 24 hour post-dose blood draw and return for the subsequent draws [N21734, April 1, 2005, Vol. 2, pg 61].

Safety monitoring included vital signs (blood pressure and heart rate) pre-dose, 12, and 24 hours post-dose. Subjects were queried for adverse events during the study. At the completion of the study, a CBC, chemistry laboratories, and a pregnancy screen were performed. Subjects could have been withdrawn from the study by the investigator for safety considerations [N21734, April 1, 2005, Vol. 2, pg 66].

Subjects returned to the study center a minimum of 14 days later for Period II and underwent the same procedure as described above, but received the alternate study medication (B if received A in Period I and A if received B in Period I).

No parameters of clinical efficacy were evaluated in this study. The following pharmacokinetic parameters were determined for loratadine and descarboethoxyloratadine (DCL) from the plasma concentration data [N21734, April 1, 2005, Vol. 2, pg 67]:

- The maximum observed concentration (C_{max})
- The time of observed Cmax (T_{max})
- The elimination rate constant (k_{el})
- The elimination half life ($T_{1/2el}$)
- The area under the concentration-time curve from time zero to the last point with measurable concentration(AUC_{0-t})
- The area under the concentration-time curve from time zero to infinity (AUC_{0-inf}).

The pharmacokinetic parameters were analyzed by ANOVA on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. For the ln-transformed, estimates for the adjusted differences between treatment means and the standard error associated with these differences was used to construct a 90% confidence interval for the ratio of the test to reference population means. To establish bioequivalence under fasting conditions, the 90% confidence interval for the ratio of the

geometric means between the products should fall within the interval 90-125% for log-transformed AUC $_{0\text{-inf}}$, AUC $_{0\text{-t}}$, and C_{max} [N21734, April 1, 2005, Vol. 2, pg 67].

10.1.1.2 Results

Study R04-1776 commenced with Period I on January 21, 2005. Period II started February 4, 2005, and was completed on February 8, 2005. The clinical study center was [redacted]

10.1.1.2.1 Subject Disposition and Demographics

A total of 72 subjects were confined for Period I, but only 70 were confined for Period II. Thus, two subjects did not undergo Period II. Subject #11 was discontinued prior to Period II due to an influenza-like illness. Subject #22 withdrew consent prior to Period II.

The mean age of the subjects was 25.2 years with an age range of 18 to 56 years. There were 29 males (40%) and 43 females (60%). The majority of the subjects were Caucasian. Only one subject was African American and 3 subjects were Hispanic [N21734, April 1, 2005, Vol. 2, pg 34-36].
Reviewer's Comment: The under-representation of non-Caucasian subjects is less than ideal. However, the innovator's product label does not list a clinically significant race-related difference in loratadine pharmacokinetics [Claritin® Product Label].

Subjects were randomized to treatment sequence AB or BA. The details of the treatments are displayed in Table 2. Two subjects were noted to have protocol deviations, which was use of ibuprofen [N21734, April 1, 2005, Vol. 3, pg 524].

Table 2 Study R04-1776 Treatment

Treatment	Product	Sponsor	Dose	Identification No.	Expiration Date
A (Test)	Loratadine NonSpil Suspension	Taro Pharmaceuticals	10 mg (10 mL of 1mg/1mL suspension)	Lot No: S189-54098	[redacted]
B (Reference)	Claritin 10mg Tablet	Schering Corporation	10mg	Lot No: 3-RXF-17	

Source [N21734, April 1, 2005, Vol. 2, pg 15-16]

10.1.1.2.2 Pharmacokinetic Endpoint Outcomes

The data from Study R04-1776 demonstrate that the key pharmacokinetic parameters for the loratadine nonspil suspension (test) and Claritin tablet (reference) were bioequivalent. According to the FDA, bioequivalence is established when the calculated CI falls between 80-125% for the ratio of the product averages (Guidance to Industry – Statistical Approaches to Establishing Bioequivalence). Table 3 is a summary of the key pharmacokinetic parameters from Study R04-1776. The data is presented for loratadine and descarboethoxyloratadine (DCL) using geometric means, ln-transformed. The 90% confidence interval for the ratio of the

geometric means of the test and reference products was determined [N21734, April 1, 2005, Vol. 2, pg 39, 333, 364, 366, 373].

Table 3 Study R04-1776 Summary of Pharmacokinetic Parameters

Parameter	TRT[1]	Mean[2] (%CV)	Pair	Ratio	90% CI
Mean Loratadine PK Parameters					
AUC_t (ng*h/mL)	A B	3.76 (135) 3.45 (132)	A/B	108.9	99.9 – 118.7
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C_{max} (ng/mL)	A B	1.41 (130) 1.43 (120)	A/B	98.9	88.8-110.2
Mean DCL PK Parameters					
AUC_t (ng*h/mL)	A B	37.7 (32) 35.9 (36)	A/B	105.2	101.4-109.1
AUC_{inf} (ng*h/mL)	A B	40.1 (37) 38.6 (50)	A/B	104.1	99.7-108.7
C_{max} (ng/mL)	A B	28.3 (44) 27.5 (36)	A/B	102.8	97.8-108.1

1 Treatment Groups: A= Taro ElixSure Loratadine (NonSpil), B=Claritin 10mg tablet
2 Geometric mean, ln-transformed
Source [N21734, April 1, 2005, Vol. 2, pg 39, 333, 364, 366, 373]

Reviewer's Comment: Although the study was randomized and open-label, the bioanalytical staff were blinded to prevent bias during analysis.

10.1.1.2.3 Safety Outcomes

Seventy out of 72 subjects received both doses of study medication (20mg loratadine). Seventy-two subjects received one dose of study medication (10mg loratadine).

Adverse Events

Of the 70 subjects who completed the study, 29 adverse events were recorded over the course of the study in 21 subjects. There were no serious adverse events (SAEs) or deaths in the study. One subject was discontinued due to influenza type symptoms. All adverse events were mild to moderate in severity. Table 4 is a summary of adverse events reported by the subjects.

Table 4 Study R04-1776 Number of Adverse Events		
Adverse Event	**Loratadine Nonspil Suspension Test A N=71**	**Claritin Tablet Reference B N=71**
All Adverse Events	15	15
Headache	3	3
Pharyngolaryngeal pain	2	2
Dizziness	2	0
Nausea/Vomiting	1	0
Nasal congestion	1	2
Lacrimation increased	1	1
Hyperhidrosis	1	0
Pallor	1	0
Lower Respiratory Tract Infection	1	0
Pharyngitis	1	0
Cough	1	0
Influenza like illness	0	2
AST/ALT increase	0	2
Stomach discomfort	0	1
Viral gastroenteritis	0	1
Dysmenorrhoea	0	1

Source [N21734, April 1, 2005, Vol. 2. 26-27]

Reviewer's Comment: It is unclear to this reviewer why the tabular data lists 30 adverse events, but the Applicant's summary states 29 adverse events.

A similar number of adverse events were reported with each study treatment. Overall, the most common adverse events were headache and pharyngolaryngeal pain. Dizziness was more common in the loratadine nonspil suspension group than in the Claritin Tablet group. Overall, the adverse event data does not suggest a safety signal for loratadine nonspil suspension; however, because of the small number of subjects and AEs, it is difficult to draw any meaningful safety conclusions from this data.

Clinical Laboratories

Laboratory studies were performed at screening at the conclusion of the study. The laboratories were reviewed and the only notable significant changes from baseline were liver function tests. Most subjects with elevated AST, ALT, or total bilirubin had elevated values at baseline. Two subjects were noted to have potentially significant elevations in ALT and AST. (The following ALT and AST values are reported as IU/L.) One subject (#29) was noted to have an increase from normal ALT and AST at baseline to ALT of 116 and AST of 328 at the end of the study. The tests were repeated 3 days later and the ALT had decreased to 69 and the AST had decreased to 73. The second subject (#55) was noted to have an increase from normal ALT and AST at baseline to ALT of 67 and AST of 165 at the end of the study. The tests were repeated 2 days later and the ALT had decreased to 45 and the AST had decreased to 55. Both subjects with elevated ALT and AST at the end of study received Claritin Tablets 10mg in Period II [N21734, April 1, 2005, Vol. 3, pg 538-585].

Reviewer's Comment: There were no clinically significant changes in laboratories associated with loratadine nonspil suspension. Because laboratories were only collected at baseline and end of study, the effects of each study medication on a subject's laboratories cannot be determined. The only potentially clinically significant change in laboratories were an increase in ALT and AST following dosing with Claritin Tablets.

Vital Signs

Vital signs were measured at screening as well as pre and post dosing during each treatment period. The vital sign data was reviewed. No clinically significant change in vital signs was noted.

10.1.1.3 Discussion and Conclusions

The data from Study R04-1776 demonstrate that the key pharmacokinetic parameters for the loratadine nonspil suspension (test) and Claritin tablet (reference) were bioequivalent under fasting conditions in healthy subjects. Overall, the adverse event data does not suggest a safety signal for loratadine nonspil suspension. In addition, there were no clinically significant changes in laboratories or vital signs. However, because of the small number of subjects in this study, it is difficult to draw any meaningful safety conclusions from this data.

10.2 Line-by-Line Labeling Review

The product labels and packages for the [redacted] 8 ounce products were reviewed in detail by the Division of Nonprescription Products. The Division of Pulmonary and Allergy Drug Products raised the following concerns about the proposed package label to the Division of Nonprescription Products.

- Carton side panel contains claims regarding the NonSpil Technology. It is unclear if these claims are supported.
- [redacted]
- The statements "spill resistant' [redacted] would not typically be allowed on prescription drug products.
- [redacted]Peach[redacted]' claim with picture of a peach would not typically be allowed on a prescription drug product.

The final product label is deferred to the Division of Nonprescription Products.

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/s/

Sally Seymour
9/2/2005 09:53:22 AM
MEDICAL OFFICER

Look at 505b2 revision

Eugene Sullivan
9/9/2005 03:42:24 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #:	NDA# 21-734	**Application Type:**	NDA
Sponsor:	Taro Pharmaceuticals	**Proprietary Name:**	[redacted] Children's [redacted]
Investigator:		**USAN Name:**	loratadine
Category:	Antihistamine	**Route of Administration:**	Oral Suspension
Reviewer:	Sally Seymour, M.D.	**Review Date:**	April 21, 2005

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	Submission Type	Comments
April1, 2005	Response to Approvable Action	13 paper volumes

REVIEW SUMMARY: This is a Medical Officer review to determine if Taro Pharmaceuticals' response to an approvable action for NDA# 21-734 is complete. NDA# 21-734 is a 505(b)(2) application for a loratadine oral suspension for children, which was originally submitted on January 19, 2004. The clinical portion of the application consisted of two clinical pharmacology studies. However, the clinical pharmacology studies did not establish the bioequivalence of Taro's loratadine oral suspension and the reference products, Claritin 10mg Tablets and Claritin Syrup. Therefore, the NDA was given an approvable action on November 19, 2004. CMC and labeling deficiencies were also communicated in the approvable letter.

In this response to approvable action, Taro Pharmaceuticals has submitted a fasting clinical pharmacology study in 72 subjects to establish the BA/BE between loratadine oral suspension and Claritin Tablets. The Sponsor has also addressed the labeling comments in the approvable letter. However, the Sponsor did not submit a safety update for loratadine.

The Sponsor requests approval of the loratadine 5mg/ 5mL suspension to be marketed in a [redacted] 8 oz (240 mL) bottle [redacted] The proposed indication is the following: temporarily relieves these symptoms due to hay fever or other upper respiratory allergies-runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat in patients 2 years of age or older. The Sponsor has proposed the trade name of [redacted] (loratadine suspension 5mg/5mL) through an agreement with [redacted]. The product is proposed to be over-the-counter.

The response appears complete and is adequate to allow a full, in-depth clinical review. However, the safety update for loratadine will be requested. The following comment will be conveyed to the Sponsor.

As stated in the approvable letter, dated November 19, 2004, you were to include a safety update according to 21 CFR 314.50(d)(5)(vi)(b). In your response, you stated that no additional safety information is available outside of that provided in the NDA. However, an additional source of safety information about loratadine is the published literature. Conduct a literature search regarding loratadine safety covering the period of time from the original NDA submission (January 19, 2004) to the present. Submit a list of the articles generated and summarize the conclusion of the literature search regarding loratadine safety.

OUTSTANDING ISSUES: Comments will be conveyed to the Sponsor

RECOMMENDED REGULATORY ACTION:

NDA, Efficacy/Label supplement: _____ **Fileable** _____ **Not Fileable**

Medical Reviewer: Sally Seymour, M.D.

Deputy Division Director: Eugene J. Sullivan, M.D., F.C.C.P.

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/s/

Sally Seymour
5/10/05 07:17:50 AM
MEDICAL OFFICER

Eugene Sullivan
5/10/05 11:18:57 AM
MEDICAL OFFICER

DIVISION DIRECTOR'S MEMORANDUM

Date: November 19, 2004

To: NDA 21-734

From: Eugene J. Sullivan, MD, FCCP
Deputy Director, Division of Pulmonary and Allergy Drug Products
HFD-570

Through: Badrul A. Chowdhury, MD PhD
Director, Division of Pulmonary and Allergy Drug Products

Product: Children's ElixSure™ - 24hour Antihistamine (loratadine oral suspension 5mg/5mL)

Applicant: Taro Pharmaceuticals USA, Inc.

Administrative and Introduction

Taro Pharmaceuticals submitted NDA 21-734 for Children's ElixSure™ 24 hour Antihistamine on January 19, 2004, under Section 505(b)(2). The PDUFA due date for the application is November 21, 2004. The product is proposed for over-the-counter use in patients 2 years of age and older for relief from symptoms due to hay fever or other upper respiratory allergies. The proposed dose is one teaspoon daily for children 2 to under 6 years of age, and two teaspoons once daily in adults and children 6 years of age and older.

As a 505(b)(2) application, approval would rely on the Agency's previous finding of safety and efficacy of loratadine, coupled with information needed to support any change from the approved product. Various formulations of loratadine have been approved for marketing in the US, first as prescription products, and more recently as over-the-counter products. Taro's formulation incorporates loratadine into a patented, viscous delivery system ("NonSpil™") that is suggested to be desirable, particularly in children, because it is less likely to spill from the spoon during administration. In order to support this difference in formulation, Taro performed two clinical pharmacology studies, comparing the bioavailability/bioequivalence of its formulation with that of two marketed loratadine products, Claritin® Tablets (Schering) and Claritin® Syrup (Schering).

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The CMC aspects of this application were reviewed by Dr. Kim. The reader is referred to his Chemistry Review for a detailed discussion. Children's ElixSure™ 24 hour Antihistamine is an oral suspension formulation consisting of 5mg/5mL loratadine and various inactive ingredients. The specific inactive ingredients and their concentrations are consistent with those covered in the FDA Inactive Ingredient database (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm). Due to the presence of the

viscosity agent Carbomer 934P, the formulation is quite viscous. The Applicant plans to market this as a "NonSpil" formulation, which will be less likely to spill from a spoon used to administer it. The viscosity of the carbomer gel is pH and temperature dependent. The maximum viscosity occurs at about neutral pH. Increased temperature results in decreased viscosity. The product will be marketed in [redacted] configurations: [redacted] 8 fl. oz. (240mL) bottle [redacted]

The drug substance is manufactured by [redacted] Fabrication, packaging, labeling, testing, storage, and distribution of the drug product will be performed by Taro Pharmaceuticals Inc., Ontario, Canada. In addition, the Applicant has provided a list of 4 contract labs to serve as alternate testing facilities. Three DMFs for the various components of the drug product, have been reviewed and are considered inadequate to support approval. Establishment evaluations of four of the five sites have been performed, and all four sites have been found to be acceptable. However, the remaining site (Taro Pharmaceuticals, Inc.) was not ready for inspection, and therefore the Office of Compliance has recommended that approval of the application be withheld. The CMC team has also identified several deficiencies, which are listed in Dr. Kim's Chemistry Review. These include deficiencies in regard to drug substance specifications and test methods, drug product release specifications and stability acceptance criteria, analytical procedures, and container closure system data. The recommendation from the CMC review team is for an Approvable action.

Clinical Pharmacology and Biopharmaceutics, and Clinical

The Applicant submitted results of two clinical pharmacology studies and a summary of safety data from various sources. The two clinical pharmacology studies were conducted in healthy adult male subjects. The studies were designed to show bioequivalence of Children's ElixSure™ 24 hour Antihistamine to the reference products after a single dose in the fasting (Study 30218) and fed (Study 30219) state. In Study 30218 there were two reference products, Claritin® Tablets (10mg) and Claritin® Syrup (1mg/mL). In Study 30219 there was one reference product, Claritin® Tablets (10mg). In both studies, the dose examined (40mg) was in excess of the labeled dose (10mg). The clinical pharmacology studies were reviewed in depth by the Office of Clinical Pharmacology and Biopharmaceutics (OCBP) Reviewer, Dr. Kim. All submitted studies and additional safety data were reviewed by the Medical Officer, Dr. Seymour. The OCBP team concluded that the pharmacokinetic profile of Children's ElixSure™ 24 hour Antihistamine was not equivalent to that of either reference product. The observed differences were such that the prior finding of efficacy for loratadine could not alone be sufficient to establish the efficacy of Taro's product.

