CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-375

MEDICAL REVIEW

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

Application Number: NDA 21-375
Application Type: NDA
Sponsor: Wyeth Consumer Healthcare
Proprietary Name: Alavert™ Allergy
Children's Dimetapp® Allergy
Category of Drug: Antihistamine
USAN/Established Name: loratadine
Route of Administration: Orally disintegrating tablet
Medical Reviewer: Charles E. Lee, M.D.
Review Date: 10/14/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type and Comments:
N21-375 N000	10/14/02	10/14/02	Response to second approvable letter
N21-375 N000 AZ	10/14/02	10/15/02	Response to second approvable letter
N21-375 N000 AC	10/14/02	10/17/02	Response to second approvable letter

RELATED APPLICATIONS (if applicable):

Application	Document Date:	Application Type:	Comments:
N21-375	8/23/01	9/5/01	Original NDA

This NDA is a 505(b)(2) application for loratadine, 10-mg orally disintegrating tablets. The sponsor is Wyeth Consumer Healthcare. The reference product is Claritin® RediTabs®, 10-mg loratadine tablets, manufactured by the Schering Corporation. The sponsor originally proposed two tradenames: Alavert™ Allergy and Children's Dimetapp® Allergy. The proposed indication is the temporary relief of symptoms due to hay fever (allergic rhinitis), including 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 one tablet (10 mg) daily, not to exceed more than one tablet in any 24-hour period. The product is not indicated for children under the age of 6 years. The application received an approvable action on 7/3/02. There were various Chemistry, Manufacturing, and Controls (CMC) deficiencies, and revised labeling was requested. The sponsor submitted a response to the approvable letter on 7/19/02. There were various CMC and labeling deficiencies that remained. The sponsor received a second approvable action on 9/18/02. The second approvable letter requested responses to the CMC deficiencies and requested revised labeling and a safety update. This document is a review of the sponsor's response to the requested revisions in labeling and of their safety update. This review does not address the CMC deficiencies. The labeling changes are acceptable to both the Division of Pulmonary and Allergy Drug Products and to the Division of Over-the-Counter Drug Products. The sponsor agrees to withdraw the Children's Dimetapp® Allergy tradename. The safety update notes that there have been 15 cases of hypospadias associated with loratadine use during pregnancy. There are no data to suggest that there is a similar increased frequency of this association in the US. DPADP notes that there is no information in the medical literature or from the innovator's (Schering's) IND and NDA databases for loratadine or desloratadine that suggests that loratadine has anti-androgenic activity. The safety update reveals no new safety signal. The sponsor has adequately addressed all other clinical deficiencies. From the clinical standpoint, this application may be approved. If approved, the sponsor should provide regular periodic updates for a three-year period on the association between hypospadias and loratadine use in pregnancy.

OUTSTANDING ISSUES: none

RECOMMENDED REGULATORY ACTION:

Approval: X **Approvable:** **Not Approvable:**

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

The sponsor also performed an updated literature review of the worldwide literature. The search was performed on PubMed utilizing the term "loratadine" for the year 2002.

3.1. AERS database

Review of the AERS database revealed 44 non-serious and serious adverse event (AE) reports for loratadine [pages 9-10-3 to 9-10-14]. The sponsor notes that no clinically meaningful differences between the event frequencies for these reports and for the previous safety data in the NDA and first safety update were noted. There was no evidence for a safety signal in elderly patients or for a safety signal related to hepatic or renal events.

The sponsor notes that there was one new case of hypospadias reported during the review period, the fifteenth reported since the original submission. The sponsor notes that all were from a line listing from the Swedish National Board of Health and Welfare, and that there were no domestically reported cases. The sponsor concludes that no definitive link can be made regarding loratadine exposure during pregnancy and the occurrence of hypospadias.

Reviewer comment:
The Agency has examined the association of hypospadias with loratadine use in pregnancy. This association has not been noted in US postmarketing data. There is no information in the medical literature or from the innovator's (Schering's) IND and NDA databases for loratadine or desloratadine that suggests that loratadine has anti-androgenic activity. The Division has discussed the Swedish data at a meeting with the Division of Drug Risk Assessment. There are no data to suggest that there is a similar increased frequency of this association in the US. Most of the cases in the Swedish database were mild, and the incidence of hypospadias among exposed cases in this database is low [Meeting minutes of 10/4/02, NDA 19-658, N000, 1/25/02, DPADP, ODS, and DOTCDP]. The potential safety benefits of drug, including lack of sedation, outweigh the potential for this weak signal.

The sponsor should agree to provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy. Spontaneous reports for hypospadias must be summarized in a separate section of the required quarterly periodic safety update reports and annual periodic safety update reports. This section of the annual periodic safety update reports should contain a thorough narrative discussion, analysis, and summary of any and all such events. The sponsor should provide an update on the Swedish data. The sponsor should also summarize information from other sources, including regulatory authorities in other countries. Information should include data listings, summary tables, analyses, and interpretation. Reports should also include information on any regulatory action taken or any changes of the marketing status of the product worldwide as a result of these or other safety-related events. A summary and analysis of the worldwide literature review for loratadine and hypospadias should also accompany each required annual periodic safety report. These reports should be required for 3 years.

These data do not reveal any other evidence of a safety signal.

3.2. DAWN Emergency Department Trend Report

Reports for respiratory agents remained stable between 2000 and 2001. Of antihistamine agents, loratadine represented only 16% (673/4112) of reports, much less than those for the most frequently mentioned upper respiratory combination products, such as acetaminophen/chlorpheniramine (35%, 1991/5697) and acetaminophen/dextromethorphan/doxylamine/pseudoephedrine (24%, 1327/5697). There were no mentions of loratadine as a single ingredient or in combination in mortality data from DAWN. The sponsor concludes that there is no information that suggests a potential for drug abuse [pages 9-10-2 to 9-10-3].

Reviewer comment:
This reviewer concurs that these data do not suggest a safety signal.

3.3. AAPCC database

Two fatalities associated with loratadine ingestion were noted in the AAPCC database for the year 2001. Both were successful suicide attempts, which involved the ingestion of multiple medications, including colchicine, ibuprofen in one case, and verapamil, atenolol, and losartan in the other. The sponsor concludes that these data do not suggest any unusual toxicity associated with overdoses of loratadine [pages 9-10-14 to 9-10-15].

Reviewer comment:
This reviewer concurs that these data do not suggest a safety signal.

3.4. Literature review

The search revealed seven articles, none of which provided any evidence of new safety signal [pages 9-10-15 to 9-10-23]. One article reported evidence of QTc prolongation associated with co-administration of loratadine and nefazodone.[1] This study was discussed in the NDA Medical Officer review [Charles E. Lee, M.D., Medical Officer Review of 6/4/02, NDA 21-375, N000, 8/23/01, page 19].

A second article of note was a case report of a 43-year old woman who was reported as having a ventricular arrhythmia 90 minutes after taking a single 10-mg loratadine tablet.[2] The sponsor points out that there was a family history of predisposition to arrhythmias and that a definitive diagnosis of torsades des pointes could not be made.

Reviewer comments:
As noted in the NDA review, it is unclear why QTc prolongation was noted in the Abernethy study when none have been noted in other drug interaction studies where loratadine and DCL levels were much higher. It is important to note that the results of

[1] Abernethy DR, Barbey JT, Franc J, Brown KS. Clin Pharmacol Ther 2001; 69: 96-103.
[2] Kuchar DL, Walker BD, and Thornburn CW. Med J Aust 2002; 176(9):429-430.

this study have been questioned by one of its co-authors.[3] Predisposition to increased QTc and ventricular tachycardia is likely to be a significant confounder for the woman who had cardiac arrhythmia.