The Cmax and AUC data from the two studies are shown in Table 1. The accepted threshold for determining bioequivalence is that the 90% confidence interval (CI) around the ratio of the means (AUC and Cmax) of the test and reference product must fall within 0.8 and 1.25. In the fasting state (Study 30218), the loratadine exposure from the test drug was below the accepted bioequivalence limits for both AUC and C_{max}, when compared to the Claritin Syrup. In addition, the loratadine exposure from the test drug was below the accepted bioequivalence limits for C_{max}, when compared to the Claritin

Tablets.[1] In the fed state (Study 30219), the loratadine exposure from the test drug was below the accepted bioequivalence limits for C_{max}, when compared to the Claritin Tablets.

Table 1. Summary of pharmacokinetic parameters of loratadine from Studies 30218 (N=45) and 30219 (N=40)

	Parameter	Treatment*	Mean (%CV)	Pair	Ratio	90% CI
Study 30218 (Fasting)						
	AUC_t (ng*h/mL)	A	44.3 (109)	A/B	0.65	**58.3 – 72.1**
		B	68.3 (91)	A/C	0.94	84.2 – 104.1
		C	47.3 (109)	B/C	1.44	129.8 – 160.6
	AUC_{inf} (ng*h/mL)	A	47.4 (109)	A/B	0.66	**59.3 – 73.5**
		B	71.8 (92)	A/C	0.95	85.3 – 105.7
		C	49.9 (109)	B/C	1.44	129.1 - 160
	C_{max} (ng/mL)	A	13.5 (109)	A/B	0.53	**45.0 – 61.6**
		B	25.6 (98)	A/C	0.81	**69.3 – 94.9**
		C	16.6 (113)	B/C	1.54	131.6 – 180.2
Study 30219 (Fed)						
	AUC_t (ng*h/mL)	A	90.1 (89)	A/C	91.4	85.5 – 97.6
		C	98.6 (90)			
	AUC_{inf} (ng*h/mL)	A	94.7 (90)	A/C	91.0	85.1 – 97.3
		C	104.1 (91)			
	C_{max} (ng/mL)	A	20.3 (85)	A/C	77.9	**67.3 – 90.1**
		C	26.0 (89)			

* Treatment Groups: A= Taro ElixSure, B= Claritin Syrup, C= Claritin Tablets

The Applicant acknowledged the observed pharmacokinetic differences, but argued that the test product should be considered to be bioequivalent to the Claritin Tablet formulation, based on the PK data for the active metabolite, desloratadine. Those data (not shown) indicate that the test product met the accepted criteria for bioequivalence when these criteria are applied to the active metabolite. The Division considered this argument, but concluded that, because both the parent and the metabolite are pharmacologically active, the two formulations could not be considered bioequivalent. The OCPB team also contacted the Office of Generic Drugs (OGD) in order to clarify their approach to bioequivalence when both the parent drug and metabolite are pharmacologically active. In that setting, OGD relies primarily on the PK data of the parent drug, with metabolite data being considered supportive. Given that the loratadine exposure was lower with the test drug, the Division determined that efficacy could not be assumed. Therefore, the Applicant will need to provide data to establish efficacy.

The OCPB Reviewer performed additional exploratory analyses excluding various outlier subjects. On the basis of these analyses, the OCPB team concluded that the presence of a few outlier subjects in the completed PK studies is not the sole cause of the inability to

[1] Of note, these data also demonstrate that the two Claritin formulations (syrup and tablet) are not themselves bioequivalent. This is not unexpected as it was identified previously, at the time of the approval of Claritin Syrup. At that time, the tablet formulation had previously been approved. The higher loratadine exposure observed with the syrup formulation was not felt to raise concerns regarding efficacy or safety.

establish bioequivalence. Therefore, it is not predicted that additional, larger PK studies would likely establish bioequivalence. It is likely that the current NoSpil formulation has the undesirable effect of delaying absorption, leading to a reduced C_{max}, despite the similar AUC.

In support of the safety of this drug, the Applicant provided safety data from the clinical pharmacology studies, and performed a review of safety information derived from the medical literature and the US Adverse Events Reporting System database. These investigations did not reveal any safety signals. Given that the safety of loratadine has previously been established, that the Applicant's review of publicly available safety data did not reveal any safety signals, and that the systemic loratadine exposure is lower with Children's ElixSure 24-hour Antihistamine as compared with the approved products, it is reasonable to conclude that acceptable safety of this product has been established.

Pharmacology and Toxicology

The Applicant did not conduct any new preclinical studies for this application. None are considered necessary for this 505(b)(2) application. The recommendation from the Pharm/Tox review team is for an Approval action.

Data Quality, Integrity, and Financial Disclosure

The two clinical pharmacology studies were performed by [redacted] Early in the review cycle, a consultation was requested from the Agency's Division of Scientific Investigation to perform a biopharmaceutical inspection of this study center. However, prior to the inspection, the Division concluded that the data from the two clinical pharmacology studies did not support approval of the product. Therefore, the consultation was rescinded, and no inspection was performed. All studies were conducted in accordance with accepted ethical standards. The Applicant provided certification that it did not engage the services of any person who has been debarred under Section 306(a). No financial disclosure issues were present. Review of the application did not raise questions regarding the quality or integrity of the data submitted.

Pediatric Considerations

The applicant is proposing an indication down to the age of 2 years and is not proposing to seek approval in patients below 2 years of age. This is acceptable because this formulation would not be suitable for children younger than 2 years of age.

Product Name

The application included reference to three distinct trade names. A consultation to the Division of Medication Errors and Tech Support for a trade name evaluation will be submitted when the Applicant formally proposes a specific trade name.

Labeling

A labeling review was performed by the Division of Over-The-Counter Drug Products. The comments and recommendations from OTC were not conveyed to the Applicant during the review period because of the decision to take an action other than approval. These comments will be conveyed in the action letter.

Action

The data submitted with this application indicate that the pharmacokinetic profile of Children's ElixSure™ 24 hour Antihistamine is not equivalent to that of either approved reference product. The observed differences are such that the prior finding of efficacy for loratadine cannot alone be sufficient to establish the efficacy of Taro's product. In addition, there are several outstanding CMC issues that preclude approval. Therefore, the action on this application will be APPROVABLE. In order to support approval, the Applicant will need to address the CMC issues, as well as the pharmacokinetic issue related to efficacy. To do this, it may choose to reformulate the product and repeat the BA/BE studies, or to conduct a clinical trial to establish efficacy.

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/s/

Eugene Sullivan
11/19/04 09:57:04 AM
MEDICAL OFFICER

Badrul Chowdhury
11/19/04 10:01:33 AM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA # 21-734	**TRADE NAME:**	Children's ElixSure-24 hr Antihistamine
APPLICANT:	Taro Pharmaceuticals, Inc.	**USAN NAME:**	Loratadine
MEDICAL OFFICER:	Sally Seymour, MD		
DEPUTY DIRECTOR:	Eugene Sullivan, MD, FCCP	**CATEGORY:**	Antihistamine
REVIEW DATE:	November 8, 2004	**ROUTE:**	Oral suspension

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
January 19, 2004	January 21, 2004	NDA 21-734	Original submission, CTD Format
April 20, 2004	April 21, 2004	NDA 21-734, N000	Response to Facsimile Inquiry
May 6, 2004	May 7, 2004	NDA 21-734, N000	Response to Filing Communication

REVIEW SUMMARY: This NDA is a 505(b) (2) application for a loratadine oral suspension as an over-the-counter (OTC) antihistamine. The Applicant is Taro Pharmaceuticals, Inc. The reference products are Claritin® 10mg Tablets and Claritin® Syrup, manufactured by Schering Plough. The Applicant has proposed the trade name of Children's ElixSure™-24 hr Antihistamine (Loratadine Oral Suspension) 5mg/5mL for the drug product. The proposed indication for Children's ElixSure™-24 hr Antihistamine is the temporary relief of the following symptoms due to hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat. The proposed dose is 2 teaspoons daily (10mg) in adults and children 6 years and over and 1 teaspoon daily (5mg) in children 2 to 6 years of age.

This application relies upon the Agency's previous finding of safety and efficacy of loratadine. The clinical portion of this application consists of two clinical pharmacology studies, Studies 30218 and 30219. The two clinical pharmacology studies show that compared to the approved products, Claritin® Tablets and Claritin® Syrup, a key pharmacokinetic parameter (C_{max}) 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.

In terms of the safety of Children's ElixSure™-24 hr Antihistamine, there were no meaningful differences between Children's ElixSure™-24 hr Antihistamine and the Claritin products in adverse events (AEs), withdrawals due to AEs, or other safety endpoints in the pivotal clinical pharmacology studies. The Applicant's review of the published literature for loratadine-associated adverse events does not provide evidence of new safety concerns. A review of the AERS database for AEs associated with loratadine also does not provide evidence of new safety concerns for loratadine.

The safety of loratadine has been established. However, because an important PK parameter for Children's ElixSure™-24 hr Antihistamine was below the bioequivalence range in the two clinical pharmacology studies, the efficacy of Children's ElixSure™-24 hr Antihistamine has not been established. Therefore, from a clinical perspective, the recommendation is for an Approvable action. A path forward would be to perform clinical studies with Children's ElixSure™-24 hr Antihistamine to demonstrate efficacy. Alternatively, the Applicant could choose to reformulate the product and perform clinical pharmacology studies with the new formulation to demonstrate bioequivalence with an approved product.

OUTSTANDING ISSUES: **None**

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	**FILEABLE**		**NOT FILEABLE**		
	APPROVAL	X	**APPROVABLE**		**NOT APPROVABLE**

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CLINICAL REVIEW OF NDA # 21-734

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendation on Approvability

In this 505(b) (2) application, Taro Pharmaceuticals has 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 (C_{max}) 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. Additional clinical studies with Children's ElixSure™-24 hr Antihistamine will be necessary to demonstrate efficacy. Although the safety of loratadine has been established, the efficacy of Children's ElixSure™-24 hr Antihistamine has not been established; therefore, from a clinical perspective, the recommendation is for an Approvable action.

1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps

Phase 4 studies are not recommended at this time because of the recommendation for an "Approvable" action.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Background and Administrative Issues

This NDA is a 505(b) (2) application for a loratadine oral suspension. The Applicant is Taro Pharmaceuticals, Inc. The 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 drug and a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the listed drug. The listed drugs for this application are Claritin® 10mg Tablets and Claritin® Syrup 5mg/5mL.

2.2. Brief Overview of Clinical Program

The Applicant requests approval of a 5mg/5mL loratadine suspension as an over-the-counter (OTC) antihistamine. The Applicant has incorporated loratadine into a patented NonSpil™ delivery system. The Applicant has proposed the trade name of Children's ElixSure™-24 hr Antihistamine (Loratadine Oral Suspension) 5mg/5mL for the drug product.

The proposed indication for Children's ElixSure 24 hr Antihistamine is the temporary relief of the following symptoms due to hay fever or other upper respiratory allergies: runny nose,

sneezing, itchy, watery eyes, and itching of the nose or throat. The Applicant proposes the following dosing:

- Adults and children 6 years and over - 2 teaspoons daily (10mg)
- Children 2 to under 6 years of age - 1 teaspoon daily (5mg).

The proposed indication and dose for Children's ElixSure 24 hr Antihistamine are the same indication and dose as the approved listed drug products.

The Applicant's clinical program relies upon two clinical pharmacology studies, Studies 30218 and 30219. Study 30218 was a single dose clinical pharmacology study that compared the bioavailability of Taro's Children's ElixSure™-24 hr Antihistamine to Claritin® 10mg Tablets and Claritin® Syrup under fasting conditions. Study 30219 was a single dose clinical pharmacology study that compared the Applicant's Children's ElixSure™-24 hr Antihistamine to Claritin® 10mg Tablets under fed conditions.

2.3. Efficacy

As noted above, this application has been submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based upon the Agency's previous findings of efficacy and safety of an approved product and a comparison of the bioavailability of the proposed new drug to that of the approved product. Therefore, if bioequivalence could be established, no clinical studies of the efficacy of the product would be required.

The reference products for this 505(b) (2) application are Claritin® 10mg Tablets and Claritin® Syrup. Loratadine has been marketed since its approval in Belgium in 1988 and since 1993 in the US. The Claritin® line of products has been marketed as non-prescription drug products in the US since November of 2002.

The two clinical pharmacology studies in this application were conducted to compare the bioavailability and bioequivalence of Children's ElixSure™-24 hr Antihistamine to the reference products. A 90% confidence interval (CI) for the ratio of the means of the AUC and C_{max} for the proposed product and approved product was determined. According to the FDA, bioequivalence is established when the calculated CI falls between 80-125% for the ratio of the product averages (Guidance to Industry – Statistical Approaches to Establishing Bioequivalence).

In general, the Applicant's product was more similar to Claritin Tablets than Claritin Syrup. However, based upon loratadine levels, the Applicant's product was not bioequivalent to Claritin Syrup, because the C_{max} of the Applicant's product was below the bioequivalence range. The 90% CI of the C_{max} of Children's ElixSure™-24 hr Antihistamine compared to Claritin Tablets was [redacted] which is below the bioequivalence range of 80-125%

The clinical pharmacology studies demonstrated that key PK parameters, based upon the active metabolite, descarboethoxyloratadine (DCL), were more similar between Children's ElixSure™-24 hr Antihistamine and Claritin Tablets. However, the efficacy of loratadine cannot be supported entirely upon the activity of the metabolite, DCL. Both loratadine and DCL demonstrate antihistamine activity and both likely contribute to the efficacy of Claritin

Tablets and Claritin Syrup. Therefore, the lower C_{max} for loratadine observed with the Applicant's product cannot be presumed to provide efficacy.

From a clinical perspective, the Applicant will need to assure the efficacy of Children's ElixSure™-24 hr Antihistamine. A path forward would be to perform clinical studies with Children's ElixSure™-24 hr Antihistamine to demonstrate efficacy. Alternatively, the Applicant could choose to reformulate and perform clinical pharmacology studies to demonstrate bioequivalence with an approved product.

2.4. Safety

Because the exposure to loratadine and DCL for Children's ElixSure 24 hr Antihistamine is no greater than the exposure to loratadine and DCL for the approved products, it is reasonable to extrapolate the Agency's previous determination of the acceptable safety profile of the Claritin products to Children's ElixSure™-24 hr Antihistamine. In addition, the Applicant supported the safety of Children's ElixSure™-24 hr Antihistamine with data from the pivotal clinical pharmacology studies, safety information for loratadine from the clinical literature, and AE reports in the US AERS database.

In the pivotal clinical pharmacology studies, there were no meaningful differences between the Applicant's product and the Claritin products in adverse events (AEs), withdrawals due to AEs, or other safety endpoints. In addition, a review of the AERS database did not provide evidence of new safety concerns. The Applicant's literature search provided no new safety signal for the use of loratadine in the intended population.

In summary, there is no evidence of a new safety signal in the two clinical pharmacology studies, the medical literature, or AERS database that has not been previously identified in the prescription labeling for Claritin. The Applicant's safety review supports the proposed indication and over-the-counter (OTC) marketing of Children's ElixSure 24 hr Antihistamine. Additional clinical studies to document safety of the Applicant's product are not required.

2.5. Dosing

The proposed dosing for Children's ElixSure 24 hr Antihistamine 5mg/5mL is the same as the dosing for the approved product, Claritin. For adults and children age 6 years and older, the proposed dose is 2 teaspoons daily (10mg). For children age 2 to 6 years, the proposed dose is 1 teaspoon daily (5mg). The directions instruct consumers to not take more than the recommended daily dose and that taking more than the recommended dose may cause drowsiness. The product labels for the proposed product and the approved product have similar directions for use.

2.6. Special Populations

The pharmacokinetics of loratadine in pediatric subjects 2 years of age and older is similar to that in healthy adults. The Applicant's review of the literature did not identify a new safety signal specific to the pediatric subpopulation. The Applicant's proposed product label recommends children 2 to under 6 years of age take 5mg daily, while adults and children 6

years of age and older take 10mg daily. The Applicant's product is not proposed for use in children under the age of 2 years.

Geriatric subjects have AUC and C_{max} values for loratadine and DCL that are approximately 50% greater than in younger subjects. In addition, the clearance of loratadine tends to be lower in the elderly compared to young adults. However, despite the higher systemic exposure, geriatric subjects did not have an increase in AEs and did not have clinically significant changes in laboratory tests or ECGs. The Applicant's proposed label makes no special recommendation for dosing for healthy geriatric consumers, which is appropriate.

The Applicant stated that there were no race-associated or gender-associated differences in the safety profile of loratadine. However, pharmacokinetic studies indicate a subset of the general population are slow metabolizers of DCL and the frequency of slow metabolizers is higher in Blacks. Slow metabolizers of DCL cannot be prospectively identified. The Division's experience has been that there are no differences in safety profiles between slow and normal metabolizers. The increased exposure to DCL in slow metabolizers is not considered to be clinically relevant in the population proposed for use.

Patients with liver or renal impairment have increased AUC and C_{max} values for loratadine compared with normal subjects. The Applicant's proposed OTC labeling recommends that consumers with liver or kidney disease ask a doctor before using the product.

There are no adequate and well-controlled studies of loratadine use in pregnant or lactating women. The safety of loratadine use in this population has not been established; therefore, the Applicant stated that loratadine should be used only if the potential benefit justifies the potential risk to the fetus or infant. The Applicant's proposed labeling appropriately instructs consumers who are pregnant or breast-feeding to ask a health professional before using the product.

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1 Introduction

This NDA is a 505(b) (2) application for a loratadine oral suspension for children. The Applicant is Taro Pharmaceuticals Inc. The Applicant requests approval of a 5mg/5 mL loratadine suspension as an over-the-counter (OTC) antihistamine. In this suspension, the Applicant has incorporated loratadine into a patented NonSpil™ delivery system. The Applicant has proposed the trade name of Children's ElixSure™-24 hr Antihistamine (Loratadine Oral Suspension) 5mg/5mL for the drug product.
Reviewer's Comment: Throughout the application, the Applicant uses several different trade names interchangeably, [redacted] The above trade name was taken from the cover letter for the application. The Applicant will need to clarify the exact trade name for the proposed product.

The proposed indication is the temporary relief of these symptoms due to hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat [1.3b]. The Applicant proposes the following dosing [1.3b]:

- Adults and children 6 years and over - 2 teaspoons daily (10mg)
- Children 2 to under 6 years of age - 1 teaspoon daily (5mg).

Reviewer's Comment: [redacted] *In the Response to Filing Communication dated May 6, 2004, the Applicant stated that Children's ElixSure is indicated for the temporary relief of these symptoms due to hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat.*

The 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 the approved product and a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved product. The Applicant's proposed indication and dosing are the same as Claritin, the approved product.

1.2 Foreign Marketing and Regulatory History

Claritin was launched in Belgium in 1988 for allergic rhinitis and chronic idiopathic urticaria. Claritin is approved in 114 countries and approved prescription free in 33 countries. Of those 33 countries, 22 sell Claritin "behind the counter," while only 8 countries (Belgium, Canada, Germany, Ireland, Netherlands, Russia, UK, and the US) sell Claritin OTC [http://www.fda.gov/ohrms/dockets/ac/02/slides/3850s1.htm]. Claritin was approved for OTC use in the US in November of 2002.

The Applicant's development plan relied on the following two PK studies:

- Study 30218 was a randomized, three-period, crossover study that compared the relative bioavailability of the ElixSure test product with Claritin Tablets and Claritin Syrup in the fasting state.
- Study 30219 was a randomized, two-way crossover study that compared the relative bioavailability of the ElixSure test product and Claritin Tablets in the fed state.

The Applicant did not request a Pre-NDA meeting with the Agency.

2. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

2.1. Chemistry, Manufacturing and Controls

Both the drug substance and drug product are manufactured by [redacted] The DMF has been referenced [2.3, page 4]. Table 1 lists the composition of the ElixSure product [2.3, page 26].

Table 1 Composition of Children's ElixSure (Loratadine Oral Suspension) 5mg/ 5mL

Component and Standard	Quantity per unit (mg/ 5 mL)	%
Purified water, USP		
Sodium hydroxide, NF		
Carbomer 934P, (Carbopol 974P), NF		
Sorbitol crystalline, NF		
Poloxamer 188, NF		
Propylene glycol, USP		
Butylparaben, NF		
Glycerin, USP		
Loratadine		
Surcralose liquid concentrate		
Masking agent		
Peach flavor		
Total weight/volume		

The ElixSure product used in both clinical pharmacology studies in this application were from the same lot. The batch size for the bioavailability studies was [redacted] The Applicant proposes a commercial scale batch size of [redacted] using the same process for the to-be-marketed formulation [2.3, page 28]. The lot numbers and expiration dates for both the ElixSure and Claritin products are shown in Table 2 [5.3.1.2.1, page 273 and 5.3.1.2.2, page 263, 302-303].

Table 2 Lot Numbers and Expiration Dates

Product	Sponsor	Identification No.	Expiration Date
Loratadine NonSpil Suspension	Taro Pharmaceuticals	Lot No: S189-54098 (EBK-L05)	[redacted]
Claritin Syrup 5mg/5mL	Schering Corporation	Lot No: 3LTN2	
Claritin 10mg Tablets	Schering Corporation	Lot No: 2-RXF-1035	

Reviewer's Comment: The commercial scale batch size cannot be more than [redacted] fold the batch size used for the clinical pharmacology studies. Therefore, the Applicant can only have a commercial scale batch size of [redacted] In a Response to Information Request, dated May 6, 2004, the Applicant revised the commercial batch size to not exceed [redacted] [N21734, Response to Information Request, May 6, 2004].

Reviewer's Comment: One of the Applicant's manufacturing sites was not ready for inspection at the time this review was finalized.

Reviewer's Comment: A detailed review of the CMC can be found in Dr. Chong-Ho Kim's CMC review of this NDA.

2.2. Animal Pharmacology and Toxicology

The Agency did not require the Applicant to conduct non-clinical safety studies because of the extensive marketing experience with loratadine. Loratadine was originally approved by the Agency as a prescription drug and now is approved for OTC use in the US.

Reviewer's Comment: Dr. Lawrence Sancilio's pharmacology/toxicology review notes that there are no new preclinical issues for Children's ElixSure-24 hr Antihistamine (Loratadine Oral Suspension) 5mg/5mL [Dr. Sancilio's Pharm/Tox Review, NDA 21-734, July 22, 2004].

2.3. Microbiology

A separate microbiology consult was not requested for this application.

2.4. Statistics

A separate Biometrics review was not performed or requested for this application. Analysis of the pharmacokinetic data from the two clinical pharmacology studies was performed by Dr. Shinja Kim, a reviewer from the Office of Clinical Pharmacology and Biopharmaceutics.

2.5. Marketing and Advertising

A consult was submitted to the Division of Drug Marketing, Advertising, and Communication (DDMAC) for evaluation of the proposed trade name. The consult is pending at the time this review was finalized.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

The Applicant conducted two clinical pharmacology studies in healthy adult male subjects to compare the bioavailability of the ElixSure product to Claritin, Studies 30218 and 30219. Study 30218 was a single dose study that compared the bioavailability of ElixSure to Claritin 10mg Tablets and Claritin Syrup under fasting conditions following a 40mg dose. Study 30219 was a single dose study that compared the bioavailability of ElixSure to Claritin 10mg tablets under fed conditions after a 40mg dose.
Reviewer's Comment: It is uncommon to have two reference products in a 505(b) (2) application. The Applicant did not provide justification or a rationale for having two reference products.

Statistical comparisons were performed to determine if the Test product was bioequivalent to the Reference product in the fasted and fed states. A 90% confidence interval (CI) for the ratio of the means of the AUC and C_{max} for the Test and Reference product was calculated to determine bioequivalence. The results of the pharmacokinetic studies for both loratadine and the active metabolite, descarboethoxyloratadine (DCL), are briefly summarized below.

3.1. Study 30218

Study 30218 was a single dose study that compared the bioavailability of Children's ElixSure™-24 hr Antihistamine (Loratadine Oral Suspension) 5mg/5mL to Claritin 10mg Tablets and Claritin 1mg/mL Syrup under fasting conditions following a 40mg dose. The results of the key pharmacokinetic parameters are summarized in Table 3.

Table 3 Study 30218 Summary of Pharmacokinetic Parameters
N=45

Parameter	TRT[1]	Mean[2] (%CV)	Pair	Ratio	90% CI
Study 30218 (Fasting) Mean Loratadine PK Parameters					
AUC_t (ng*h/mL)	A	44.3 (109)	A/B	0.65	***58.3-72.1***
	B	68.3 (91)	A/C	0.94	84.2-104.1
	C	47.3 (109)	B/C	1.44	129.8-160.6
AUC_{inf} (ng*h/mL)	A	47.4(109)	A/B	0.66	***59.3-73.5***
	B	71.8(92)	A/C	0.95	85.3-105.7
	C	49.9(109)	B/C	1.44	129.1-160
C_{max} (ng/mL)	A	13.5(109)	A/B	0.53	***45.0-61.6***
	B	25.6 (98)	A/C	0.81	***69.3-94.9***
	C	16.6(113)	B/C	1.54	131.6-180.2
Study 30218 (Fasting) Mean DCL PK Parameters					
AUC_t (ng*h/mL)	A	222.8(42)	A/B	1.01	95.8-105.8
	B	221.3(41)	A/C	1.07	101.8-112.5
	C	208.2(42)	B/C	1.06	101.1-111.7
AUC_{inf} (ng*h/mL)	A	238.3(46)	A/B	1.01	95.4-106.0
	B	237(46)	A/C	1.06	100.3-111.4
	C	225.5(46)	B/C	1.05	99.7-110.8
C_{max} (ng/mL)	A	16.5 (37)	A/B	0.84	***79.0-90.0***
	B	19.6(38)	A/C	1.09	102.4-116.7
	C	15.1(41)	B/C	1.30	121.3-138.4

1 Treatment Groups: A= Taro ElixSure Loratadine, B= Claritin Children's Syrup, C=Claritin 10mg tablet
2 Geometric means, ln-transformed

- Based upon loratadine levels, in the fasting state the
  - AUC of ElixSure compared to Claritin Tablet
    - Within bioequivalence range
  - AUC of ElixSure compared to Claritin Syrup
    - Below bioequivalence range
  - C_{max} ElixSure compared to Claritin Tablet
    - Below bioequivalence range
  - C_{max} ElixSure compared to Claritin Syrup
    - Below bioequivalence range
- Based upon DCL levels, in the fasting state
  - AUC ElixSure compared to Claritin Tablet
    - Within bioequivalence range
  - AUC ElixSure compared to Claritin Syrup
    - Within bioequivalence range
  - C_{max} ElixSure compared to Claritin Tablet
    - Within bioequivalence range
  - C_{max} ElixSure compared to Claritin syrup
    - Below bioequivalence range

The Division's OCPB reviewer, Dr. Shinja Kim, determined one subject to be a slow metabolizer of DCL. Subject #26, who is 26 years of age and Black, had approximately 3-, 4-, and 3- fold higher AUC_t, AUC_{inf}, and $t_{1/2}$ of DCL, respectively compared to the mean

values. The Division's experience has been that there are no differences in safety profiles between slow and normal metabolizers. The increased exposure to DCL in slow metabolizers is not considered to be clinically relevant in the population proposed for use.

3.2. Study 30219

Study 30219 was a single dose study that compared the bioavailability of Children's ElixSure™-24 hr Antihistamine (Loratadine Oral Suspension) 5mg/5mL to Claritin 10mg Tablets under fed conditions following a 40mg dose. The results of the key pharmacokinetic parameters are summarized in Table 4.

Table 4 Study 30219 Summary of Pharmacokinetic Parameters
N=40

Study 30219 (Fed) Mean Loratadine PK Parameters					
Parameter	**TRT[1]**	**Mean[2](%CV)**	**Pair**	**Ratio**	**90% CI**
AUC_t (ng*h/mL)	A B	90.1(89) 98.6(90)	A/B	91.4	85.5-97.6
AUC_{inf} (ng*h/mL)	A B	94.7(90) 104.1(91)	A/B	91.0	85.1-97.3
C_{max} (ng/mL)	A B	20.3(85) 26.0(89)	A/B	77.9	***67.3-90.1***
Study 30219 (Fed) Mean DCL PK Parameters					
AUC_t (ng*h/mL)	A B	218.2(39) 220.8(39)	A/B	98.8	95.3-102.5
AUC_{inf} (ng*h/mL)	A B	234.8(41) 239.6(41)	A/B	98.0	94.8-101.3
C_{max} (ng/mL)	A B	14.9(41) 16.5(40)	A/B	89.9	83.3-97.1

1 Treatment Groups: A=Taro ElixSure Loratadine 5mg/mL; B=Claritin 10mg tablet
2 Geometric means, ln-transformed

- Based upon loratadine levels, in the fed state
  - AUC ElixSure compared to Claritin Tablet
    - Within bioequivalence range
  - C_{max} ElixSure compared to Claritin Tablet
    - Below bioequivalence range
- Based upon DCL levels, in the fasting state
  - AUC ElixSure compared to Claritin Tablet
    - Within bioequivalence range
  - C_{max} ElixSure compared to Claritin Tablet
    - Within bioequivalence range

Reviewer's Comment: The Applicant did not provide justification for using 40mg of loratadine instead of the recommended dose of 10mg. Presumably, the higher dose of loratadine provides increased levels of loratadine and DCL providing better

characterization of exposure. Although loratadine is not approved for a 40mg dose, in the setting of a closely monitored clinical study, a 40mg dose of loratadine is acceptable.

Reviewer's Comment: The Applicant conducted both of these studies in males and used gender as an inclusion criterion. The Applicant justified the use of only males by stating that Claritin is a pregnancy category B medication and the Applicant did not want to risk exposure to women of child bearing potential. In addition, there is no reason to believe exposure to loratadine is influenced by gender.

3.3. Discussion

Based upon loratadine levels, Children's ElixSure 24-hr Antihistamine (Loratadine Suspension) 5mg/5mL is not bioequivalent to Claritin Syrup as several of the key pharmacokinetic parameters fall below the bioequivalence range. Although Children's ElixSure is more similar to Claritin Tablets than Claritin Syrup, Children's ElixSure is not bioequivalent to Claritin tablets because the C_{max} for Children's ElixSure is lower than the C_{max} for Claritin Tablets in both studies. The 90% CI of the ratio of the mean C_{max} of Children's ElixSure versus Claritin Tablets is [redacted], which is below the accepted bioequivalence range of 80-125%. A C_{max} of loratadine below the bioequivalence range raises a question of the efficacy of Children's ElixSure.

In the Filing Communication, dated April 13, 2004, the Agency notified the Applicant that a preliminary review of the clinical pharmacology studies revealed some of the key pharmacokinetic parameters important for establishing bioequivalence with the Reference products were outside the bioequivalence range. The Applicant responded in a Response to Filing Communication, dated May 6, 2004, and provided the following rationale (bulleted points):

- Loratadine is rapidly absorbed and metabolized to the active metabolite DCL.
- DCL exhibits more potent pharmacologic activity than loratadine:
  - H1 receptor binding activity (14-18 times)
  - Guinea pig models of bronchoconstriction (3.6-20 times)
  - Histamine-induced wheal and flare reactions (2-3 times).
- DCL, the active metabolite, is currently marketed as Clarinex®.

Reviewer's Comment: Although in vitro studies suggest DCL may be more potent, the relative antihistamine activity of DCL and loratadine in humans is not known. Similarly, wheal and flare reactions may suggest DCL is more potent, but the indication sought in this application is for symptoms [redacted] *Both DCL and loratadine likely contribute to the efficacy of Claritin Tablets and Claritin Syrup. Therefore, the efficacy of loratadine cannot be supported entirely upon the activity and pharmacokinetics of the metabolite, DCL. The PK of DCL can be supportive. The lower C_{max} for loratadine observed with the Applicant's product in both studies cannot be presumed to provide efficacy.*

- The Applicant provided PK data from the Claritin Syrup application (NDA# 20-641) obtained from the SBOA. The Applicant noted that in the Claritin Syrup application,

the loratadine syrup was bioequivalent to the conventional loratadine tablet for the major metabolite (DCL) and was comparable for the parent loratadine.

- The Applicant provided the following direct quotes from the Medical Officer Review in the SBOA for Claritin Syrup.
  - "loratadine syrup is BE to the conventional loratadine tablet for the major metabolite and is comparable for parent loratadine"
  - "If one assumes that DCL is at least as active as loratadine in antihistaminic activity in humans, then the PK comparison used for the dose extrapolation should be based primarily on the PK of DCL."

Reviewer's Comment: The Claritin Syrup application is quite complex in that a direct comparison between the tablet and syrup was not conducted. The Sponsor conducted two crossover PK studies utilizing the syrup, tablets, and a third loratadine formulation, Zydis. Indeed, when a cross study comparison was performed, Claritin Syrup was BE to Claritin Tablets, based upon DCL levels, but not loratadine levels. However, the Applicant failed to mention that based upon loratadine levels, the PK parameters for Claritin Syrup were actually above the bioequivalence range. Therefore, the efficacy of Claritin Syrup was not called into question because the systemic exposure of loratadine was actually higher for the syrup than for the comparator. Thus, compared to Claritin Tablets, Claritin Syrup provided similar levels for the major metabolite and higher concentrations for the parent compound. The following table illustrates that Claritin Syrup demonstrated higher exposure than the tablet or Zydis formulation.

Summary of PK Studies for Claritin Syrup (NDA# 20-641) ***(Two crossover studies, single dose, 10mg loratadine)***				
	Study C92-025-50		*Study C91-339-01*	
Mean Loratadine PK Parameters				
	Syrup	*Zydis formulation*	*Zydis formulation*	*Tablet*
Cmax (ng/mL)	*3.62*	*2.65*	*2.56*	*2.11*
AUC_{0-t} (ng hr/mL)	*10.1*	*6.33*	*6.14*	*4.64*
Mean DCL PK Parameters				
Cmax (ng/mL)	*3.65*	*3.46*	*3.72*	*3.66*
AUC_{0-t} (ng hr/mL)	*38.8*	*40.8*	*49.1*	*48.4*

The second quote listed above from the SBOA for Claritin Syrup was taken from a section of the MO Review discussing efficacy and the determination of an appropriate dose of Claritin Syrup in adults. The following quote immediately follows the second above quote in the MO Review: "The relative antihistaminic activity of DCL and loratadine in human is not known. Therefore, an objective approach in dose determination requires the to-be-marketed dose of loratadine syrup to yield systemic levels of both loratadine and DCL equal to or higher than that of adults who take 10mg of loratadine tablet."