The weight of the evidence from the other drug interaction and cardiac safety studies is that elevated loratadine and DCL levels do not produce QTc and QT interval prolongation. The literature review does not provide evidence for any new safety signal.

In summary, this reviewer concurs with the sponsor that the safety update reveals no new safety signal.

4. SUMMARY AND RECOMMENDATIONS

The sponsor has provided a response to deficiencies in the approvable letter of 9/18/02. The sponsor has adequately addressed all clinical deficiencies. From the clinical standpoint, this application may be approved.

The sponsor should agree to provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy. Spontaneous reports for hypospadias must be summarized in a separate section of the required quarterly periodic safety update reports and annual periodic safety update reports. This section of the annual periodic safety update reports should contain a thorough narrative discussion, analysis, and summary of any and all such events. The sponsor should provide an update on the Swedish data. The sponsor should also summarize information from other sources, including regulatory authorities in other countries. Information should include data listings, summary tables, analyses, and interpretation. Reports should also include information on any regulatory action taken or any changes of the marketing status of the product worldwide as a result of these or other safety-related events. A summary and analysis of the worldwide literature review for loratadine and hypospadias should also accompany each required annual periodic safety report. These reports should be required for 3 years.

[3] Barbey JT. Clin Pharmacol Ther 2002; 71:403

Reviewed by:

/S/

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

/S/

Mary Purucker, M.D., Ph.D.
Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Purucker/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-570/Zeccola/CSO
HFD-560/Hu/Medical Reviewer
HFD-560/Martin/Interdisciplinary Reviewer

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MEDICAL OFFICER
concur

were able to deal effectively the potential for confusion through use of appropriate labeling. Finally the sponsor points out that tradenames are commercial speech, and that the Agency may not prohibit use of an extended brand name unless it is inherently misleading and no other measure will eliminate confusion [pages 2-5-3 to 2-5-6].

Reviewer comment:
DOTCDP concluded that the brand name "Children's Dimetapp Allergy" is not acceptable and that it is not in the best interest of consumers to have the same brand name for a sedating and less-sedating antihistamine. DPADP concurs with the comments from DOTCDP.

2.2. Asterisk after the phrase "Non-drowsy"

The Agency asked the sponsor to add an asterisk after the phrase "Non-drowsy." The Agency asked that the asterisk should direct the consumer to a statement at the bottom of the principal display panel (PDP), ' [redacted] See Drug Facts panel." The sponsor agreed to the asterisk, but proposes the statement "When taken as directed. See Drug Facts panel" in place of [redacted] n [redacted] See Drug Facts panel" [pages 2-5-6 to 2-5-7].

Reviewer comment:
The sponsor's proposed statement "When taken as directed. See Drug Facts panel" is acceptable to DOTCDP. DPADP concurs with the comments from DOTCDP.

2.3. [redacted] tablet

The sponsor has accepted a change from [redacted] Disintegrating Tablets" to "Orally Disintegrating Tablets" as the name for the dosage form. The sponsor proposes the phrase ' [redacted] ' to replace the phrase [redacted] ' and proposes to add the phrase "Melts in the mouth" above the red ribbon on the PDP [pages 2-5-7 to 2-5-9].

Reviewer comment:
It is acceptable to DOTCDP for the sponsor to replace the phrase [redacted] *' with* [redacted] *The phrase "Melts in the mouth" is also acceptable to DOTCDP. DPADP concurs with the comments from DOTCDP.*

2.4. [redacted]

The sponsor was asked to delete the phrase [redacted] ' from the Directions section of Drug Facts. The sponsor has deleted this phrase and has proposed "Tablet melts in mouth. Can be taken with or without water."

Reviewer comment:
It is acceptable to DOTCDP for the sponsor to replace the phrase [redacted] *with "Tablet melts in mouth. Can be taken with or without water." DPADP concurs with the comments from DOTCDP.*

2.5. Child resistant package

The sponsor was asked to add the statement [redacted] if the package was not child resistant. The sponsor notes that loratadine (OTC) is not subject to the provisions of the Poison Prevention Packaging Act (PPPA), but also notes that testing has been conducted on a blister configuration similar to that intended for the market in accordance with 16 CFR Part 1700. The test results support that the package meeting the PPPA standards and that the labeling statement is not warranted. The sponsor notes that additional testing on the final market package configuration will be conducted, and that if the results of the study indicate that the package does not meet the PPPA standards, that the statement will be incorporated into the label.

Reviewer comment:
There are no objections from the clinical reviewer from DPADP the sponsor's response to this point.

3. SAFETY UPDATE

The sponsor included a safety update covering the period since the original safety update for the NDA was submitted in May 2002. The sponsor performed a literature review of the worldwide literature using Medline, Embase, Biosis, Derwent Patent, and SciSearch. The search was limited to literature published in 2002. The search revealed three articles, none of which provided any new safety signal. The sponsor noted that there was no additional information available from the AERS postmarketing surveillance database, and no new information regarding overdose or abuse potential for loratadine. The sponsor noted a study conducted by the Netherlands Pharmacovigilance Foundation which examined the spontaneous adverse events with less-sedating antihistamines to determine the risk of developing a cardiac arrhythmia and compared the risk before and after some of these products were recalled from OTC status. There were 737 cases of arrhythmia, of which 43 occurred in association with a less-sedating antihistamine. Of those cases associated with less-sedating antihistamines, terfenadine represented 44.2%, cetirizine represented 23.3%, loratadine represented 16.3%, and fexofenadine represented 9.3%. The sponsor notes that the increased risk can be partly explained by the increased attention surrounding this subject and the subsequent rise in arrhythmia reports.

Reviewer comment:
As noted in the Medical Officer NDA review, the weight of evidence from epidemiologic studies, as well as that from the CDER OTC Switch Review Team, suggests that the risk of ventricular arrhythmias and rhythm disturbances with loratadine is likely to be in the expected background range for the general population. This reviewer concurs with the sponsor that the safety update reveals no new safety signal.

4. SUMMARY AND RECOMMENDATIONS

The sponsor has provided a response to deficiencies in the approvable letter of 7/3/02. The sponsor has adequately addressed all other clinical deficiencies, and except for the "Children's Dimetapp Allergy" tradename, the proposed labeling changes are acceptable. From the clinical standpoint, this application may be approved if an agreement can be reached on an acceptable tradename.

Reviewed by:

/S/

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

/S/

Mary Purucker, M.D., Ph.D.
Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Purucker/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-570/Zeccola/CSO
HFD-560/Hu/Medical Reviewer

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/s/

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9/16/02 01:48:19 PM
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Marianne Mann
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MEDICAL OFFICER

MEDICAL TEAMLEADER REVIEW

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

APPLICATION #:	NDA 21-375	APPLICATION TYPE:	505(b)2
SPONSOR:	Whitehall-Robins Healthcare/ AHPC	PRODUCT/PROPRIETARY NAME:	Alavert/ Dimetapp Allergy
INDICATION:	Hay fever	USAN / Established Name:	Loratadine
CATEGORY OF DRUG:	Antihistamine	ROUTE OF ADMINISTRATION/ DOSAGE FORM:	Oral/ Orally Disintegrating Tablet
MEDICAL REVIEWER:	Purucker	REVIEW DATE:	17 June 2002

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	Stamp Date:	Submission type/Comments:
23 August 2001	5 Sept. 2001	Initial submission; 505(b)2 vs. Claritin Reditabs and OTC switch application

RELATED APPLICATIONS

Document Date:	Document ID #:	Comments:
	ANDA 75-822	Generic Claritin® Reditabs™, ESI Lederle

Overview of Application/Review: Whitehall-Robins Healthcare has submitted a 505(b)2 application for loratadine 10 mg orally disintegrating tablets. The reference product is Schering-Plough's Claritin ® Reditabs.™ The application includes a proposal to "switch" loratadine from prescription-only to OTC status. The proposed indication is for the temporary relief of the symptoms of hay fever, ——— ———————. The product labeling contains language generally consistent with the OTC monograph for antihistamines (21 CFR 341.72), but omitting the ——————— information under the *Warnings* section (see below).