- Taro included a cross-study comparison of PK values by adjusting the PK parameters of 40mg Children's ElixSure to a 10mg dose. Taro presented two tables comparing the PK parameters of the adjusted dose of ElixSure versus PK parameters obtained in studies conducted for the Claritin Syrup application.

Reviewer's Comment: The Applicant provided a cross study comparison of PK data from the Claritin Syrup NDA and Children's ElixSure 24-hr Antihistamine. The Applicant's cross study comparison is not valid due to differences in study design, assays, etc. For example: the cross study comparison provided by the Applicant indicated that the Cmax (based upon loratadine levels and corrected for a 10mg dose) for ElixSure was 3.38 ng/mL, which is higher than the Claritin tablet Cmax (2.11 ng/mL) exposure in the Claritin Syrup PK studies. However, this does not correlate with the Applicant's own PK studies in which ElixSure has a lower Cmax than the Claritin Tablet.

- The Applicant concluded that the clinical pharmacology studies demonstrate the bioavailability of the ElixSure product is comparable to the reference Claritin Syrup based on DCL after dosing under fasting conditions, and that the bioavailability of the ElixSure product is comparable to the reference Claritin Tablets based on both loratadine and DCL under fasting and fed conditions.

Reviewer's Comment: Although the bioavailability is comparable between the Applicant's product and the Reference products, Children's ElixSure 24-hr Antihistamine is not bioequivalent based upon a lower C_{max} for loratadine, which may affect the efficacy of Children's ElixSure 24-hr Antihistamine. The Applicant's rationale does not alleviate the concern of the potential decreased efficacy of Children's ElixSure 24-hr Antihistamine.

3.4. Conclusions

The Applicant conducted two clinical pharmacology studies to compare the bioavailability of Children's ElixSure 24-hr Antihistamine product to Claritin Syrup and Claritin Tablets. Statistical comparisons were performed to determine if the proposed product was bioequivalent to the approved products in the fasted and fed states. The clinical pharmacology studies in this application show that based upon the loratadine parent compound, Children's ElixSure 24-hr Antihistamine is not bioequivalent to either Claritin product. The C_{max} of loratadine in Children's ElixSure 24-hr Antihistamine is lower than the C_{max} of loratadine in Claritin Syrup or Claritin Tablets, which raises the possibility of a decrease in efficacy of Children's ElixSure 24-hr Antihistamine and does not support the approval of this application.

Reviewer's Comment: For a more detailed discussion of the clinical pharmacology studies, refer to the review by Dr. Shinja Kim, the Division's OCPB reviewer.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

The sources of clinical data utilized for this review were:

- The two clinical pharmacology studies provided with this submission
- AERS Data Base for loratadine provided with this submission
- Medline search of the published literature on loratadine safety
- Summary basis of approval for Claritin® Syrup provided with this submission
- Safety information from the FDA Advisory Committee Meeting held on May 11, 2001, which addressed the issue of switching loratadine to OTC

4.2. Overview of the Two Bioavailability Studies

Study 30218 [5.3.1.2.1, page 304-322]

Study 30218 was a pivotal clinical pharmacology study that compared the bioavailability of the Applicant's Children's ElixSure 24-hr Antihistamine (loratadine suspension) 5mg/5mL to the reference product, Claritin. The study compared the following:

- Children's ElixSure 24-hr Antihistamine 40 mg (40 mL of 5mg/5mL suspension)
- Claritin Tablets 40mg (4 x 10mg tablets)
- Claritin Syrup 40 mg (40mL of 5mg/5 mL syrup).

The study was performed in healthy subjects under fasting conditions. The study design was a single center, single dose, open-label, randomized, 3-period, 6-sequence crossover pharmacokinetic study in 51 healthy adult males. Samples were collected before dosing (0 hours) and at 0.250, 0.500, 0.667, 0.75, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 12.0, 24.0, 48.0, and 72.0 hours post-dosing for loratadine and DCL (descarboethoxyloratadine) levels. DCL is an active metabolite of loratadine. Patients were confined to the study site from at least 10 hours pre-dose until after the 24-hour post-dose blood draw. A washout period of 14 days separated the treatment periods. Safety monitoring included adverse events, hematology, urinalysis, and blood chemistry studies [5.3.1.2.1, page 317].

Study 30219 [5.3.1.2.2, page 260-279]

Study 30219 was a clinical pharmacology study that compared the bioavailability of the Applicant's Test product to the reference product, Claritin. The study compared the following:

- Children's ElixSure 24-hr Antihistamine 40 mg (40 mL of 5mg/5mL suspension)
- Claritin Tablets 40mg (4 x 10mg tablets).

The study was performed in healthy subjects under fed conditions. The study design was a single center, randomized, single dose, open-label, 2-way crossover comparative bioavailability study under fed conditions in 50 healthy adult males. Subjects were fed a high-fat, high-caloric breakfast and dosed 30 minutes after starting the meal. Samples were

collected before dosing (0 hours) and at 0.250, 0.500, 0.667, 0.75, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 12.0, 24.0, 48.0, and 72.0 hours post-dosing for loratadine and DCL levels. Subjects were confined to the research facility from at least 11 hours prior to drug administration until after the 24 hour post-dose blood draw. Single oral doses were separated by a washout period of 14 days. Safety monitoring included adverse events, hematology, urinalysis, and blood chemistry studies [5.3.1.2.2, page 304].

4.3. Post-marketing Experience

Children's ElixSure 24-hr Antihistamine has not been marketed either inside or outside of the United Sates. The Reference product Claritin was approved by the FDA in April of 1993 (NDA# 19-658) and became available OTC in the US in November 2002. This submission included a review of post-marketing adverse events for loratadine contained in the Agency's Adverse Events Reporting System (AERS) data base.

4.4. Literature Review

The Applicant provided some references from literature in this submission. The majority of the references focused on the pharmacokinetics of loratadine; however, some articles also encompassed safety. This reviewer also performed a focused Medline literature search on the safety of loratadine.

5. CLINICAL REVIEW METHODS

5.1. Conduct of the Review

The two clinical pharmacology studies in this application, Studies 30218 and 30219, were individually reviewed with a focus on safety findings. There was no Integrated Summary of Efficacy because the drug development program was based upon clinical pharmacology studies. No clinical studies were performed. A detailed analysis of the pharmacokinetic data was performed by the OCPB reviewer.

Safety data supporting this application was reviewed in depth. The safety review included safety data from the clinical pharmacology studies, data from the US AERS database, and the published literature.

5.2. Data Quality and Integrity

An inspection of one of the clinical study sites was initially requested. The request was subsequently withdrawn when the Division determined that the PK studies did not support approval.

5.3. Ethical Standards

According to the protocol for both clinical pharmacology studies, informed consent was obtained from all subjects prior to initiation of study procedures. According to the Applicant, both clinical pharmacology studies were conducted in accordance with Good Clinical Practices [5.3.1.2.1, page 271 & 5.3.1.2.2, page 261].

The Applicant provided a Debarment Certification, in which the Applicant certified that it did not use and would not use the services of any person debarred under Section 306(a) and 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with their application [1.3.a].

5.4. Financial Disclosure

The Applicant provided a financial disclosure statement for the principle investigators, [redacted] which stated the following: 1) The Applicant certified that it has not entered into any financial arrangement with the principle investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study. 2) The Applicant certified that the principle investigators did not disclose a proprietary interest in the proposed product or a significant equity in the Applicant. 3) The Applicant certified that neither of the principle investigators was the recipient of significant payments [1.3.a].

6. INTEGRATED REVIEW OF EFFICACY

This application was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved product and a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved product.

The approved products for this 505(b)(2) application are Claritin® (loratadine) 10mg tablets and Claritin Syrup 5mg/5mL. Loratadine has been marketed since its approval in Belgium in 1988 and since 1993 in the US. The Claritin line of products has been marketed as an over-the counter medication in the US since November 2002. Therefore, the efficacy and safety of loratadine for OTC use has been previously reviewed by the Agency.

The Applicant conducted two clinical pharmacology studies to compare the bioavailability of Children's ElixSure 24-hr Antihistamine product to Claritin Syrup and Claritin Tablets. Statistical comparisons were performed to determine if the proposed product was bioequivalent to the approved products in the fasted and fed states. The clinical pharmacology studies in this application show that based upon the loratadine parent compound, Children's ElixSure 24-hr Antihistamine is not bioequivalent to either Claritin product. The C_{max} of loratadine for Children's ElixSure 24-hr Antihistamine is lower than the C_{max} of loratadine for Claritin Syrup or Claritin Tablets, which raises the possibility of a decrease in efficacy of Children's ElixSure 24-hr Antihistamine and does not support the approval of this application. The Applicant may need to conduct clinical studies to demonstrate the efficacy of Children's ElixSure 24-hr Antihistamine.

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Findings

It is reasonable to extrapolate the Agency's previous determination of the acceptable safety profile of the Claritin products to Children's ElixSure™-24 hr Antihistamine. In addition, the Applicant supported the safety of Children's ElixSure™-24 hr Antihistamine with data from their pivotal clinical pharmacology studies, safety information for loratadine from the clinical literature, and AE reports in the US AERS database.

Integrated safety data from the applicant's clinical pharmacology studies show no evidence of a new safety signal. There were no meaningful differences in adverse events (AEs) between the proposed and approved products. There were no withdrawals due to AEs, no serious adverse events (SAEs) or deaths in the clinical pharmacology studies. In addition, a review of the AERS database did not provide evidence of new safety concerns.

The Applicant's literature search provided no new safety signal for the use of loratadine in the intended population. The Applicant's literature search did not, however, address the issue of the association of hypospadias with loratadine use during pregnancy, which was noted in Sweden. The potential safety signal has been addressed with the Office of Drug Safety, which did not note a similar association in US post-marketing data. Recently, the CDC analyzed data from the National Birth Defects Prevention Study and determined that women who used loratadine in early pregnancy had no increased risk for second or third degree hypospadias.[2] The Applicant's proposed labeling appropriately instructs pregnant consumers to ask a health professional before using the product.

In summary, there is no evidence of a safety signal in the literature or the AERS database that has not been previously identified in the prescription labeling for Claritin. The Applicant's safety review supports the proposed indication of its product. Additional clinical studies to document safety of the Test product are not required.

7.2. Methods and Content

The sources of clinical data utilized for the Integrated Review of Safety were:

- Integrated safety data from the Applicant's clinical pharmacology studies
- AERS database for spontaneous adverse event reports loratadine
- Medline search of the published literature on loratadine safety
- Applicant's review of information regarding drug abuse and overdose for loratadine
- Applicant's review of potential for drug interactions for loratadine
- Review of safety data addressing special populations
- Review of safety information from the FDA Advisory Committee Meeting held on May 11, 2001, which addressed the issue of switching loratadine to OTC status

7.3. Safety Findings from Clinical Pharmacology Studies

Integrated safety data from the Applicant's clinical pharmacology studies shows no evidence of a safety signal. AEs were more frequently reported with the approved products (40%

Claritin Tablets, 40% Claritin Syrup) than with the Applicant's ElixSure product (25%). Adverse events occurring more frequently for the Applicant's formulation and in more than one subject compared to the approved products were the following: headache, sleepiness, abdominal pain/sore stomach, and nausea/vomiting. Other AEs reported in subjects taking the proposed product were reported in one or fewer subjects. A detailed review of the integrated safety data from the two pivotal bioequivalence studies in this application follows.

7.3.1. Description of Studies

Study 30218 was a single center, single dose, open-label, randomized, 3-period crossover study in 51 healthy adult males designed to compare the bioavailability of the Applicant's ElixSure loratadine suspension 5mg/5mL and the reference products, Claritin 10mg Tablets and Claritin 5mg/5mL syrup, under fasting conditions following a 40mg dose. Each subject received 40mg of the test product, 40mg of Claritin Tablets, and 40 mg Claritin Syrup during this three period study. Single oral doses were separated by a washout period of 14 days [5.3.1.2.1, page 304-322].

Study 30219 was a single center, randomized, single dose, open-label, 2-way crossover study in 50 healthy adult males designed to compare the bioavailability of the Applicant's ElixSure loratadine suspension 5mg/5mL and the reference product, Claritin 10 mg tablets, under fed conditions following a 40mg dose. Each subject received 40mg of the test product and 40mg of Claritin Tablets during this two period study. Single oral doses were separated by a washout period of 14 days [5.3.1.2.2, page 260-279].

7.3.2. Demographics

Table 5 displays the demographic data for the 101 enrolled subjects in the two pivotal clinical pharmacology studies. The mean age for both studies was 34-37 with an age range of 18-69 years [5.3.1.2.1, page 280; 5.3.1.2.2, pages 269-270].

N=101	Number of Subjects n (%)
Men	101 (100)
Women	0 (0)
Caucasian	75 (74)
American Hispanics	14 (14)
African American	12 (12)

Reviewer's Comment: The under-representation of women and subjects of non-Caucasian race is less than ideal. However, the innovator's product label does not specify a clinically significant gender-related or race-related difference in loratadine pharmacokinetics [Claritin® Prescription Product Label].

7.3.3. Disposition

Of the 101 subjects enrolled in the two clinical pharmacology studies, only 94 completed the studies. One subject was withdrawn from the study due to concomitant therapy required for an adverse event (amoxicillin for gum swelling). The other five subjects were either withdrawn for not showing up to the clinical facility or elected to withdraw for no specified reason [5.3.1.2.1, page 275; 5.3.1.2.2, page 264].

Reviewer's Comment: No subjects withdrew from the clinical pharmacology studies secondary to AEs.

7.3.4. Patient Exposure

Exposure to study medication is summarized in Table 6, which takes into account the subject withdrawals for the clinical pharmacology studies. A total of 97 subjects were exposed to the Applicant's proposed drug product, while 98 subjects were exposed to the Claritin Tablet product and 47 were exposed to the Claritin Syrup product [5.3.1.2.1, pages 275, 428-431; 5.3.1.2.2, pages 264, 409-412].

Table 6 Patient Exposure

Study	Medication	Single Dose	# Subjects
30218			51
	Taro ElixSure Loratadine Oral Suspension 5mg/5mL (Test)	40 mg	47
	Schering Claritin 10mg Tablets (Reference)	40 mg	48
	Schering Claritin Syrup 5mg/5mL (Reference)	40 mg	47
30219			50
	Taro ElixSure Loratadine Oral Suspension 5mg/5mL (Test)	40 mg	50
	Schering Claritin 10mg Tablets (Reference)	40 mg	50

7.3.5. Adverse Events

Adverse events (AEs) occurring in the two clinical pharmacology studies were integrated and are presented in Table 7 [5.3.1.2.1, page 291-293] and [5.3.1.2.2, page 266 & 276].

Table 7 Adverse Events Reported During Clinical Pharmacology Studies

Adverse Event	ElixSure Loratadine (5mg/5mL) Test N = 97	Claritin Syrup (5mg/5mL) Reference N=47	Claritin Tablet (10mg) Reference N=98
All Adverse Events n (%)	24 (25%)	19 (40%)	39 (40%)
Headache	4 (4)	2 (4)	3 (3)
Pain/redness at catheter site	2 (2)	4 (9)	3 (3)
Sleepiness	2 (2)	0 (0)	4 (4)
Abdominal pain/sore stomach	2 (2)	1 (2)	0 (0)
Nausea/vomiting	2 (2)	0 (0)	0 (0)
Low hemoglobin or hematocrit	1 (1)	5 (10)	4 (4)
High AST or ALT	1 (1)	2 (4)	0 (0)
Hot flushes	1 (1)	0 (0)	1 (1)
Loose stools	1 (1)	0 (0)	1 (1)
Fatigue	1 (1)	0 (0)	1 (1)
Seeing black	1 (1)	0 (0)	0 (0)
Protein in urine	1 (1)	0 (0)	2 (2)
High glucose	1 (1)	0 (0)	2 (2)
Low back pain	1 (1)	0 (0)	1 (1)
Dizziness	1 (1)	0 (0)	4 (4)
Low MCHC	1 (1)	0 (0)	0 (0)
Knee pain	1 (1)	0 (0)	0 (0)
Sore/Scratchy throat	0 (0)	3 (6)	2 (2)
Stuffy nose	0 (0)	1 (2)	2 (2)
Redness/itchiness of leg	0 (0)	0 (0)	2 (2)
Trouble sleeping	0 (0)	0 (0)	1 (1)
Red cells in urine	0 (0)	0 (0)	1 (1)
Swelling of gums	0 (0)	0 (0)	1 (1)
High creatinine	0 (0)	0 (0)	1 (1)
Cough	0 (0)	0 (0)	1 (1)
Feels feverish	0 (0)	0 (0)	1 (1)
Sweaty palms	0 (0)	0 (0)	1 (1)
Scratch on thumb	0 (0)	1 (2)	0 (0)

AEs were more frequently reported with the reference products (40% Claritin Tablets, 40% Claritin Syrup) than with the Applicant's ElixSure Loratadine product (25%). Adverse events occurring more frequently for the test formulation and in more than one subject compared to the reference products were the following: headache, sleepiness, abdominal pain/sore stomach, and nausea/vomiting. Other AEs reported in subjects taking the test product were reported in one or fewer subjects.