The application is supported by two PK studies, a single-dose Bioequivalency (BE) and a single-dose, cross-over Food Effect study, demonstrating bioequivalency between the new product and the reference drug. The OTC switch is supported primarily by a comprehensive review of drug safety, including post-marketing databases, published literature, the PK studies cited above, and publicly available data from the joint OTC/Pulmonary-Allergy Drugs Advisory Committee meeting of May, 2001. Specific safety issues related to cardiac conduction, the finding of "hypospadias" in a non-US pregnancy database, and the occurrence of "——————" of desloratadine in the general population do not appear to be of such magnitude as to preclude an OTC switch of this product.

With regard to Trade Name, the sponsor has proposed to use either "Alavert" or "Dimetapp Allergy." The latter is not acceptable because of likely confusion with the sponsor's currently marketed product, which contains brompheniramine. This has been communicated to the sponsor. With regard to labeling, the sponsor has omitted the monograph ——————— warning and has instead included a "non-drowsy" claim. Although a significant departure from the monograph, this labeling is supported by the available data and is reasonable from a public health perspective given the frequent occurrence of sedation and cognitive impairment associated with the marketed OTC antihistamines.

Outstanding Issues: None.

Recommended Regulatory Action:

N drive location:

NDAs: Efficacy / Label Supp.: ___X___ Approvable _____ Not Approvable

Signed: Medical Team Leader: _____ Date: _____

Office Director: _____ Date: _____

Overview

The submission is a 505(b)2 application for Loratadine 10 mg orally disintegrating tablets from Whitehall-Robins Healthcare (WHR), a division of American Home Health Care Products (AHCP). The reference product is Schering-Plough's Claritin® Reditabs™. The sponsor has included a proposal to "switch" loratadine from prescription-only to OTC status. The proposed dose is 10 mg once daily, the age range is ≥ 6 years, and the proposed indication per monograph is for the temporary relief of the symptoms of hay fever. The sponsor also proposes to include "non-drowsy" on the product label, to distinguish loratadine from the more sedating, marketed OTC antihistamines.

Contents of Application

The application includes two pivotal PK studies submitted to ANDA 75-822 (ESI Lederle), a Bioequivalence (BE) and a Food Effect (BA) study. The first study showed the two products to be BE based on the 90% CI for AUC_t, AUC_∞ , and C_{max} for log-transformed plasma concentrations of both loratadine (L) and its major metabolite desloratadine (DCL). The Food Effect study showed the products to be "similar" (L: 90% CI were 85 – 130%; DCL: 90% CI were 80 – 125%), meaning the test product was slightly more BA than the comparator for loratadine, but not for DCL. Overall, OCPB concluded that the two products were BE. The two PK studies had enrolled a total of 151 male and female subjects. Four were found to be "slow metabolizers" of DCL. These four reported no AE potentially attributable to the drug product. No new safety signals emerged from these studies.

To support the OTC switch of loratadine, the sponsor submitted a safety review comprised of data from post-marketing databases, including AERS, as well as a review of the peer-reviewed medical literature. Also cited was FDA's presentation at the May, 2001 joint OTC/DPADP Advisory Committee meeting discussing the evidence in support of "switching" loratadine, cetirizine, and fexofenadine from prescription-only to OTC status. Each of these sources generally supported the safety of loratadine in an OTC setting.

Special Safety Considerations with this Application

There are three specific issues regarding the safety of loratadine that deserve special mention: first, the drug's impact on cardiac conduction, second, it's relationship to the birth defect hypospadias, and third, the presence of "poor" or "slow" metabolizers" of DCL in the population.

The potential for some antihistamines to prolong the QT_c, leading to the potentially lethal arrhythmia Torsades du Pointes is well-known. In general, *in vitro* studies with loratadine show it does not affect I_{kr} or cardiac repolarization. Clinical PK/PD and drug interaction studies have not demonstrated prolongation of the QT_c-interval. A widely-quoted paper[1] contradicting the latter statement is presently under scrutiny by one of its authors because of serious methodological flaws.[2]

A recent epidemiological study conducted in Sweden showed a possible relationship between loratadine use in early pregnancy and the occurrence of hypospadias in male newborns. This information was shared with the Agency near the end of the review cycle for this product. In response to this, ODS conducted an independent review of these data as well as a search of

the AERS database for similar cases in the US. ODS concluded that no comparable signal of hypospadias could be discerned in the US population at this time. Also, ODS was uncertain about whether all the cases of hypospadias cited in the Swedish database should have been included in the calculations. From a scientific or pre-clinical perspective, hypospadias as a specific teratological finding is not predicted by animal models. The pharmacology of loratadine does not suggest a mechanism by which hypospadias may occur, such as an anti-androgenic effect, for example. At the time of this review, the weight of scientific evidence argues against hypospadias being attributable to loratadine use during early pregnancy.

Prior FDA submissions to the Claritin® and Clarinex® NDA's have indicated that 5 – 10% of the population may have the "slow metabolism" of DCL phenotype. While the consequences of this finding are incompletely understood, no specific safety signal has emerged to date that is attributable to this phenotype. Post-marketing and Poison Control databases indicate a wide safety margin in overdose situations. The two PK studies submitted with this application are consistent with these findings.

Other Issues

The sponsor submitted a request for a waiver for pediatric studies, arguing that the dosage form was inappropriate for very young children, and that there was no unmet pediatric need for this moiety given the availability of safe and effective alternatives. The waiver was granted by the Agency because safety data for the moiety in the pediatric age range < 6 years already existed. These data had been submitted to the Agency by the innovator in response to a Written Request for loratadine. Exclusivity had been granted.

Other issues include the precise wording that will be acceptable to convey the message that loratadine does not have the same sedating properties as the currently marketed OTC antihistamines, and which Trade Name the sponsor will be permitted to market this product under. The Agency strongly disapproves of "Dimetapp Allergy" because of likely confusion by consumers with the marketed product, containing the sedating antihistamine brompheniramine.

This application is recommended for approval. At the time of this review, there were minor labeling issues under internal review, but nothing that would preclude a tentative approval for this NDA.

References

1. Abernathy DR, Barbey JT, Franc J, Brown KS, *Clinical Pharmacology and Therapeutics* 2001; 69: 96-103.
2. Barbey JT, *Clinical Pharmacology and Therapeutics* 2002; 71: 5.