Reviewer's Comment: There were no clinically meaningful differences in AEs between the proposed and approved products.

Reviewer's Comment: Subject #26 was identified by the Division's OCPB Reviewer to be a slow metabolizer. Subject #26 experienced headache, sore throat, blocked nose, and low hemoglobin post dosing with Claritin Tablets [5.2.1.2.1, page 291-292].

The AEs from the two clinical pharmacology studies do not point to a safety signal for the Applicant's product. Due to the limited number of subjects, limited number of non-Caucasians, and lack of women in the clinical pharmacology studies, an association between AEs and gender and race or ethnicity cannot be determined. In addition, subjects in both studies were between the ages of 18-69 years of age; therefore, no subgroup analysis of AES for pediatric subjects or subjects ≥ 65 years of age was performed.

7.3.6. Serious Adverse Events and Deaths

There were no serious adverse events or deaths among subjects in the two clinical pharmacology studies.

7.3.7. Withdrawals due to Adverse Events

There were no withdrawals due to adverse events among subjects in the two clinical pharmacology studies.

7.3.8. Vital Signs

Vital signs were not safety endpoints in the Applicant's clinical pharmacology studies.

7.3.9. Physical Examination

Physical examination was not a safety endpoint in the Applicant's clinical pharmacology studies.

7.3.10. Laboratory Studies

Laboratory studies were performed at screening and at the end of the study. Abnormalities in laboratory values were reported as adverse events in Table 7.

7.3.11. ECGs

ECGs were performed at screening, but were not safety a safety endpoint in the Applicant's clinical pharmacology studies.

7.4. Literature Review of Safety

The Applicant provided many references regarding the safety of loratadine, including the summary for the basis of approval (SBOA) for Claritin Syrup (NDA# 20-641), the SBOA for Clarinex (NDA# 21-363), and multiple articles addressing the pharmacokinetics of loratadine. The Applicant's brief review of the safety of loratadine from the clinical literature did not identify any new safety concerns or AEs associated with loratadine use, which have not been previously identified.

The following is a review of the safety of loratadine based upon the clinical literature and safety information from the FDA Advisory Committee Meeting held on May 11, 2001, which addressed the issue of switching loratadine to OTC status.

7.4.1. Cardiac Events

The Applicant did not provide any articles or reports regarding cardiac events with loratadine use. For the FDA Advisory Committee Meeting on May 11, 2001, the OTC Switch Review Team conducted a review of the AERS database and identified ventricular

arrhythmias and sudden death associated with loratadine use as a potential area of concern. Careful reviews of the cases revealed confounding factors in the majority of cases, which precluded a definitive conclusion that loratadine use was causally related to the reported AE. The Executive Summary on Risk Issues summarized the report of the OTC Switch Review Team on the safety assessment of antihistamines and addressed the cardiac safety of loratadine. The OTC Switch Review Team noted that there was a potential safety signal for ventricular arrhythmias, but the data was inconclusive and suggested that if such events were causally-related to loratadine, they are extremely rare [http://www.fda.gov/ohrms/dockets/ac/01/briefing/3737b1.htm].

7.4.2. Hepatotoxicity

The Applicant did not provide any articles regarding hepatotoxicity with loratadine use. This reviewer's Medline search identified an article with two cases of hepatotoxicity associated with loratadine use.[1] One case was a 42 year old woman who developed submassive hepatic necrosis and received a liver transplant one month after a cholecystectomy. She had been taking loratadine for 14 months prior to the cholecystectomy. The second case was a 33 year old man who developed hepatitis three weeks after taking loratadine. His liver enzyme tests returned to normal after two months. Rare reports of hepatic toxicity, including hepatic necrosis, were noted in the prescription labeling for Claritin.

Reviewer's Comment: Both cases were confounded by exposure to other medications.
Reviewer's Comment: The rare occurrences of liver-related events reported with loratadine use were discussed during the FDA Advisory Committee Meeting on May 11, 2001, which addressed the issue of switching loratadine to OTC status. The Executive Summary of Risk Issues stated that there was no clear causal relationship between loratadine use and the occurrence of hepatic failure, however, the possibility that loratadine use may very rarely result in hepatic failure could not be excluded. The reporting rate for hepatic failure in association with the use of loratadine was several-fold lower than the calculated background rate of hepatic failure [www.fda.gov/ohrms/dockets/ac/01/briefing/3737b1.htm].

7.4.3. Seizures

The Applicant did not address or identify loratadine use with the possible association of seizures. The OTC Switch Review Team Executive Summary of Risk Issues noted 43 cases of seizures reported in association with loratadine use. The FDA staff concluded that a causal association was possible or likely in 26 of the cases, but that this may represent a class effect of antihistamines [www.fda.gov/ohrms/dockets/ac/01/briefing/3737b1.htm]. Seizures were listed in the Claritin® prescription labeling in the Adverse Reaction section.

7.4.4. Hypospadias

The Applicant did not address the possible association between hypospadias and loratadine use during pregnancy, which was noted in the Swedish Medical Birth Registry. The issue of the possible association between hypospadias and loratadine use during pregnancy has been explored by the Agency through the Office of Drug Safety and determined not to be a significant issue. In addition, the CDC analyzed data from the National Birth Defects Prevention Study and determined that no increased risk for second or third degree

hypospadias existed among women who used loratadine in early pregnancy.[2] The Applicant's product label instructs the pregnant consumer to consult a health professional before using the product, which is appropriate.

7.4.5. Special Populations

The pharmacokinetics of loratadine in pediatric subjects 2 years of age and older is similar to that in healthy adults. The type and frequency of AEs in pediatric subjects are similar to those seen in the adult population [2.5.3, page 8]. Geriatric subjects have AUC and C_{max} values for loratadine and DCL that are approximately 50% greater than in younger subjects. In addition, the clearance of loratadine tends to be lower in the elderly compared to young adults. However, despite the higher systemic exposure, geriatric subjects did not have an increase in AEs and did not have clinically significant changes in laboratory tests or ECGs.

The Applicant stated that in clinical studies to support the approval of Claritin, there was no evidence of a gender or race associated difference in the safety profile of loratadine [2.5.3, page 8]. However, pharmacokinetic studies indicate a subset of the general population are slow metabolizers of DCL and the frequency of slow metabolizers is higher in Blacks. Slow metabolizers of DCL cannot be prospectively identified. The Division's experience has been that there are no differences in safety profiles between slow and normal metabolizers. The increased exposure to DCL in slow metabolizers is not considered to be clinically relevant in the population proposed for use.

Patients with liver or renal impairment have increased AUC and C_{max} values for loratadine compared with normal subjects. The Applicant states that patients with liver or renal impairment should be given a lower initial dose [2.5.3, page 9]. The Applicant's proposed product label recommends consumers with liver or kidney disease to ask a doctor.

There are no adequate and well-controlled studies of loratadine use in pregnant or lactating women. The safety of loratadine use in this population has not been established; therefore, the Applicant stated that loratadine should be used only if the potential benefit justifies the potential risk to the fetus or infant. The Applicant's product label instructs the pregnant consumer to consult a health professional before using the product, which is appropriate.

7.4.6. Drug-Drug Interaction

The Applicant provided information from the previous prescription labeling for the reference drug, Claritin, which noted that increased plasma concentrations (AUC_{0-24}) of loratadine and/or descarboethoxyloratadine were observed in normal volunteers following co-administration of loratadine 10 mg once daily with therapeutic doses of erythromycin, cimetidine, and ketoconazole. However, there were no clinically relevant changes in the safety profile of loratadine, as assessed by ECG parameters, clinical laboratory tests, vital signs, and adverse events. There were no significant effects on QTc intervals, and no reports of sedation or syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations (AUC_{0-24}) of erythromycin decreased 15% with co-administration of loratadine relative to that observed with erythromycin alone.

7.5. Post-marketing Surveillance

The Applicant provided a tabular listing of post-marketing adverse event reports for Claritin and loratadine that were submitted to the FDA AERS database during the period from November 1, 1997, through December 30, 2002 [Response to Information Request, May 6, 2004, Section 5]. The Applicant did not provide a summary or analysis of the AERS database reports. This reviewer examined the AERS tabular listing provided by the Applicant and determined the following:

- Ten most commonly reported AEs:
  - Dyspnea
  - Headache
  - Nausea
  - Dizziness
  - Drug Ineffective
  - Chest pain
  - Condition aggravated (no details provided)
  - Abdominal pain
  - Pyrexia

In general, the most commonly reported AEs noted in the post-marketing safety database are similar to those noted in clinical trials, which were listed in the Claritin product label prior to the OTC switch.

- 25 deaths reported – no additional information provided

Reviewer's Comment: It is not surprising to have some deaths reported in the AERS database considering the very large market of Claritin and other loratadine products.
Reviewer's Comment: The Applicant did not provide events reported in the AERS database, which may be gender specific or specific to the pediatric subpopulation.

7.6. Safety Update

The Applicant did not provide a safety update during the review period. Children's ElixSure 24 hr Antihistamine is currently not marketed in the US.

7.7. Drug Withdrawal, Abuse, and Overdose Experience

The Applicant stated that there is no information to indicate that abuse or dependence occurs with loratadine. In addition, the Applicant stated that no information pertinent to withdrawal and/or rebound effects was found [2.7.4, page 15].
Reviewer's Comment: This reviewer noted 50 reports of drug abuse/drug addict/drug addiction in the AERS database tabular listing submitted by the Applicant. Because no further details are provided, it is difficult to draw any conclusions as the reports are potentially confounded with concomitant medication use.

As noted in the Claritin product label, the Applicant states that somnolence, tachycardia, and headache have been reported with overdoses of loratadine greater the 10mg (40 to 180mg). The Applicant also reports that extrapyramidal signs and palpitations have been reported in children with overdoses of greater than 10mg of loratadine syrup.
Reviewer's Comment: This reviewer noted 40 reports of overdose listed in the submitted AERS database tabular listing. A Medline search using the search terms loratadine and overdose produced several articles. One article was a case of an intentional overdose of

300mg of loratadine in a 6 year old child, which resulted in minor elevation of blood pressure and heart rate.[3] *The limited amount of data in the clinical literature regarding the overdose of loratadine prevents drawing any definitive conclusions.*

7.8. Adequacy of Safety Testing

The safety of the Applicant's formulation for use in the intended population relies on the Agency's previous finding of safety for loratadine. In addition, the safety data from the Applicant's two clinical pharmacology studies, the published literature, and the AERS Data Base are consistent with the Agency's previous finding of safety for loratadine. Overall, the body of safety data available for this review is sufficient to establish the safety of the Applicant's formulation of loratadine for use in the intended clinical population.

7.9. Labeling Safety Issues and Post-marketing Commitments

The review of safety for the Applicant's product did not raise any safety concerns that require modification of the proposed label.

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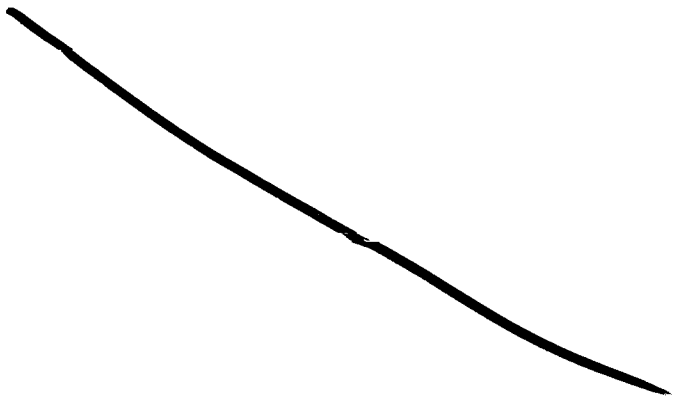
8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The proposed dosing for adults and children is the same as for the approved product. The Applicant proposes the following dosing for the Children's ElixSure Allergy Loratadine Suspension [1.3b]:

- Adults and children 6 years and over - 2 teaspoons daily (10mg)
- Children 2 to under 6 years of age - 1 teaspoon daily (5mg).

The package label states to not take more than the above recommended daily doses. In addition, the Warning section of the label instructs the consumer not to use more than the recommended dose and that taking more than the recommended dose may cause drowsiness [1.3b].

Regarding administration, the directions on the product label state "use this product only with the enclosed teaspoon and do not overfill. The enclosed teaspoon holds 5 mL when filled level to top rim. Level by mildly shaking or tapping the spoon." [1.3b]



9. USE IN SPECIAL POPULATIONS

9.1. Pediatric

The Applicant stated that the pharmacokinetics of loratadine in children 2 to 5 years of age is similar to that in healthy adults [2.5.3, page 9]. Claritin's product label recommends 10mg loratadine for children 6 years of age and older and 5mg loratadine for children 2 to 6 years of age. The Applicant's proposed product label recommends similar dosing [1.3.b].

Reviewer's Comment: The Applicant's proposed product label recommends the same dosing as Claritin, which is appropriate.

9.2. Elderly

The Applicant stated that a trend toward reduced plasma clearance and prolonged plasma elimination half-life for loratadine was seen in a study of 12 healthy geriatric subjects (66 to 78 years old) who received 40mg of loratadine. The study showed that the clearance of loratadine tends to be lower in the elderly compared to young adults.[4] All physical exams, laboratory tests, ECGs were considered clinically unremarkable during the study. In addition, no AEs were reported in the study. The prescription label for Claritin notes that geriatric subjects have AUC and C_{max} values for loratadine and DCL that are approximately 50% greater than in younger subjects. Claritin's product label does not make special recommendation for dosing in healthy elderly adults. The Applicant's proposed label makes no special recommendation for dosing for healthy geriatric consumers [1.3.b].

Reviewer's Comment: The Applicant's proposed labeling, which does not propose special recommendations for dosing in healthy geriatric consumers, is appropriate.

9.3. Gender

The Applicant stated that the AEs noted in the clinical trials conducted by Schering to support the approval of Claritin did not differ significantly with respect to sex [2.5.3, page 8]. A PubMed literature search was performed by this reviewer and no additional information regarding the safety and efficacy of loratadine based upon gender was discovered. However, a study on the effect of sex on the pharmacokinetics of DCL did show that, based upon DCL levels, females tended to have a slightly higher C_{max} and AUC.[5]

Reviewer's Comment: The Applicant's product label does not have specific instructions related to gender, which is appropriate.

9.4. Race

The Applicant stated that the AEs noted in the clinical trials conducted by Schering to support the approval of Claritin did not differ significantly with respect to race [2.5.3, page 8]. A study sponsored by Schering-Plough on the effect of race and sex on the pharmacokinetics of DCL did show that, based upon DCL levels, black subjects typically had a higher Cmax and AUC than Caucasians.[5]

Reviewer's Comment: The prescription product label for Clarinex (descarboethoxyloratadine, DCL) states that pharmacokinetic studies indicate a subset of the general population are slow metabolizers of DCL and the frequency of slow metabolizers is higher in Blacks. Slow metabolizers of DCL cannot be prospectively identified. Although not noted in the PK studies for Clarinex, patients who are slow metabolizers may be more susceptible to dose-related adverse events. The increased exposure to DCL in slow metabolizers was not considered to be clinically relevant in the population proposed for use and, therefore, no change in dosage was recommended for either Claritin or Clarinex based upon race.

Reviewer's Comment: The Applicant's product label does not have specific instructions related to race, which is appropriate.

9.5. Hepatic Impairment

As noted in the previous prescription labeling for Claritin, the Applicant stated that patients with hepatic impairment should be given a lower initial dose of loratadine. Patients with liver disease had increased AUC and C_{max} for loratadine, but the AUC and C_{max} for DCL were similar to normal subjects. The Applicant's proposed product label instructs consumers with liver disease to ask a doctor [1.3.b].

Reviewer's Comment: The Applicant's proposed labeling instructions are appropriate for consumers with liver disease.

9.6. Renal Impairment

Patients with renal disease (creatinine clearance < 30 mL/min) have an increased AUC and C_{max} for loratadine and DCL. The Applicant stated that patients with renal insufficiency (GFR <30 mL/min) should be given a lower initial dose [2.5.3, page 9]. As noted in the prescription product label for Claritin, adults and children 6 years of age and over with renal insufficiency (GFR <30mL/min), the starting dose should be 10mg every other day. In children 2 to 5 years of age with renal insufficiency, the starting dose should be 5mg every other day. The Applicant's proposed product label instructs consumers with renal disease to ask a doctor [1.3.b].

Reviewer's Comment: The Applicant's proposed labeling instructions are appropriate for consumers with renal disease.

9.7. Pregnancy and Lactation

There are no adequate and well-controlled studies of loratadine use in pregnant or lactating women. The safety of loratadine use in this population has not been established; therefore, the Applicant stated that loratadine should be used only if the potential benefit justifies the potential risk to the fetus or infant [2.5.3, page10]. A discussion of the possible association between hypospadias and loratadine use in pregnancy has been explored by the Agency through the Office of Drug Safety and determined not to be a significant issue. The Applicant's proposed product label instructs consumers who are pregnant or breastfeeding to consult a health care professional before use [1.3.b].