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/s/

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6/20/02 12:04:37 PM
MEDICAL OFFICER

Robert Meyer
6/21/02 10:27:10 AM
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MEDICAL OFFICER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

Application Number: N21-375 **Application Type:** NDA
Sponsor: Whitehall Robins Healthcare, Inc. **Proprietary Name:** Alavert™
Dimetapp® Allergy
Category of Drug: Antihistamine **USAN/Established Name:** loratadine
Route of Administration: orally disintegrating tablet
Medical Reviewer: Charles E. Lee, M.D. **Review Date:** 6/5/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type:
N21-375 N000 BL	5/24/02	5/29/02	Response to information request

RELATED APPLICATIONS (if applicable):

Application	Document Date:	CDER Stamp Date:	Application Type:
N21-375	8/23/01	9/5/01	NDA submission

Whitehall-Robins Healthcare, Inc. has submitted a 505(b)(2) application for a 10-mg orally disintegrating tablet form of loratadine. The reference product is Claritin® RediTabs, 10-mg. The proposed indication is for the temporary relief of symptoms [redacted] hay fever [redacted] runny nose, sneezing, itchy watery eyes, and itching of the nose or throat. The Division of Over-the-Counter Drug Products (DOTCDP) asked the sponsor to submit proposals on how best to communicate in the OTC labeling the relative nature of their "non-drowsy" claim. The sponsor was also asked to comment on the promotional claim [redacted] and [redacted] in light of the fact that the USP name for this dosage form is "orally disintegrating tablet." The sponsor's submission includes the following:

- Response to comments on the "non-drowsy" claim
- Response to comments on the [redacted] claim
- A change to the "Uses" section of the Drug Facts section of the principal display panel
- A revised principal display panel for the sponsor's Dimetapp® product

DOTCDP has asked the Division of Pulmonary and Allergy Drug Products to review the sponsor's submission. In general, the sponsor's response to comments on the "non-drowsy" claim is acceptable. The Chemistry, Manufacturing, and Controls reviewer will comment on the [redacted] claim. The proposed change in language in the "Uses" section of Drug Facts is acceptable. The sponsor's choice of a Dimetapp® as a second trade name for their product is not acceptable because of the potential for consumers to confuse this product with other Dimetapp® products. Recommendations to be communicated to DOTCDP are included.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION:

Comments to be communicated to DOTCDP

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

1. GENERAL INFORMATION AND BACKGROUND

Whitehall-Robins Healthcare, Inc has submitted a 505(b)(2) NDA for loratadine, 10-mg orally disintegrating tablets. The reference product is Claritin® RediTabs, 10-mg. The sponsor has proposed two trade names: Alavert Allergy™ and Dimetapp Allergy®. A 505(b)(2) submission was chosen for this product in order to "switch" the drug product to OTC status. The reference product is currently prescription only. The proposed indication is for the temporary relief of symptoms due to hay fever, including runny nose, sneezing, itchy watery eyes, and itching of the nose or throat.

In a communication to the sponsor on 5/16/02, the Division of Over-the-Counter Drug Products (DOTCDP) noted that the incidence of drowsiness in patients taking 10-mg loratadine is lower than antihistamine drug products currently available OTC. Drug levels in some patients with hepatic and renal impairment, the elderly, and those taking other medications that impair loratadine clearance might be expected to be higher than in patients in the general population. Higher blood levels would also be expected in patients who might take more than the recommended dose. The incidence of drowsiness is of particular concern in these patients. The sponsor was asked to submit proposals on how best to communicate the relative nature of the "non-drowsy" claim in the OTC labeling.

The sponsor was also asked to comment on the [redacted] and [redacted] promotional claims, in light of the fact that the USP name for this dosage form is "orally disintegrating tablet."

This sponsor's submission includes the following:

- Response to comments on the "Non-drowsy" claim
- Response to comments on the [redacted] claim
- A change to the "Uses" section of the Drug Facts section of the label
- A revised principal display panel for the sponsor's Dimetapp® product

These are reviewed below.

2. "NON-DROWSY" CLAIM

The sponsor notes that patients who take two to four times the recommended dose experience more somnolence than those who take the standard 10-mg dose. Current labeling for the reference product, Claritin® RediTabs®, advises that any population with impaired clearance of loratadine may experience somnolence. The current package insert notes that PK data show that certain populations, such as those with hepatic or renal impairment or the elderly, may have a greater degree of exposure to loratadine or its metabolites. The Adverse Reactions section of label states that the rates of adverse events (AEs) did not differ significantly based on age, gender, or race, however. The sponsor makes the following proposals.

1. Regarding patients taking more than the recommended dose
The sponsor proposes to amend the Warnings section of the label to read, "When using this product do not use more than directed. Taking more than directed may cause drowsiness."

Reviewer comment:
The proposal is acceptable, and the language effectively communicates that there is a risk of sedation with use of greater than recommended doses.

2. Regarding patients with hepatic and renal disease
The sponsor's initial proposed labeling included a statement that read, "Ask a doctor before use if you have liver or kidney disease." The sponsor proposes to revise this statement to read, [redacted]

Reviewer comment:
In general, this proposal is acceptable. Specifically, it would be preferable to communicate to the consumer why a doctor should be consulted and that a dosage adjustment may be needed. This reviewer would recommend that this statement read, "Ask a doctor before use if you have liver or kidney disease. Your doctor should determine if you need a different dose."

3. Regarding use in the elderly
The sponsor notes that neither the current package insert for the reference product nor the published literature has shown a correlation between age and somnolence related to loratadine. The sponsor points out that the Adverse Reactions portion of the current package insert states that the adverse event (AE) rates did not differ significantly due to age. The sponsor does not propose to amend the proposed labeling regarding use in the elderly.

Reviewer comment:
As the sponsor notes, neither the current package insert for the reference product nor the published literature has shown a correlation between age and somnolence related to loratadine. An abstract submitted in support of this application actually showed a slightly lower incidence of somnolence in those ≥65 years of age (3%) than in those <65 years (5%).[1] Both of these figures are similar to the incidence of somnolence that would be expected with placebo. It would seem that one would expect a higher rate of somnolence in this population because of their higher plasma levels. However, there is no strong evidence that an increase in somnolence in this population occurs, and this reference suggests that the frequency of somnolence might actually be similar to that noted with placebo. This reviewer agrees with the sponsor, and concurs that no amendment to the original proposed labeling is necessary regarding use in the elderly.

Certain drugs, such as erythromycin, cimetidine, and ketoconazole, interfere with the metabolism of loratadine. Patients who take loratadine with these drugs develop increased levels of loratadine and its metabolites. Likewise, one would expect a higher

[1] Lorber RR, Danzig MR, Ludwig G, et. al. J Allergy Clin Immunol 1994;93(1 part 2):163.

incidence of somnolence in these individuals, but as with the elderly, increased levels of somnolence have not been reported. The current Claritin® labeling notes that there were no clinically relevant changes in the safety profile of loratadine in two small drug interaction studies, and no dose adjustment is recommended. In this reviewer's opinion, no amendment to the sponsor's original proposed labeling is necessary regarding the potential for somnolence from drug interaction.

3. [redacted] CLAIM

The sponsor notes that their intent in using the term [redacted] was to inform the consumer that the product disintegrates on contact with the tongue, unlike a traditional tablet that is swallowed. The sponsor points out that the term is more consumer-friendly than the proposed official UPS designation, "[redacted] disintegrating tablet." The sponsor also points out that other OTC products are referred to as quick dissolving (Maalox Quick Dissolve Chewable Antacid tablets and Benadryl FastMelt dissolving tablets). The sponsor presents dissolution data in support of the [redacted] claim and notes that the term "[redacted] disintegrating tablet" is not yet officially a USP designation. Regardless of the dissolution properties of the drug or the inclusion of the official USP name on the labeling, the sponsor requests that the term [redacted] remains as a descriptor for the dosage form.

Reviewer comment:
The Chemistry, Manufacturing, and Controls (CMC) reviewer will comment on the sponsor's dissolution data. The CMC reviewers will recommend appropriate language to describe the dosage form in product labeling.

The sponsor's labeling also includes a statement that "The mint flavored [redacted] tablet melts in your mouth [redacted] This statement implies that [redacted] disintegration results in more [redacted] absorption and more [redacted] onset of action. This implied superiority claim should be deleted. The Clinical Pharmacology and Biopharmaceutics reviewer will also comment on this claim.

4. CHANGE TO USES SECTION OF DRUG FACTS

The sponsor proposes to change the Uses section of drug facts from:

> "Temporarily relieves these symptoms due to hay fever [redacted]

To the following:

> "Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:"

Reviewer comment:
This change uses language that is specified in 21 CFR 341.72. This amendment to the original proposed labeling is acceptable.

5. REVISED PRINCIPAL DISPLAY PANEL DIMETAPP®

The sponsor proposes a revised principal display panel for their loratadine product to be marketed as "Dimetapp®." The sponsor has changed the focus for the Dimetapp® product to the children's allergy market. The revision to the principal display panel includes a claim that Dimetapp® is a ' ——— ' and a change of the term ' ——— ' to ' ——— '

Reviewer comment:
As noted in the Medical Officer review for the NDA submission, and as previously noted in the Medical Officer 45-day filing review, the second trade name proposed by the sponsor, "Dimetapp®," will not be acceptable because of potential confusion with other Dimetapp® products. These products contain other drugs such as brompheniramine and pseudoephedrine. None of them contain loratadine.

Even if the second trade name were acceptable, the claim ' ——— ' ——— would not be, as it implies to the consumer that the drug product, not the brand, is pediatrician recommended.

The term ——— also would be problematic, as it is not descriptive of instructions in the Directions section of Drug Facts, which states that the tablet ———

Reviewed by:

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

Mary Purucker, M.D., Ph.D.
Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Purucker/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/Zeccola/CSO
HFD-560/M. Chang/Supervisory CSO
HFD-560/Hu/Medical Reviewer

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/s/

Charles Lee
6/6/02 09:29:56 PM
MEDICAL OFFICER

Mary Purucker
6/7/02 02:09:30 PM
MEDICAL OFFICER

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

Application Number: NDA 21-375
Application Type: NDA
Sponsor: Whitehall Robins Healthcare, Inc.
Proprietary Name: Alavert™ Allergy
Dimetapp® Allergy
Category of Drug: Antihistamine
USAN/Established Name: loratadine
Route of Administration: Orally disintegrating tablet
Medical Reviewer: Charles E. Lee, M.D.
Review Date: 6/4/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type and Comments:
N21-375	8/23/01	9/5/01	NDA
N21-375 N000 PW	1/2202	1/23/02	Request for pediatric waiver
N21-375 N000 BM	2/4/02	2/6/02	Safety information, special populations
N21-375 N000 BP	5/3/02	5/7/02	Response to information request
N21-375 N000 SU	5/23/02	5/24/02	Safety update

RELATED APPLICATIONS (if applicable):

Application	Document Date:	Application Type:	Comments:

This NDA is a 505(b)2 application for loratadine, 10-mg orally disintegrating tablets. The sponsor is Whitehall-Robins Healthcare, Inc. The reference product is Claritin® RediTabs®, 10-mg loratadine tablets, manufactured by the Schering Corporation. The sponsor has proposed two trade names: Alavert™ Allergy and Dimetapp® Allergy. The proposed indication is the temporary relief of symptoms due to hay fever (allergic rhinitis), including 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 one tablet (10 mg) daily, not to exceed more than one tablet in any 24 hours period. The product is not indicated for children under the age of 6 years. The sponsor's development plan relied on two pharmacokinetics and bioavailability studies. The sponsor has succeeded in demonstrating that under both fasting and fed conditions, their loratadine 10-mg orally disintegrating tablet is bioequivalent to the reference standard. A greater degree of bioavailability for loratadine was noted when the proposed product was given under fed conditions compared with under fasting conditions. No food effect on bioavailability of DCL was noted. The increased bioavailability of loratadine under the fed condition has been previously demonstrated and is noted in labeling for the reference product. The sponsor provided an integrated summary of safety that included data from their pivotal bioequivalence studies, review of the published literature, and data from various safety databases, including the Agency's Adverse Event Reporting System (AERS). The small amount of safety data from their pivotal bioequivalence studies reveals no new safety signal. There is no evidence that there is a potential for abuse, and there is a wide margin of safety in overdose. The sponsor's safety data identifies no special toxicity associated with loratadine. The incidence of QT prolongation and arrhythmia appear to be similar to the background rates for these events. The safety profile for loratadine in large postmarketing safety databases is similar to that noted in labeling, and supports the proposed use in the intended population. The sponsor's has succeeded in demonstrating that their product is bioequivalent to the approved reference product and has adequately supported the safety of their product. From a clinical perspective, this reviewer recommends an approval action.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION:

Approval: X **Approvable:** **Not Approvable:**

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

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EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendations on approvability

The sponsor has presented adequate and convincing data from their bioequivalence and bioavailability studies to support the differences between their product and the reference product, thereby meeting approvability criteria for a 505(b)2 application. In addition, the sponsor has provided convincing evidence of safety of their product and adequately supports the proposed switch from prescription to OTC marketing status. From a clinical perspective, this reviewer recommends an approval action.

1.2. Recommendations on Phase 4 studies and risk management steps

No Phase 4 studies are recommended. The sponsor should be discouraged from using two different trade names for their product to avoid consumer confusion.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief overview of clinical program

This NDA is a 505(b)2 application for loratadine, 10-mg orally disintegrating tablet. The sponsor is Whitehall-Robins Healthcare, Inc. This application is based 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 the approved reference product. The reference product is Claritin® RediTabs®, 10-mg loratadine tablets. The sponsor's development plan relied on two pharmacokinetics and bioavailability studies. These were: (1) Study 99-104-MA, a single dose bioavailability study that compared the bioavailability of loratadine 10-mg orally disintegrating tablets to Claritin® RediTabs® 10-mg loratadine tablets under fasting condition, and (2) Study 99-105-MA, a single dose clinical pharmacology study that compared loratadine 10-mg orally disintegrating tablets under fed and fasting conditions and compared the bioavailability of the proposed loratadine product to the reference product under fed conditions.

The sponsor proposed two trade names: Alavert Allergy™ and Dimetapp Allergy®. The proposed indication is for the temporary relief of symptoms due to hay fever (allergic rhinitis), including 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 one tablet (10 mg) daily, not to exceed more than one tablet in any 24 hours period. The product is not indicated for children under the age of 6 years.

2.2. Efficacy

As noted above, the sponsor's application was based upon a comparison of the bioavailability and bioequivalence of the proposed new drug to an approved reference product, and relied on the Agency's previous findings of efficacy and safety. In their two pivotal bioavailability and bioequivalence studies, the sponsor demonstrated that, under

both fasting and fed conditions, their loratadine 10-mg orally disintegrating tablet is bioequivalent to the reference standard, Schering Claritin® RediTabs® 10-mg tablet. A greater degree of bioavailability for loratadine was noted when the proposed product was given under fed conditions compared with under fasting conditions. The increased bioavailability of loratadine under the fed condition has been previously demonstrated and is noted in labeling for the reference product. No food effect on bioavailability was noted for descarboethoxyloratadine (DCL), the major human metabolite of loratadine.

2.3. Safety

The small amount of safety data from the sponsor's pivotal bioequivalence studies reveals no new safety signal. There is no evidence that there is a potential for abuse, and there is a wide margin of safety in overdose. The sponsor's safety data identifies no special toxicity to be associated with loratadine. The incidence of QT prolongation and arrhythmia appears to be similar to the background rates for these events. The safety profile for loratadine in large postmarketing safety databases is similar to that noted in current labeling for the innovator, and supports the proposed use in the intended population. The sponsor has adequately supported the safety of their product.