Reviewer's Comment: The Applicant's product label instructs the pregnant consumer to consult a health professional before using the product, which is appropriate.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Conclusions Regarding Safety and Efficacy

This NDA is an application for Children's ElixSure™-24 hr Antihistamine. The 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 and a comparison of the bioavailability and bioequivalence of the proposed Test drug to that of the approved Reference product. The reference products are Claritin® Tablets 10-mg and Claritin® Syrup. The proposed indication is the following: temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat. The proposed dose for adults and children 6 years and older is 10mg (2 teaspoons) daily and 5mg (1 teaspoon) daily for children 2 year of age to under 6. The product is not indicated for children under the age of 2 years.

The Applicant's development plan consisted of two clinical pharmacology studies to compare the bioavailability and bioequivalence of Children's ElixSure™-24 hr Antihistamine to the approved Claritin products. A 90% confidence interval (CI) for the ratio of the means of the AUC and C_{max} for the proposed and approved product was determined.

Based upon loratadine levels, the Applicant's product was not bioequivalent to Claritin Syrup, because the C_{max} for the Applicant's product was below the bioequivalence range. In general, the Applicant's product was more similar to Claritin Tablets than Claritin Syrup. However, a key pharmacokinetic parameter fell below the bioequivalence range. Based upon loratadine levels in the fasting state, the 90% CI of the C_{max} of Children's ElixSure™-24 hr Antihistamine compared to Claritin Tablets was [redacted] which is below the bioequivalence range.

The clinical pharmacology studies demonstrated that key PK parameters based upon descarboethoxyloratadine (DCL, active metabolite of loratadine) levels were more similar between Children's ElixSure™-24 hr Antihistamine and Claritin Tablets. However, the efficacy of loratadine cannot be supported entirely upon the activity of the metabolite, DCL. Both loratadine and DCL demonstrate antihistamine activity and both likely contribute to the efficacy of Claritin Tablets and Claritin Syrup. Therefore, the lower C_{max} for loratadine observed with the Applicant's product cannot be presumed to provide efficacy.

Because the exposure to loratadine and DCL for Children's ElixSure 24 hr Antihistamine is not greater than the exposure to loratadine and DCL for the approved products, it is reasonable to extrapolate the Agency's previous determination of the acceptable safety profile of the Claritin products to Children's ElixSure™-24 hr Antihistamine. In addition, the Applicant supported the safety of Children's ElixSure™-24 hr Antihistamine with data from the pivotal clinical pharmacology studies, safety information for loratadine from the clinical literature, and AE reports in the US AERS database.

In the clinical pharmacology studies, there were no meaningful differences between the proposed and approved products in adverse events (AEs), withdrawals due to AEs, or other safety endpoints. In addition, a review of the AERS database did not provide evidence of new safety concerns.

In summary, there is no evidence of a safety signal that has not been previously identified in the prescription labeling for Claritin, the literature, or the AERS database. The Applicant's safety review supports the proposed indication and over-the-counter (OTC) marketing of Children's ElixSure 24 hr Antihistamine. Additional clinical studies to document safety of the Applicant's product are not required.

10.2. Recommendations on Approvability

In this 505(b)(2) application, Taro Pharmaceuticals has 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 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. Although the safety of loratadine has been established, the efficacy of Children's ElixSure™-24 hr Antihistamine has not been established; therefore, from a clinical perspective, the recommendation is for an Approvable action. A path forward would be to perform clinical studies with Children's ElixSure™-24 hr Antihistamine to demonstrate efficacy. Alternatively, the Applicant could choose to reformulate and perform clinical pharmacology studies to demonstrate bioequivalence with an approved product.

10.3. Labeling

Since Children's ElixSure™-24 hr Antihistamine is intended for OTC use, the Division of OTC Drug Products performed a detailed review of the proposed package label and provided recommendations for labeling revisions.

APPENDIX

1. DETAILED STUDY REVIEWS

1.1. Study # 30218

Title: A Randomized, 3-Way Crossover, Bioequivalence Study of Loratadine 5mg/5mL NonSpil Suspension and Claritin Administered as 1 x 40mL (5mg/5mL) Non-Spil Suspension or 4 x 10mg Tablets or 1 x 40mL (5mg/5mL) Syrup in Healthy Subjects under Fasting Conditions

Reviewer's Comment: The Applicant uses the term Non-Spil Suspension for Children's ElixSure 24 hr Antihistamine throughout both study protocols and reports.

1.1.1. Protocol

1.1.1.1. Investigators and Centers

Study 30218 was performed at the following single site.

R. Larouche, MD (Principle Investigator)
Anapharm Inc.
5160, Boul. Décarie, suite 500
Montréal, Québec, Canada [2.7.1.2, page 1]
Reviewer's Comment: The Applicant clarified the study site in a Response to Information Request, dated April 20, 2004.

1.1.1.2. Objective/Rationale

The objective of this study is to compare the rate and extent of absorption of loratadine 5mg/5mL NonSpil suspension (Test) versus Claritin Syrup 5mg/5mL (Reference) and Claritin 10mg Tablets (Reference) under fasting conditions following a 40mg dose [5.3.1.2.1, page 312].

1.1.1.3. Overall Design

The study design was a single center, single dose, bioequivalence, open-label, randomized, 3-period, 6-sequence crossover study [5.3.1.2.1, page 312]. Single oral doses were separated by washout periods of at least 14 days [5.3.1.2.1, page 271].

1.1.1.4. Study Population

The study population was 51 healthy adult non-smoking male volunteers, who were 21 to 67 years of age. Pertinent exclusion criteria included clinically significant medical illness, clinically significant abnormal laboratory tests, drug, tobacco or alcohol use, BMI > 30, recent use of prescription medications (14 days), OTC medications (7 days) or medications which affect hepatic drug metabolism (30 days) [5.3.1.2.1, page 271, 312-314].

Reviewer's Comment: The Applicant excluded female subjects because of the potential risk of loratadine to the human fetus [5.3.2.1, page 312].

1.1.1.5. Study Procedures

Screening procedures were performed within 28 days prior to administration of study medication. Screening procedures included: history and physical exam, ECG, chemistry and hematology labs, HIV and hepatitis screening, urinalysis, and urine drug screen [5.3.1.2.1, page 314 and322].

Informed consent was obtained from all subjects prior to initiation of study procedures. Subjects were required to abstain from the following food/beverage items prior to study drug administration [5.3.1.2.1, page 314]:

- Xanthine or caffeine containing food or beverages (48 hours)
- Energy drinks (48 hours)
- Alcohol (24 hours)
- Grapefruit products, supplements, vitamins (7 days).

Subjects were confined to the study site at least 10 hours before taking the study drug and were randomized into the following three separate treatment groups listed in Table 8 [5.3.1.2.1, page 273]:

Table 8 Study 30218 Treatment Groups

Treatment Code	Product	Sponsor	Dose	Identification No.	Expirary Date
A (Test)	Loratadine NonSpil Suspension	Taro Pharmaceuticals	40 mg (40 mL of 5mg/5mL suspension)	Lot No: S189-54098 (EBK-L05)	[redacted]
B (Reference 1)	Claritin Syrup 5mg/5mL	Schering Corporation	40mg (40mL of 5mg/5mL syrup)	Lot No: 3LTN2	
C (Reference 2)	Claritin 10mg Tablets	Schering Corporation	40mg (4 x 10mg tablets)	Lot No: 2-RXF-1035	

Reviewer's Comment: The Applicant did not provide justification for using a 40mg dose of loratadine instead of the proposed labeled dose of 10mg.

After a supervised overnight fast of at least 10 hours, subjects were dosed in the mornings between 8:00 and 9:40am with 240 mL of water, followed by a fast of 4 hours. Meals were controlled and were identical for all periods. Except water given with study medication, no fluids were allowed from 1 hour before dosing until 1 hour post-dose. Water was provided *ad libitum* at all other times [5.3.1.2.1, page 273 & 316].

Blood samples for pharmacokinetic measurements were collected before dosing (0 hours) and at 0.250, 0.500, 0.667, 0.75, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 12.0, 24.0, 48.0, and 72.0 hours post-dosing. Subjects were allowed to leave the study center after the 24 hour post dose blood draw and return for the subsequent draws. A total volume of blood drawn from each subject completing this study did not exceed 665 mL. A washout period of at least 14 days separated the treatment periods [5.3.1.2.1, page 316].

1.1.1.6. Pharmacokinetic Parameters

No parameters of clinical efficacy were evaluated in this study.

The following pharmacokinetic parameters were determined for loratadine and descarboethoxyloratadine (DCL) from the plasma concentration data [5.3.1.2.1, page 319]:

- The maximum observed concentration (C_{max})
- The time of observed Cmax (T_{max})
- The elimination rate constant (k_{el})
- The elimination half life ($T_{1/2el}$)
- The area under the concentration-time curve from time zero to the last non-zero concentration (AUC_{0-t})
- The area under the concentration-time curve from time zero to infinity (AUC_{0-inf}).

1.1.1.7. Safety Evaluations

Subjects were monitored for adverse events throughout the study. Hematology tests were performed on each subject prior to Period 3 [5.3.1.2.1, page 274 and 322]. At the conclusion of the study, hematology, chemistry laboratory tests (including liver function tests), and urinalysis were performed [5.3.1.2.1, page 322]. Subjects could have been withdrawn from the study by the investigator for safety considerations [5.3.1.2.1, page 317].

1.1.1.8. Statistical Plan

The pharmacokinetic parameters were analyzed by ANOVA on untransformed T_{max}, k_{el}, and $T_{1/2el}$ and on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} at the alpha level of 0.05. Ratio of means (Test/Reference) and 90% geometric confidence intervals for the ratio of means, based on least-squares means from the ANOVA of the ln-transformed data were calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. As stated in the protocol, the criteria for average bioequivalence for loratadine is the 90% geometric confidence interval of the ratio (Test/Reference) of least-squares means from the ANOVA of the ln-transformed AUC_{0-inf}, AUC_{0-t}, and C_{max} within the range of 80% to 125% [5.3.1.2.1, page 319-320].

1.1.2. Results

1.1.2.1. Subject Disposition and Demographics

A total of 56 subjects were confined for Period 1, but only 51 were enrolled in the study and dosed with medication. A total of 45 subjects completed the study. One subject was withdrawn from the study due to concomitant therapy required for an adverse event (amoxicillin for gum swelling). Of the other five subjects, two elected to withdraw for no specified reason and the other three elected to withdraw by not showing up to the clinical facility [5.3.1.2.1, page 275].

All subjects were male with a mean age of 34 and an age range of 18 to 67 years. The racial composition was 40 Caucasian (78%), 6 American Hispanics (12%), and 5 Blacks (10%) [5.3.1.2.1, page 280].

Reviewer's Comment: The under-representation of women and subjects of non-Caucasian race is less than ideal. However, the innovator's product label does not list a clinically

significant gender-related or race-related difference in loratadine pharmacokinetics [Claritin® Product Label].

1.1.2.2. Pharmacokinetic Endpoint Outcomes

Table 9 is a summary of the key pharmacokinetic parameters from study 30218 [2.7.1, page 4-12]. The data is presented for loratadine and descarboethoxyloratadine (DCL) using geometric means, ln-transformed. As shown below, the 90% confidence interval for the ratio of the geometric means of the Test and Reference products was determined.

Study 30218 (Fasting) Mean Loratadine PK Parameters					
Parameter	**TRT[1]**	**Mean[2] (%CV)**	**Pair**	**Ratio**	**90% CI**
AUC_t (ng*h/mL)	A	44.3 (109)	A/B	0.65	***58.3-72.1***
	B	68.3 (91)	A/C	0.94	84.2-104.1
	C	47.3 (109)	B/C	1.44	129.8-160.6
AUC_{inf} (ng*h/mL)	A	47.4(109)	A/B	0.66	***59.3-73.5***
	B	71.8(92)	A/C	0.95	85.3-105.7
	C	49.9(109)	B/C	1.44	129.1-160
C_{max} (ng/mL)	A	13.5(109)	A/B	0.53	***45.0-61.6***
	B	25.6 (98)	A/C	0.81	***69.3-94.9***
	C	16.6(113)	B/C	1.54	131.6-180.2
Study 30218 (Fasting) Mean DCL PK Parameters					
AUC_t (ng*h/mL)	A	222.8(42)	A/B	1.01	95.8-105.8
	B	221.3(41)	A/C	1.07	101.8-112.5
	C	208.2(42)	B/C	1.06	101.1-111.7
AUC_{inf} (ng*h/mL)	A	238.3(46)	A/B	1.01	95.4-106.0
	B	237(46)	A/C	1.06	100.3-111.4
	C	225.5(46)	B/C	1.05	99.7-110.8
C_{max} (ng/mL)	A	16.5(37)	A/B	0.84	***79.0-90.0***
	B	19.6(38)	A/C	1.09	102.4-116.7
	C	15.1(41)	B/C	1.30	121.3-138.4

1 Treatment Groups: A= Taro ElixSure Loratadine (NonSpil). B= Claritin Children's Syrup, C=Claritin 10mg tablet
2 Geometric means, ln-transformed

Based upon loratadine levels, the C_{max} of the ElixSure product compared to both Claritin tablet and syrup does not support bioequivalence; however, the C_{max} based upon DCL levels is within the bioequivalent range for the tablet comparator, but just outside the bioequivalence range for the syrup comparator. The Applicant did not provide a justification for these PK parameters being outside the bioequivalence range.

1.1.2.3. Safety Outcomes

1.1.2.3.1. Withdrawals

As stated above, 51 subjects were dosed with study medication, but only 45 subjects completed the study. Subject #21 experienced swelling of the gums, for which his dentist prescribed amoxicillin. The patient was withdrawn from the study due to concomitant medication use. The other five subjects (Nos. 11, 18, 20, 33, and 46) either elected to

withdraw without a specified reason or did not return to the clinical facility [5.3.1.2.1, page 275 and 277].

1.1.2.3.2. Adverse Events

Of the 45 subjects who completed the study, 55 post-dose adverse events were recorded. There were no serious adverse events (SAEs) or deaths in the study. Table 10 is a summary of post dose adverse events reported by the subjects in order of frequency (except pain at catheter site and scratch on thumb, which were considered not related to study medication) [5.3.1.2.1, page 291-293].

Table 10 Study 30218 Post Dose Adverse Events

Adverse Event	ElixSure Loratadine Test A	Claritin Syrup Reference B	Claritin Tablet Reference C
All Adverse Events N (%)	14 (31%)	19 (42%)	22 (49%)
Headache	4	2	2
Nausea/Vomiting	2	0	0
Low Hgb or Hct	1	5	2
High AST or ALT	1	2	0
Hot flushes	1	0	1
Loose Stools	1	0	1
Fatigue	1	0	0
Seeing black	1	0	0
Sore/Scratchy Throat	0	3	2
Stuffy Nose	0	1	2
Dizziness	0	0	3
Sleepiness	0	0	2
Abdominal Pain	0	1	0
Swelling of gums	0	0	1
High creatinine	0	0	1
High glucose	0	0	1
Cough	0	0	1
Feels feverish	0	0	1
Sweaty palms	0	0	1
Scratch on thumb	0	1	0
Pain at catheter site	2	4	1

N= number of subjects
% subjects = N/45 total subjects who completed study

Fewer adverse events were reported with the Test product compared to the Reference formulations, 31% vs. 42% and 49%, respectively. Overall, the most common adverse events were: headache and low hemoglobin/hematocrit. A few adverse events were unique to the Test formulation: nausea/vomiting, fatigue, and seeing black, while headache was more common in the Test product group. Although no subject withdrew from the study due to an adverse event, one adverse event required treatment with amoxicillin for gum swelling. As mentioned above, that subject was withdrawn due to use of a prohibited concomitant medication.

Reviewer's Comment: Because of the small number of subjects and AEs, it is difficult to draw any meaningful safety conclusions from this data.

1.1.2.3.3. Clinical Laboratory

Laboratory studies were performed at screening, prior to period three and at the conclusion of the study. Abnormalities were reported as adverse events and are included above in Table 10. All abnormal laboratory results were normal on follow up evaluation with the exception of four subjects, whose results remained abnormal (No. 1 ALT 66, No. 3 ALT 82, No. 39 Hgb 116 g/L, No. 41 Hgb 124 g/L). Letters were sent to their family practitioner for follow up [5.3.1.2.1, page 274-275, 277-278].

1.1.3. Discussion and Conclusions

1.1.3.1. Pharmacokinetics

The purpose of this single dose study in healthy male volunteers under fasting conditions, was to compare the bioavailability between the ElixSure test product and Claritin Syrup and Claritin 10mg tablets. The 90% confidence interval for the ratio of the geometric means of the C_{max} and AUC are utilized for discussion of the pertinent findings from Study 30218.

Based upon loratadine levels, the Applicant's Test product was not bioequivalent to either Claritin product, because the C_{max} for the Applicant's Test product was below the bioequivalence range. In general, the Applicant's Test product was more similar to Claritin Tablets than Claritin Syrup. However, based upon loratadine levels in the fasting state, the 90% CI of the C_{max} of Children's ElixSure™-24 hr Antihistamine compared to Claritin Tablets was 69.3-94.9%, which is below the bioequivalence range.

The key PK parameters based upon descarboethoxyloratadine (DCL, active metabolite of loratadine) levels were more similar between Children's ElixSure™-24 hr Antihistamine and Claritin Tablets and Claritin Syrup. However, the efficacy of loratadine cannot be supported entirely upon the activity of the metabolite, DCL. Both loratadine and DCL demonstrate antihistamine activity and both likely contribute to the efficacy of Claritin Tablets and Claritin Syrup. Therefore, the lower C_{max} for loratadine observed with the Applicant's product cannot be presumed to provide efficacy.

1.1.3.2. Safety Evaluations

Because of the small number of subjects in this study, it is difficult to draw conclusions regarding safety based upon the safety data from this study. However, there were no significant differences between the ElixSure product and the Claritin products for AEs or other safety variables; therefore, no safety signals were noted.

1.2. Study # 30219

Title: A Randomized, 2-Way Crossover, Bioequivalence Study of Loratadine 5mg5/mL NonSpil Suspension and Claritin Administered as 1 x 40mL (5mg/5mL) NonSpil Suspension or 4 x 10mg Tablets in Healthy Subjects Under Fed Conditions [5.3.1.2.2, page 291].

Reviewer's Comment: The Applicant uses the term Non-Spil Suspension for Children's ElixSure 24 hr Antihistamine throughout both study protocols and reports.

1.2.1. Protocol

1.2.1.1. Investigator and Center

[redacted]

1.2.1.2. Objective/Rationale

The objective of this study is to compare the rate and extent of absorption of loratadine 5 mg/5mL non-spill suspension (test) versus Claritin 10mg tablets (reference) under fed conditions following a 40mg dose [5.3.1.2.2, page 299].

1.2.1.3. Overall Design

The study design was a single center, single dose, bioequivalence, open-label, randomized, 2-period, 2-sequence crossover study [5.3.1.2.2, page 299]. Single oral doses were separated by washout periods of at least 14 days [5.3.1.2.2, page 303].

1.2.1.4. Study Population

The study population was 52 healthy adult non-smoking male volunteers, who were 18 years of age and older. Pertinent exclusion criteria included clinically significant medical illness, clinically significant abnormal laboratory tests, drug, tobacco or alcohol use, BMI > 30, recent use of prescription medications (14 days), OTC medications (7 days) or medications which affect hepatic drug metabolism (30 days) [5.3.2.2, page 300-301].

1.2.1.5. Study Procedures

Screening procedures were performed within 28 days prior to administration of study medication. Screening procedures included: history and physical exam, ECG, chemistry and hematology labs, HIV and hepatitis screening, urinalysis, and urine drug screen [5.3.1.2.2, page 302].

Informed consent was obtained from all subjects prior to initiation of study procedures. Subjects were required to abstain from the following food/beverage items prior to study drug administration [5.3.1.2.2, page 301]:

- Xanthine or caffeine containing food or beverages or energy drinks (48 hours)
- Alcohol (24 hours)

- Grapefruit products, supplements, vitamins (7 days).

Subjects were confined to the study site at least 11 hours before taking the study drug and were randomized into the following two treatment groups listed in Table 11 [5.3.1.2.2, page 263, 302-303].

Table 11 Study 30219 Treatment Groups

Treatment Code	Product	Sponsor	Dose	Identification No.	Expirary Date
A (Test)	Loratadine NonSpil Suspension	Taro Pharmaceuticals	40 mg (40 mL of 5mg/5mL suspension)	Lot No: S189-54098 (EBK-L05)	[redacted]
B (Reference)	Claritin 10mg Tablets	Schering Corporation	40mg (4 x 10mg tablets)	Lot No: 2-RXF-1035	

Reviewer's Comment: The Applicant did not provide justification for using a 40mg dose of loratadine instead of the proposed labeled dose of 10mg.

After a supervised overnight fast of at least 10 hours and 30 minutes, subjects were served a high-fat, high-caloric breakfast of between 800 and 1000 calories. Subjects were required to completely consume the breakfast prior to drug administration. Subjects were dosed with the Test or Reference product in the mornings between 7:00 and 8:38 am with 240 mL of water, followed by a fast of 4 hours. Meals were controlled and were identical for all periods. With the exception of the volume administered at the time of dosing and with the pre-dose breakfast, fluids were not permitted from 1 hour before dosing to 1 hour after dosing, but water was permitted *ad libitum* at all other times [5.3.1.2.2, page 263-264].

Blood samples for pharmacokinetic measurements were collected before dosing (0 hours) and at 0.250, 0.500, 0.667, 0.75, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 12.0, 24.0, 48.0, and 72.0 hours post-dosing. Subjects were allowed to leave the study center after the 24 hour post dose blood draw and return for the subsequent draws. A total volume of blood drawn from each subject completing this study did not exceed455 mL. A washout period of at least 14 days separated the treatment periods [5.3.1.2.2, page 264, 303].

1.2.1.6. Pharmacokinetic Parameters

No parameters of clinical efficacy were evaluated in this study.

The following pharmacokinetic parameters were determined for loratadine and descarboethoxyloratadine (DCL) from the plasma concentration data [5.3.1.2.2, page 306]:

- The maximum observed concentration (C_{max})
- The time of observed Cmax (T_{max})
- The elimination rate constant (k_{el})
- The elimination half life ($T_{1/2el}$)
- The area under the concentration-time curve from time zero to the last non-zero concentration (AUC_{0-t})
- The area under the concentration-time curve from time zero to infinity (AUC_{0-inf}).

1.2.1.7. Safety Parameters

Subjects were monitored for adverse events throughout the study. At the conclusion of the study, hematology, chemistry laboratory tests (including liver function tests), and urinalysis were performed [5.3.1.2.2, page 304]. Subjects could have been withdrawn from the study by the investigator for safety considerations [5.3.1.2.2, page 305].

1.2.1.8. Statistical Plan

The pharmacokinetic parameters were analyzed by ANOVA on untransformed T_{max}, k_{el}, and $T_{1/2el}$ and on ln-transformed AUC $_{0\text{-}t}$, AUC $_{0\text{-}inf}$, and C_{max} at the alpha level of 0.05. Ratio of means (Test/Reference) and 90% geometric confidence intervals for the ratio of means, based on least-squares means from the ANOVA of the ln-transformed data were calculated for AUC $_{0\text{-}t}$, AUC $_{0\text{-}inf}$, and C_{max}. As stated in the protocol, the criteria for average bioequivalence for loratadine is the 90% geometric confidence interval of the ratio (Test/Reference) of least-squares means from the ANOVA of the ln-transformed AUC $_{0\text{-}inf}$, AUC $_{0\text{-}t}$, and C_{max} should be within the range of 80% to 125% [5.3.1.2.2, page 307].

1.2.2. Results

1.2.2.1. Subject Disposition and Demographics

A total of 50 subjects were enrolled in the study and dosed with medication. Of the 50 enrolled subjects, 49 subjects completed the study. One subject was withdrawn from the study due to missing several blood samples [5.3.1.2.2, page 264].

All subjects were male with a mean age of 37 and an age range of 18 to 69 years. The racial composition was 35 Caucasian (70%), 8 American Hispanics (16%), and 7 Blacks (14%) [5.3.1.2.2, pages 269-270].

Reviewer's Comment: The under-representation of women and subjects of non-Caucasian race is less than ideal. However, the innovator's product label does not list a clinically significant gender-related or race-related difference in loratadine pharmacokinetics [Claritin® Product Label].

1.2.2.2. Pharmacokinetic Endpoint Outcomes

Table 12 is a summary of the key pharmacokinetic parameters from study 30219 [2.7.1, page 16-17]. The data is presented for loratadine and descarboethoxyloratadine (DCL) using geometric means, ln-transformed. As shown below, the 90% confidence interval for the ratio of the geometric means of the Test and Reference products was determined.

Table 12 Study 30219 Summary of Pharmacokinetic Parameters					
Study 30219 (Fed) Mean Loratadine PK Parameters					
Parameter	**TRT[1]**	**Mean[2](%CV)**	**Pair**	**Ratio**	**90% CI**
AUC_t (ng*h/mL)	A B	90.1(89) 98.6(90)	A/B	91.4	85.5-97.6
AUC_{inf} (ng*h/mL)	A B	94.7(90) 104.1(91)	A/B	91.0	85.1-97.3
C_{max} (ng/mL)	A B	20.3(85) 26.0(89)	A/B	77.9	***67.3-90.1***
Study 30219 (Fed) Mean DCL PK Parameters					
AUC_t (ng*h/mL)	A B	218.2(39) 220.8(39)	A/B	98.8	95.3-102.5
AUC_{inf} (ng*h/mL)	A B	234.8(41) 239.6(41)	A/B	98.0	94.8-101.3
C_{max} (ng/mL)	A B	14.9(41) 16.5(40)	A/B	89.9	83.3-97.1

1 Treatment Groups: A=Taro ElixSure Loratadine 5mg/mL ; B=Claritin 10mg tablet
2 Geometric means. ln-transformed

The AUC data for loratadine and DCL from the fed study supports bioequivalence but the C_{max} of loratadine for the test product is below the bioequivalence range of 80-125%. The Applicant did not provide a justification for the C_{max} being outside the bioequivalence range. However, based upon DCL, the Cmax and AUC data for the test product is within the bioequivalence range.

1.2.2.3. Safety Outcomes

1.2.2.3.1. Withdrawals

As stated above, 50 subjects were dosed with study medication, but only 49 subjects completed the study. Subject #31 was withdrawn from the study due to missing several blood draws [5.3.1.2.2, page 264].

1.2.2.3.2. Adverse Events

Of the 49 subjects who completed the study, 27 post-dose adverse events were recorded. There were no serious adverse events (SAEs) or deaths in the study. Table 13 is a summary of post-dose adverse events reported by the subjects [5.3.1.2.2, page 266 & 276].

Table 13 Study 30219 Post Dose Adverse Events

Adverse Event	ElixSure Loratadine Test A	Claritin Tablet Reference B
All Adverse Events N (%)	10 (20%)	17 (35%)
Sleepiness	2	2
Sore Stomach	2	0
Protein in urine	1	2
High glucose	1	1
Low Back Pain	1	1
Dizziness	1	1 (during catheter insertion)
Low MCHC	1	0
Knee pain	1	0
Fatigue/Less energy	0	1
Red cells in urine	0	1
Low Hgb or Hct	0	2
Redness of catheter site	0	1
Headache	0	1
Redness of leg	0	1
Itchiness of leg	0	1
Trouble Sleeping	0	1
Pain at catheter site	0	1

N= number of subjects
% subjects = N/49 total subjects who completed study

Reviewer's Comment: The original submission did not contain all the AEs for Study 30219. The Applicant provided the additional data during the review period [Response to Information Request, April 20, 2004].

Few adverse events were reported with the Test product compared to the Reference product 20% vs. 35%, respectively. Overall, the most common AE was sleepiness, which was similar in the Test and Reference treatment groups. Sore stomach, knee pain, and low MCHC were unique to the Test group.

1.2.2.3.3. Clinical Laboratory

At the conclusion of the study (approximately 3 days post-dose in Period 2), hematology, chemistry, and urinalysis were performed [5.3.1.2.2, page 266]. Abnormalities were reported as adverse events and are included above in Table 13. All abnormal laboratory results were normal on follow up testing with the exception of three subjects (No. 9 U_{prot} 0.3 g/L, No. 18 Hgb 126 g/L, No. 25 U_{prot} 1 g/L and 5-10 RBC/HPF in urine) who the investigator was unable to contact for follow up testing. Letters were sent to their family practitioner for follow-up [5.3.1.2.2, page 266-267].

1.2.3. Discussion and Conclusions

1.2.3.1. Pharmacokinetics

The purpose of this single dose study in healthy male volunteers under fed conditions, was to compare the bioavailability between the ElixSure test product and Claritin 10mg Tablets.

The 90% confidence interval for the ratio of the geometric means of the C_{max} and AUC are utilized for discussion of the pertinent findings from Study 30219. Based upon loratadine levels, the AUC data supports the bioequivalence of the Test and Reference product; however, the C_{max} is below the bioequivalence range. Based upon DCL levels, the AUC and C_{max} for the Test product are within the bioequivalence range. However, the efficacy of loratadine cannot be supported entirely upon the activity of the metabolite, DCL. Both loratadine and DCL demonstrate antihistamine activity and both likely contribute to the efficacy of Claritin Tablets and Claritin Syrup. Therefore, the lower C_{max} for loratadine observed with the Applicant's product cannot be presumed to provide efficacy.

1.2.3.2. Safety Evaluations

Because of the small number of subjects in this study, it is difficult to draw conclusions regarding safety based upon the safety data from this study. However, there were no significant differences between the Test ElixSure product and the Reference Claritin products for AEs or other safety variables; therefore, no safety signals were noted.

2. DETAILED LABELING CHANGES OR REVISED DRUG LABEL

Because Children's ElixSure 24 hr Antihistamine is proposed for OTC use, a detailed review of the proposed product label was conducted by the Division of Over the Counter Drug Products.

Appendix: Study 30219

CITATIONS

[1] Schiano TD, Somashekhar V, et al. Subfulminant liver failure and severe hepatotoxicity caused by loratadine use. *Ann Int Med* 1996; 125(9): 738-740.

[2] Evaluation of an Association between Loratadine and Hypospadias-United States, 1997-2001. *MMWR Weekly* 2004; 53(10): 219-221.

[3] Cobb DB, Watson WA, Fernandez MC. High-dose loratadine exposure in a six-year-old child. *Vet Hum Toxicol* 2001; 43(3): 163-4.

[4] Hilbert J, Moritzen V, et al. The Pharmacokinetics of Loratadine in Normal Geriatric Volunteers. *J Int Med Res 1988; 16:50-60.*

[5] Affrime M, Banfield C, Gupta S, et al. Effect of Race and Sex on Single and Multiple Dose Pharmacokinetics of Desloratadine. *Clin Pharmacokinet* 2002; 41 Suppl 1:21-28.

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/s/

Sally Seymour
11/8/04 08:17:38 AM
MEDICAL OFFICER

Eugene Sullivan
11/8/04 09:04:24 AM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA # 21-734	**TRADE NAME:**	Children's ElixSure – 24 hr Antihistamine
APPLICANT/SPONSOR:	Taro Pharmaceuticals	**USAN NAME:**	Loratadine
MEDICAL OFFICER:	Sally Seymour, MD		
DEPUTY DIRECTOR:	Eugene Sullivan, MD, FCCP	**CATEGORY:**	Anti-histamine
DUE DATE:	March 21, 2004	**ROUTE:**	Oral suspension

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
January 19, 2004	January 21, 2004	NDA 21-734	

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

This NDA (NDA#21-734) is a 505(b)(2) application for a loratadine oral suspension for children. The Sponsor, Taro Pharmaceuticals, requests approval of a 5mg/ 5mL suspension to be marketed in a [redacted] 8 oz (240 mL) bottle [redacted] This NDA is proposed as an over-the-counter (OTC) antihistamine. [redacted] in patients 2 years of age or older." [2.2, page 1] The Sponsor has proposed the trade name of Children's ElixSure™-24 hr Antihistamine (Loratadine Oral Suspension) 5mg/5mL for the drug product. The reference drug for this 505(b)(2) submission is Claritin® 10mg tablets and Claritin® syrup. This NDA is a paper submission in the CTD (Common Technical Document) format.

The Sponsor's application includes reports of two pharmacokinetics and bioavailability studies: Study 30218 and Study 30219. Study 30218 is a single center, single dose, randomized, 3-period, 6-sequence crossover study in 51 healthy adult males comparing the Sponsor's proposed Loratadine ElixSure (5mg/5mL) with Claritin tablets (10mg) and Claritin syrup (5mg/5mL) under fasting conditions. Study 30129 is a single center, randomized, single dose, 2-way crossover study in 50 healthy adult males comparing the Sponsor's Loratadine ElixSure (5mg/5mL) and Claritin tablets under fed conditions. A preliminary review of the PK studies revealed that some of the key PK parameters important for establishing bioequivalence with the reference product were outside the bioequivalence range of 80-125%. The clinical implication of these results will be a review issue.

The submission appears adequate to allow a full, in-depth clinical review; therefore, the application is fileable. Comments will be conveyed to the Sponsor.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	**SAFE TO PROCEED**	___	**CLINICAL HOLD**		
NDA/SUPPLEMENTS:	X	**FILEABLE**	___	**NOT FILEABLE**		
	___	**APPROVAL**	___	**APPROVABLE**	___	**NOT APPROVABLE**
OTHER ACTION:						

I. General Information

This NDA is a 505(b)(2) application for a Loratadine oral suspension for children. The Sponsor, Tayo Pharmaceuticals Inc., requests approval of a 5mg/5 mL suspension to be marketed in a [redacted] 8 oz (240 mL) bottle [redacted]. This NDA is proposed as an over-the-counter (OTC) antihistamine. The proposed indication is the [redacted] in patients 2 years of age or older." [2.2, page 1] The Sponsor has proposed the trade name of Children's ElixSure™-24 hr Antihistamine (Loratadine Oral Suspension) 5mg/5mL for the drug product. The Sponsor has provided a paper submission in the CTD format.