2.4. Dosing

The proposed dose for adults and children ages 6 years and older is one 10-mg tablet once daily. The directions instruct the patient not to take more than one tablet in any 24-hour period. The directions note that the tablet dissolves [redacted] in the mouth, and that the product may be taken with or without water [labeling\proposed.pdf, page 2]. Current labeling of the reference product, Claritin® RediTabs® (loratadine 10 mg, orally disintegrating tablets) also notes that tablet disintegration occurs [redacted] and that the product may be taken with or without water. The Chemistry, Manufacturing, and Controls (CMC) reviewers will recommend appropriate language to describe the dosage form in product labeling.

2.5. Special populations

Compared with normal individuals, patients with hepatic impairment have increased C_{max}, AUC, and $T_{1/2}$ for loratadine and patients with renal impairment have increased $T_{1/2}$ for loratadine. No dosage adjustment for patients with liver or kidney disease is included in the label, but the sponsor has proposed the text, "Ask a doctor before use if you have liver or kidney disease." The sponsor notes that the Claritin label recommends a modified dosage schedule, 10 mg every other day, in patients with hepatic and renal impairment. The sponsor appropriately addresses use of the product in patients with hepatic and renal impairment.

The innovator's product labeling states that the recommended dose for children 6 years of age and older is one 10-mg RediTab® once daily. The sponsor proposes the same dose for their product for children 6 years and older. The sponsor's proposed labeling states that the consumer should contact a doctor before using the product in children under 6 years of age. The sponsor appropriately addresses use of the product in the pediatric population.

The sponsor has requested a partial waiver of pediatric studies in patients from birth to less than 6 years of age because the product contains 10 mg of loratadine, an inappropriate dose for children of this age group. The sponsor's request for partial waiver of pediatric studies is appropriate and should be granted. Safety data for children exist for loratadine, and the sponsor's product is not likely to result in a therapeutic meaningful benefit in children less than 6 years of age because an age-appropriate formulation of loratadine is currently approved and marketed.

The sponsor's review of the literature and of the Agency's Adverse Event Reporting System (AERS) database does not suggest an increased risk for the elderly patients who use loratadine. Although the current label for the innovator's product notes that the AUC and C_{max} of loratadine and DCL in healthy patients greater than 65 years of age were approximately 50% greater than that observed in younger subjects, no dosage adjustment is recommended because a wide margin of safety exists. The sponsor states that the T_{max} and $T_{1/2}$ were similar to those of healthy young volunteers. As with the innovator's product, no dose adjustment is recommended in labeling for patients greater than 65 years of age.

There were 154 patients enrolled in the pivotal clinical pharmacology studies and the majority of subjects in the pivotal clinical pharmacology studies were of Caucasian race. Females represented 52.0% of subjects and males represented 48.0% of subjects in the pivotal clinical pharmacology studies. It not possible to draw conclusions regarding the safety of the product in these special populations from these studies because of the small number of patients.

There recently has been an epidemiology study conducted in Sweden that noted an increased frequency of hypospadias in women who took loratadine during their pregnancies [Memorandum to Robert Meyer MD from Carolyn A. McCloskey, MD, 5/3/02]. The sponsor of the reference product, Schering Laboratories, [redacted] The Agency has asked an independent teratology expert to review these data. The Division has discussed the Swedish data at a meeting with the Division of Drug Risk Assessment. There are no data to suggest that there is a similar increased frequency of this association in the US. There is no preclinical information that would suggest a mechanism for this association. It is unclear if this association represents a true signal. Similar associations of congenital defects have been noted for drugs that are currently marketed in the OTC setting, such as aspirin and nonsteroidal anti-inflammatory drugs (NDSAIDs). At this time, this does not appear to be an approvability issue. This possible association warrants further study and observation. Labeling will be changed accordingly if a signal is noted.

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1. Introduction

This NDA is a 505(b)2 application for loratadine, 10-mg orally disintegrating tablet. The sponsor is Whitehall-Robins Healthcare, Inc. The reference product is Claritin® RediTabs®, 10-mg. The sponsor has proposed two trade names: Alavert Allergy™ and Dimetapp Allergy®. A 505(b)2 submission has presumably been chosen for this product in order to "switch" the drug product to OTC status. The reference product is currently prescription only. The proposed indication is for the temporary relief of symptoms due to hay fever (allergic rhinitis), including 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 one tablet (10 mg) daily, not to exceed more than one tablet in any 24 hours period. The product is not indicated for children under the age of 6 years [labeling\proposed.pdf, pages 1-6].

Loratadine is a tricyclic antihistamine, and is one of the second generation antihistamines. Second generation antihistamines tend to be less sedating and less likely to have anticholinergic side effects than first generation antihistamines. Loratadine is currently marketed by the Schering Corporation as a prescription drug in various forms under the Claritin® line of products. The current indications for Claritin® include the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and the treatment of chronic idiopathic urticaria. The recommended dose for adults and children ages 6 years and older is 10 mg once daily. The sponsor is seeking approval of this product as an over-the-counter (OTC) medication. The sponsor submitted an electronic application, and supplied paper copies of the clinical section of the application to the medical reviewer.

There has been much recent public interest in a switch for loratadine from prescription status to OTC status. California Blue Cross/Blue Shield (now WellPoint) has previously submitted a Citizen's Petition requesting OTC status for "non-sedating" (second generation) antihistamines, including loratadine. The petition was based on a review of approximately 300 relevant publications, and included meta-analyses of data extracted from these publications. The Agency recently solicited information from the public on the regulation of OTC drug products at a two-day OTC Drug Products Advisory Committee Meeting [Docket 00N-1256, 6/28/00-6/29/00, http://www.fda.gov/ohrms/dockets/dockets/00n1256/00n1256.htm]. At this meeting the Agency heard opinions on the suitability of second generation antihistamines, such as loratadine, for OTC switches. In addition, at a meeting on 5/11/01, the Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products discussed this issue and concluded that loratadine demonstrated a risk/benefit profile suitable for an OTC antihistamine [http://www.fda.gov/ohrms/dockets/ac/cder01.htm, Pulmonary-Allergy Drugs Advisory Committee].

The sponsor's application is based 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 the approved reference product.

The sponsor's development plan relied on two pharmacokinetics and bioavailability studies:

- Study 99-104-MA, a single dose clinical pharmacology study that compared the bioavailability of loratadine 10-mg orally disintegrating tablets to Claritin® RediTabs® 10-mg loratadine tablets under fasting conditions
- Study 99-105-MA, a single dose clinical pharmacology study that compared loratadine 10-mg orally disintegrating tablets under fed and fasting conditions and compared the bioavailability of the proposed loratadine product to the reference product under fed conditions

1.2. Foreign marketing and regulatory history

Loratadine is available as a prescription product in 80 countries. It is available as a "behind the counter" non-prescription product in 17 countries, and is available as an OTC product in five countries—Canada, Australia, New Zealand, the Philippines, and the United Kingdom. It has not been withdrawn from any market or switched from non-prescription to prescription status [summary\summary.pdf, page 6].

Loratadine was first approved in the US on 4/12/93 as Claritin® 10-mg tablets, NDA 19,658, for the treatment of symptoms of seasonal allergic rhinitis. The reference product for this application, Claritin® RediTabs®, 10-mg orally disintegrating tablets, was approved on 12/26/96. Claritin® is currently indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria (CIU) in patients 2 years of age or older. The sponsor has proposed an OTC switch for their product only for the allergic rhinitis indication, but not for the CIU indication.

2. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

2.1. Chemistry, Manufacturing, and Controls

ESI-Lederle had previously filed ANDA 75-822 for loratadine 10-mg orally disintegrating tablets as a generic prescription product. The reference product for the ESI-Lederle product was Claritin RediTabs®. ESI-Lederle is a sister division of Whitehall-Robins within the American Home Products Corporation. The sponsor, Whitehall-Robins, has subsequently chosen to pursue a 505(b)2 path for approval of their product as an OTC switch.

[redacted] manufactures Loratadine drug substance for the sponsor at a facility in [redacted]. The composition of the drug product is displayed below in Table 2.1. Mannitol, microcrystalline cellulose, and crospovidone are the main excipients [summary\summary.pdf, page 8].

Table 2.1 Alavert™ (loratadine orally disintegrating tablets), composition [summary\summary.pdf, page 8].

Ingredient	Role	%W/W	mg per tablet
Loratadine	Active ingredient		10.0
Mannitol, USP			
Microcrystalline cellulose, NF			
Crospovidone, NF			
Aspartame, NF			
Sodium bicarbonate, USP			
Citric acid, USP			
Magnesium stearate, NF			
Colloidial silicon dioxide, NF			
Natural and artificial flavor			

Reviewer comment:
The reference product, Claritin® RediTabs® contains 10.0 mg of loratadine, and citric acid, gelatin, mannitol, and mint flavor as excipients.

The drug product, loratadine 10-mg orally disintegrating tablets, will be marketed by Whitehall-Robins Healthcare. [redacted] developed the drug product, and will be responsible for commercial manufacturing and packaging [summary\summary.pdf, page 11].

Details on the drug product used in the pivotal biopharmaceutical studies are provided in Table 2.2. The batches were considered to be full-scale in size. The sponsor states that all batches were made using basically the same manufacturing process [summary\summary.pdf, page 12]. The sponsor was asked to provide an exact description the differences between the to-be-marketed product and the product used in the pivotal clinical pharmacology studies. The sponsor states that the formulation used in the studies was identical to the to-be-marketed formulation [N21-375, 5/3/02, hpbio\biosum.pdf, page 1].

Table 2.2 Batch numbers of sponsor's drug product used in this application [summary\summary.pdf, page 12; cmc\invest.pdf page 2].

Batch number	Manufacturing date	Manufacturing site	Use
990033	November, 1999		Demonstration NDA stability
990043	November, 1999		NDA stability Clinical biostudy batch
710151	May, 2001		NDA stability

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Under both fasting and fed conditions, for loratadine, 90% confidence intervals for $AUC_{0\text{-}inf}$ and C_{max} were within limits for bioequivalence compared to the reference standard. For DCL, under both fasting and fed conditions, 90% confidence intervals for $AUC_{0\text{-}inf}$ and C_{max} were within limits for bioequivalence compared to the reference standard. The sponsor has demonstrated that under both fasting and fed conditions, their loratadine 10-mg orally disintegrating tablet is bioequivalent to the reference standard, Schering Claritin RediTabs® 10 mg tablet [summary\summary.pdf, pages 16, 20].

A greater degree of bioavailability for loratadine was noted when the proposed product was given under fed conditions compared to fasting conditions. No food effect on bioavailability of DCL was noted. The increased bioavailability of loratadine, but not DCL, under the fed condition has been previously demonstrated and is noted in labeling for the reference product, Claritin® RediTabs®. The reference product was only studied in the fasted state in the food effects study in this application [summary\summary.pdf, page 20]. Four subjects in these studies were identified as "poor metabolizers," evidenced by markedly elevated exposure and prolonged half-life to DCL (approximately a five-fold increase). More detail on the pharmacokinetics of the product may be found further below in the review of the individual studies (Appendix, Clinical Studies) and in Dr. Kim's clinical pharmacology and biopharmaceutics review [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-375].

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

This submission includes complete reports of two studies, Studies 99-104-MA and 99-105-MA. Study 99-104-MA was a single dose study that compared the bioavailability of loratadine 10-mg orally disintegrating tablets to Claritin® RediTabs® 10-mg loratadine tablets under the fasting condition. Study 99-105-MA was a single dose study that compared loratadine 10-mg orally disintegrating tablets under fed and fasting conditions and compared the bioavailability of the proposed loratadine product to the reference product under fed conditions [summary\summary.pdf, pages 14-20]. These studies are summarized in Table 4.1. More detailed descriptions of these studies follow below.

4.1. Study 99-104-MA

Study 99-104-MA was a clinical pharmacology study that compared the bioavailability of loratadine 10-mg orally disintegrating tables and Claritin® RediTabs® 10-mg loratadine tablets under fasted conditions. The study was a randomized, single dose, two-way crossover bioavailability study conducted in 130 healthy male and female subjects. One hundred thirty patients completed the study. A 28-day washout period separated the two treatment periods [hpbio\bio\99104ma.pdf, page 8]. Safety endpoints reported included adverse events, vital signs, physical examination, and laboratory studies [hpbio\bio\99104ma.pdf, pages 51, 56]. ECGs were performed only at the start of the study and were not safety endpoints in this study [hpbio\bio\99104ma.pdf, pages 14, 51, 56].

4.2. Study 99-105-MA

Study 99-105-MA was a clinical pharmacology study that compared loratadine 10-mg orally disintegrating tablets under fed and fasting conditions and compared the bioavailability of the proposed loratadine product to the reference product under fed conditions. The study was a single dose, randomized, three-way crossover study. Twenty-four healthy male and female subjects were enrolled, and all 24 subjects completed the study. A 21-day washout period separated the two treatment periods [hpbio\bio\99105ma.pdf, page 6]. Safety endpoints included adverse events and physical examination [hpbio\bio\99105ma.pdf, page 51]. Laboratory studies and ECGs were performed at the beginning and end of the study and data were not

Table 4.1. Summary of studies, NDA 21-375 [summary\summary.pdf, pages 14-20].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects,
99-104-MA	Bioavailability	Loratadine, 10-mg orally disintegrating tablet Claritin® RediTabs®, 10-mg loratadine tablet	Single dose	Single center, randomized, active-controlled, fasting, two-way crossover	130	Healthy females and males, 18-65 years
99-105-MA	Fed and fasted bioavailability	Claritin® RediTabs®, 10-mg loratadine tablet, fed Loratadine, 10-mg orally disintegrating tablet, fed Loratadine, 10-mg orally disintegrating tablet, fasted	Single dose	Single center, randomized, fed and fasting, three-way crossover	24	Healthy females and males, 18-65 years

examined as safety endpoints [hpbio\bio\99105ma.pdf, pages 14, 51; N21-375, 5/3/02, hpbio\hpbiosum.pdf, page 1].

5. CLINICAL REVIEW METHODS

A summary of review methods follows, and includes a description of the conduct of the review and an assessment of data quality.

5.1. Conduct of the review

There were two pivotal clinical pharmacology studies included in this application. The sponsor's application was submitted under Section 505(b)2 of the FD&C Act, which permits approvals to be based upon the Agency's previous findings of safety and efficacy of the active drug and adequate information supporting the differences between the new drug and an approved reference product. This regulatory route also permitted the sponsor to propose a "switch" from prescription only to OTC status for loratadine, which has been supported by safety data submitted in the application.

The two pivotal clinical pharmacology studies were 99-104-MA, and 99-105-MA. These studies were individually reviewed, with a focus on safety findings. There was no Integrated Summary of Efficacy because there were no clinical studies. Safety data supporting this application was reviewed in depth. These data included the sponsor's integrated safety data from the pivotal clinical pharmacology studies. The sponsor also included a review of safety information from the published literature, and a review of safety information from various safety databases, including AERS, and an additional review of the safety of loratadine in the elderly and in patients with hepatic and renal impairment.