The innovator's product, Claritin® (loratadine), is currently approved for the following indications: runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat due to hay fever or other upper respiratory allergies as well as chronic idiopathic urticaria. The following formulations are approved for the respective age groups:

- Claritin® Children's 24 Hour Non-Drowsy Allergy Syrup (5mg/5mL) for adults and children > 6 years of age 2 teaspoons daily and 1 teaspoon daily for children 2-6 years of age
- Claritin® Non-Drowsy 24 Hour Tablets 10mg QD for adults and children > 6 years of age
- Claritin® Reditabs 24 Hour Non-Drowsy Orally Disintegrating Tablets 10 mg QD for adults and children > 6 years of age.

In December 2002, Claritin became available over-the-counter. In addition to the above formulations, many generic formulations of loratadine are now also available OTC.

The Sponsor's application is 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 the approved reference product and a comparison of the bioavailability and bioequivalence of the proposed new drug to those reference products. The Sponsor's drug development program is based on establishing that their 5mg/5mL suspension produces equivalent exposures to that of the approved and marketed Claritin® product. In this application, the Sponsor has submitted reports of two pharmacokinetic and bioavailability studies. The individual studies are described in depth in the Clinical Studies section of this review.

II. Regulatory and Foreign Marketing History

A. Regulatory History

Loratadine is an approved drug substance for the indication of relief of nasal and non-nasal symptoms of SAR and management of idiopathic chronic urticaria. The following NDAs for the reference product are held by Schering Plough:

- NDA # 19658 Loratadine tablets approved in April 1993
- NDA #20641 Loratadine syrup approved in October of 1996
- NDA #20704 Loratadine Reditabs approved in December of 1996

In December 2002, Claritin became available OTC in the above formulations. Since coming into the OTC market, many generic formulations of loratadine are now also available.

IND #68,067 for Children's ElixSure Loratadine Oral Suspension was submitted in September of 2003 by Taro Pharmaceuticals. In this IND, the Sponsor proposed a pediatric PK/BA study. At the time of the IND, two adult PK/BA studies were ongoing in Canada. The Division reviewed the submission and asked for justification for the pediatric PK/BA study, since the Sponsor was already conducting two PK/BA studies in adults.

The Sponsor did not request a Pre-NDA meeting.

B. Foreign Marketing History

Little information regarding the foreign marketing history of Claritin was provided in this submission. However, the following information was obtained from the April 22, 2002 FDA Advisory Committee meeting focusing on Claritin for OTC use and the indication of chronic idiopathic urticaria. Claritin was launched in Belgium in 1988 for allergic rhinitis and chronic idiopathic urticaria. Claritin is approved in 114 countries and approved prescription free in 33 countries. Of those 33 countries, 22 sell Claritin "behind the counter," while only 8 countries (Belgium, Canada, Germany, Ireland, Netherlands, Russia, UK, and the US) sell Claritin OTC.

III. Items Required for Filing (21 CFR 314.50)

The Sponsor has provided the following necessary elements to review this NDA.

Table 1. Necessary Elements

Item	Status	Location (paper)
Application Form (FDA 356h)	Present	Module 1, Section 1 (1.1)
Index / Table of Contents	Present	1.2
Format	CTD	
Samples (if applicable) and Labeling	N/A	
Proposed Package Insert	N/A	
Proposed Label	Present	1.3.b and 1.3.c
Summary	Present	Module 2
Labeling	Present	1.3.b and 1.3.c
Marketing History	Present	2.5, page 7-11
Chemistry, Manufacturing, & Controls (CMC)	Present	2.3
Non-clinical Pharmacology and Toxicology	Present	2.4 and 2.6.6

Item	Status	Location (paper)
Human Pharmacokinetics and Bioavailability	Present	2.6.4, 2.7.1
Clinical	Present	2.5 and 2.7
Benefits vs. Risks	Present	2.5, page 11
CMC	Present	Module 3
Environmental Impact statement	Request for Categorical Exclusion under 21 CFR 25.31(a)	1.3.a (Request for categorical exclusion)
Non-clinical Pharmacology and Toxicology	N/A	
Human Pharmacokinetics and Bioavailability	Present	5.3
Clinical		Module 5
Integrated Summary of Effectiveness (subsets for age, gender, and race)	N/A	
Integrated Summary of Safety	N/A	
Potential for Abuse	Present	2.7.4.5.6
Benefits vs. Risks	Present	2.5.6
Statements of Good Clinical Practice:	Present	5.3.1.2.1, pg 271 and 5.3.2.2, pg 261
Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures		5.2.1.2.1, pg 272 and 5.3.2.2, pg 262
Auditing information		
Safety Updates	Present	Summary 2.7.4; AERS/ADR search CDROM
Statistics	Combined with Clinical	5.3
Case Report Tabulations		
Case Report Forms (for patients who died or did not complete studies due to AEs)	N/A	
Patent Information	Present	1.3.a (patent information)
Patent Certification	Present	1.3.a (patent certifications)
Investigator Debarment Certification	Present	1.3.a (debarment certifications)
Field copy certification (if applicable)	Present	1.3.a (filed copy certifications)
User Fee Cover Sheet	Present	1.3.a (user fee cover sheet)
Financial Disclosure	Present	1.3.a (financial disclosure information)
Claimed Marketing Exclusivity	N/A	
Pediatric Use	N/A	

Reviewer's Comment: The Sponsor has provided a CDROM of the AERS/ADR data for Claritin. The Sponsor should provide a tabular summary of the frequencies of these adverse events and a narrative analysis and conclusions based upon this summary.

IV. Clinical Studies

This submission refers to two clinical pharmacology studies. The studies are summarized in Table 2 and a more detailed description of the studies follows.

Table 2. Summary of Bioavailability Studies

Study #	Study Type	Design	Treatment Groups	Subjects
30218	Bioavailability, fasting, study	Single center, single dose, BA, open-label, randomized, 3-period, 6-sequence crossover , fasting state	[redacted] loratadine suspension 40mg (5mg/5mL) oral Claritin® Syrup 40mg (40 mL of 5mg/5mL) oral, Reference B Claritin® Tablets 40mg (4 x 10mg tablets) oral, Reference C	51 healthy males, age 18 years and older
30219	Bioavailability, fed, study	Single center, single dose, BA, open-label, randomized, 2-way crossover, fed state	[redacted] loratadine suspension 40mg (5mg/5mL) oral Claritin® Tablets 40mg (4 x 10mg tablets) oral, Reference B	50 healthy males, age 18 years and older

Study 30218 [5.3.1.2.1, page 304-322]

Study 30218 was a clinical pharmacology study that compared the bioavailability of the Sponsor's [redacted] loratadine suspension 5mg/mL to the reference product, Claritin. The study compared the following:

- Loratadine [redacted] suspension 40 mg (40 mL of 5mg/5mL suspension)
- Claritin tablets 40mg (4 x 10mg tablets)
- Claritin syrup 40 mg (40mL of 5mg/5 mL syrup)

The study was performed in healthy subjects under fasting conditions. The study design was a single center, single dose, bioequivalence, open-label, randomized, 3-period, 6-sequence crossover study in 51 healthy adult males. Samples were collected before dosing (0 hours) and at 0.250, 0.500, 0.667, 0.75, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 12.0, 24.0, 48.0, and 72.0 hours post-dosing for loratadine and DCL (descarboethoxyloratadine) levels. DCL is an active metabolite of loratadine. The total volume of blood drawn from each subject did not exceed 665 mL [5.3.1.2.1, page 316]. Patients were confined to the study site from at least 10 hours pre-dose until after the 24-hour post-dose blood draw. A washout period of 14 days separated the treatment periods. Safety monitoring included adverse events, hematology, urinalysis, and blood chemistry studies [5.3.1.2.1, page 317]. Six patients prematurely withdrew from the study. Five patients did not provide a reason for withdrawal from the study. One patient was withdrawn because of concomitant use of amoxicillin. There were no withdrawals from the study due to AEs. No SAEs or deaths were noted; however, 55 adverse events were recorded [5.3.1.2.1, page 277].

Reviewer's Comment: Females were excluded because of possible evidence of human fetal risk associated with loratadine use [2.7.1, page 2].

The following table is a summary of the PK results for study 30218 [2.7.1, page 4-12].

Table 3. Results of Bioavailability Study 30218

Study 30218 (Fasting) Mean Loratadine PK Parameters					
Parameter	**TRT**	**Mean (%CV)**	**Pair**	**Ratio**	**90% CI**
AUC_t (ng*h/mL)	A	44.3 (109)	A/B	0.65	***58.3-72.1***
	B	68.3 (91)	A/C	0.94	84.2-104.1
	C	47.3 (109)	B/C	1.44	129.8-160.6
AUC_{inf} (ng*h/mL)	A	47.4(109)	A/B	0.66	***59.3-73.5***
	B	71.8(92)	A/C	0.95	85.3-105.7
	C	49.9(109)	B/C	1.44	129.1-160
C_{max} (ng/mL)	A	13.5(109)	A/B	0.53	***45.0-61.6***
	B	25.6 (98)	A/C	0.81	***69.3-94.9***
	C	16.6(113)	B/C	1.54	131.6-180.2
Study 30218 (Fasting) Mean DCL PK Parameters					
AUC_t (ng*h/mL)	A	222.8(42)	A/B	1.01	95.8-105.8
	B	221.3(41)	A/C	1.07	101.8-112.5
	C	208.2(42)	B/C	1.06	101.1-111.7
AUC_{inf} (ng*h/mL)	A	238.3(46)	A/B	1.01	95.4-106.0
	B	237(46)	A/C	1.06	100.3-111.4
	C	225.5(46)	B/C	1.05	99.7-110.8
C_{max} (ng/mL)	A	13.8(37)	A/B	0.84	***79.0-90.0***
	B	19.6(38)	A/C	1.09	102.4-116.7
	C	15.1(41)	B/C	1.30	121.3-138.4

A Taro ElixSure Loratadine
B Claritin Children's Syrup
C Claritin 10mg tablet

Based upon loratadine levels, the C_{max} of the ElixSure product compared to both Claritin tablet and syrup does not support bioequivalence; however, the C_{max} based upon DCL levels is within the bioequivalent range for the tablet comparator, and just outside the bioequivalence range for the syrup comparator. In addition, the 90% CI of the loratadine AUC for the ElixSure product compared to Claritin syrup is outside the bioequivalence range of 80-125%. The Sponsor does not provide a justification for these PK parameters being outside the bioequivalence range.

Reviewer's Comment: The clinical implication of some of the PK parameters of the parent compound being outside the bioequivalence range will be a review issue.

Study 30219 [5.3.2.2, page 260-279]

Study 30219 was a clinical pharmacology study that compared the bioavailability of the Sponsor's [redacted] loratadine suspension 5mg/mL to the reference product, Claritin. The study compared the following:

- Loratadine [redacted] suspension 40 mg (40 mL of 5mg/5mL suspension)
- Claritin tablets 40mg (4 x 10mg tablets)

The study was performed in healthy subjects under fed conditions. The study design was a single center, randomized, single dose, open-label, 2-way crossover comparative

bioavailability study under fed conditions in 50 healthy adult males. Subjects were fed a high-fat, high-caloric breakfast and dosed 30 minutes after starting the meal. Samples were collected before dosing (0 hours) and at 0.250, 0.500, 0.667, 0.75, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 12.0, 24.0, 48.0, and 72.0 hours post-dosing for loratadine and DCL levels. The total volume of blood drawn from each subject did not exceed 455 mL [5.3.1.2.2, page 303]. Subjects were confined to the research facility from at least 11 hours prior to drug administration until after the 24 hour post-dose blood draw. Single oral doses were separated by a washout period of 14 days. Safety monitoring included adverse events, hematology, urinalysis, and blood chemistry studies [5.3.1.2.2, page 304]. One subject was withdrawn from the study due to missing several consecutive blood sampling points. There were no withdrawals from the study due to AEs. No SAEs or deaths were noted; however, 27 adverse events were recorded [5.3.1.2.2, page 266].

Reviewer's Comment: Females were excluded because of possible evidence of human fetal risk associated with loratadine use [2.7.1, page 2].

The following table is a summary of the PK results for study 30219 [2.7.1, page 16-17].

Table 4. Summary of Bioavailability Study 30219

Study 30219 (Fed) Mean Loratadine PK Parameters					
Parameter	**TRT**	**Mean (%CV)**	**Pair**	**Ratio**	**90% CI**
AUC_t (ng*h/mL)	A B	90.1(89) 98.6(90)	A/B	91.4	85.5-97.6
AUC_{inf} (ng*h/mL)	A B	94.7(90) 104.1(91)	A/B	91.0	85.1-97.3
C_{max} (ng/mL)	A B	20.3(85) 26.0(89)	A/B	77.9	***67.3-90.1***
Study 30219 (Fed) Mean DCL PK Parameters					
AUC_t (ng*h/mL)	A B	218.2(39) 220.8(39)	A/B	98.8	95.3-102.5
AUC_{inf} (ng*h/mL)	A B	234.8(41) 239.6(41)	A/B	98.0	94.8-101.3
C_{max} (ng/mL)	A B	14.9(41) 16.5(40)	A/B	89.9	83.3-97.1

A Taro ElixSure Loratadine
B Claritin 10mg tablet

The AUC data from the fed study supports bioequivalence but the C_{max} of the ElixSure is low and the 90% CI is outside the bioequivalence range of 80-125%. The Sponsor does not provide a justification for the C_{max} being outside the bioequivalence range.

Reviewer's Comment: In this fed study (30219), a higher loratadine AUC and Cmax were noted for both the ElixSure product and the Claritin reference product. In studies conducted

by Schering for approval of Claritin, a food effect was noted and documented in the Clinical Pharmacology section of the Claritin prescription product label.

[redacted]

Although a difference in pharmacokinetics was noted in the fed state for Claritin, the Dosage and Administration section of the label does not recommend administration in either a fed or fasting state. The clinical significance of the difference in pharmacokinetics between ElixSure and Claritin in the fed and fasting state will be a review issue.

V. DSI Review / Audit

A DSI audit will be requested since the studies were conducted at a single center.

VI. Brief Review of Proposed Labeling

Proposed package labeling has been included in this submission [1.3.b, page 1-24]. A brief review was performed. A few labeling concerns are noted below:

[redacted]

A detailed label review will be performed later in the course of review of this NDA.

[redacted]

VII. Timeline for Review

Write-up will be concomitant with the review process. The schedule for review is displayed in the table below. Clinical review will focus primarily on safety and will be performed for each study before moving to the next study. The review of the Safety Data/Updates will take place next and will be complete by 6/15/04. Label review will be complete by 7/15/04. Draft review will be complete by 8/15/04.

Table 5. Timeline for Review

Milestone	Target Date for Completion
Stamp Date	January 21, 2004
Filing Meeting	March 8, 2004
Study 30218	April 15, 2004
Study 30219	May15, 2004
Safety Data/Updates	June 15, 2004
Label Review	July 15, 2004
Draft Review	August 15, 2004
Wrap-up Meeting	September 2004
Division Goal Date	November 5, 2004
PDUFA Date (10 months)	November 21, 2004 (Sunday)

VIII. Summary

This NDA (NDA#21-734) is a 505(b)(2) application for a loratadine oral suspension for children. The Sponsor, Taro Pharmaceuticals, requests approval of a 5mg/ 5mL suspension to be marketed in a [redacted] 8 oz (240 mL) bottle [redacted] oz (28 mL) bottle. This NDA is proposed as an over-the-counter (OTC) antihistamine. The proposed indication is the [redacted] in patients 2 years of age or older." [2.2, page 1] The Sponsor has proposed the trade name of Children's ElixSure™-24 hr Antihistamine (Loratadine Oral Suspension) 5mg/5mL for the drug product. The reference drug for this 505(b)(2) submission is Claritin 10mg tablets and Claritin Syrup. This NDA is a paper submission in the CTD (Common Technical Document) format.

The Sponsor's application includes reports of two pharmacokinetics and bioavailability studies: Study 30218 and Study 30219. Study 30218 is a single center, single dose, randomized, 3-period, 6-sequence crossover study in 51 healthy adult males comparing the Sponsor's proposed Loratadine ElixSure (5mg/5mL) with Claritin tablets (10mg) and Claritin syrup (5mg/5mL) under fasting conditions. Study 30129 is a single center, randomized, single dose, 2-way crossover study in 50 healthy adult males comparing the Sponsor's Loratadine ElixSure (5mg/5mL) and Claritin tablets under fed conditions. A preliminary review of the PK studies revealed that some of the key PK parameters important for establishing bioequivalence with the reference product were outside the bioequivalence range of 80-125%. The clinical implication of these results will be a review issue.

The submission appears adequate to allow a full, in-depth clinical review. The submission is fileable.

IX. Decision

The submission appears adequate to allow a full, in-depth clinical review; therefore, the application is fileable.

X. Comments to Applicant

The following comments will be conveyed to the Sponsor.

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 (ElixSure™ Loratadine) 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 ElixSure™ Loratadine was provided. During the review process, the Division will need to consider the clinical implication of the difference in pharmacokinetics between Claritin® and ElixSure™ .

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.

Reviewed by:

Sally Seymour, M.D.

Medical Officer, Division of Pulmonary and Allergy Drug Products

Eugene Sullivan, M.D.

Deputy Director, Division of Pulmonary and Allergy Drug Products

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/s/

Sally Seymour
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