5.2. Data quality

DSI audit was not requested. Both studies in this application were clinical pharmacology studies. There were no efficacy or safety studies included in the development program for this drug product.

5.2.1. Ethical standards and financial disclosure

The following items were included in this submission:

- Debarment certification [other\debar.pdf]
- Financial disclosure statement [other\alertfinancial.pdf]
- Statements of Good Clinical Practice [hpbio\bio\99104ma.pdf, pages 4-55, hpbio\bio\99105.pdf, pages 49-50]

The sponsor certified that to the best of their knowledge, they did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application. The sponsor certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The sponsor certified that the clinical investigators did not have a proprietary interest in the

proposed product or a significant equity in the sponsor. The sponsor certified that no investigator was the recipient of significant payments.

Overall, the data in this application appear to be acceptable for review in this reviewer's opinion.

6. INTEGRATED REVIEW OF EFFICACY

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 safety and efficacy of the active drug and provision of adequate support for the differences between the new drug product and the approved reference product. The clinical pharmacology studies included in this application established the bioequivalence of the new drug to the test product, therefore no clinical studies of the efficacy of the product or integrated summary of efficacy were required.

7. INTEGRATED REVIEW OF SAFETY

Integrated review of safety data supporting this application follows below.

7.1. Summary and conclusions

At a joint meeting on 5/11/01, the Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products determined that loratadine has a safety profile acceptable for OTC marketing [http://www.fda.gov/ohrms/dockets/ac/cder01.htm, Pulmonary-Allergy Drugs Advisory Committee]. The Agency conducted the review of safety of loratadine for this meeting, and at that time, the sponsor of the reference product opposed a switch to OTC marketing status. The focus of this section of the review is therefore on the case that the sponsor has made for the safety of loratadine.

The sponsor provided an integrated review of safety that included data from their pivotal bioequivalence studies, review of the published literature, and from various safety databases, including AERS. The small amount of safety data from their pivotal bioequivalence studies reveals no new safety signal. There is no evidence that there is a potential for abuse, and there is a wide margin of safety in overdose. The sponsor's safety data identifies no special toxicity associated with loratadine. The incidence of QT prolongation and arrhythmia appear to be similar to the background rates for these events. The safety profile for loratadine in large postmarketing safety databases is similar to that noted in labeling, and supports the proposed use in the intended population. In summary, the sponsor's integrated review of safety supports the proposed indication of their product.

7.2. Content

The sponsor included the following data in their Integrated Summary of Safety:

- Safety data related to loratadine from their pivotal studies
- Adverse event (AE) data from studies published in the medical literature, from the FDA AERS, Canadian PMS, and American Association of Poison Control Center safety databases

- Safety data from clinical studies published in the medical literature.

The sponsor also provided an additional assessment of safety in geriatric patients, and patients with hepatic and renal impairment, a review of which is also included below [N21-375 N000 BM, 2/4/02]. This additional assessment included data from the summary basis of approval for Claritin® and the Claritin® package insert, published literature through 2001, and the FDA AERS data file for the period 11/1/97 though 9/30/00 [N21-375 N000 BM, 2/4/02, clinstat\other\responsetofdarequestforinformat.pdf, page 2].

These data were reviewed in preparation of this overview of safety.

7.3. Safety data presented in the Integrated Summary of Safety

Review of safety data presented by the sponsor in their Integrated Summary of Safety follows.

7.3.1. Integrated safety data, pivotal studies

A review of the integrated safety data from the two pivotal bioequivalence studies in this application follows.

7.3.1.1. Description of pivotal studies

There were two pivotal clinical pharmacology studies in this application. One was a bioequivalence study and the second was a bioavailability and food effects study. Both were single dose studies. These studies are briefly described below.

Study 99-104-MA was a randomized, open-label, single dose, two-way crossover study designed to compare the bioavailability of ESI Lederle—— dissolving tables and Schering (Claritin® RediTabs®) 10 mg loratadine tablets under fasting conditions [hpbio\bio\99104ma.pdf, pages 1, 5]. There was a washout period of 28 days between study periods [hpbio\bio\99104ma.pdf, pages 1, 5, 8, 42].

Study 99-105-MA was a randomized, open-label, single dose, 3-way crossover study designed to compare the bioavailability of the ESI Lederle product under fed and fasting conditions. In addition, the bioavailability of the proposed loratadine product was compared with the reference loratadine product under fed conditions [hpbio\bio\99105ma.pdf, page 1].

7.3.1.2. Demographics

There were 154 patients enrolled in the pivotal clinical pharmacology studies. The majority of subjects were Caucasian (118/154, 76.6%). Hispanic subjects represented 13.6% (21/154) of the population in these studies, followed by subjects of Black (6.5%, 10/154), American Indian (1.3%, 2/154), and Asian (2.0%, 3/154) races. Females represented 52.0% (50/154) of subjects and males represented 48.0% (74/154) of subjects in these studies. The mean age for subjects in these studies was 34.3 years. Subjects

ranged from 18 to 65 years of age [hpbio\bio\99104ma.pdf, pages 19-22; hpbio\bio\99105ma.pdf, page 17].

7.3.1.3. Disposition

Of the 154 subjects enrolled, 152 subjects completed the pivotal studies. All patients that withdrew from the studies were from Study 99-104-MA. Two patients withdrew after completing the first study period and were not exposed to the test product [hpbio\bio\99104ma.pdf, pages 15, 18-22; hpbio\bio\99105ma.pdf, page 17].

7.3.1.4. Exposure

Exposure to study medication is summarized in Table 7.1. A total of 152 patients were exposed to a single dose of the sponsor's proposed formulation of loratadine orally disintegrating tablets [hpbio\bio\99104ma.pdf, pages 15, 18-22; hpbio\bio\99105ma.pdf, page 17].

Table 7.1. Exposure, pivotal studies, NDA 21-375 [hpbio\bio\99104ma.pdf, pages 15, 18-22; hpbio\bio\99105ma.pdf, page 17].

Characteristic	Drug tested	Subjects exposed	Daily dose, duration
99-104-MA			
	Loratadine orally disintegrating tablets (test product)	128	Single dose
	Claritin® RediTabs® (reference product)	130	Single dose
99-105-MA			
	Loratadine orally disintegrating tablets (test product)	24	Single dose
	Claritin® RediTabs® (reference product)	24	Single dose

7.3.1.5. Adverse events

AEs occurring in the pivotal studies are integrated and presented in Table 7.2.
AEs occurring more frequently with test medication than with reference medication included nasal congestion, dysmenorrhea, pharyngeolaryngeal pain, URI, and cough [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 58-60].

Table 7.2. Adverse events occurring in more than one patient and more frequently in loratadine orally disintegrating tablet, 10 mg than for reference, Schering Claritin® RediTab®, 10 mg, Studies 99-104-MA and 99-105-MA, integrated data [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 58-60].

Adverse event	Loratadine Orally Disintegrating Tablet, 10 mg Test Product (A) N = 154		Schering Claritin® RediTab®, 10 mg Reference Product (B) N =154	
	N	(%)	n	(%)
All adverse events	42	(27.3)	49	(31.8)
Nasal congestion	4	(2.6)	0	(0)
Dysmenorrhea	3	(1.9)	2	(1.3)
Pharyngeolaryngeal pain	2	(1.3)	1	(0.6)
URI, not otherwise specified	2	(1.3)	0	(0)
Cough	2	(1.3)	1	(0.6)

7.3.1.6. SAEs and deaths

There were no SAEs or deaths in the pivotal bioequivalence studies [hpbio\bio\99104ma.pdf, page 14; hpbio\bio\99105ma.pdf, pages 14, 23-26].

7.3.1.7. Withdrawals due to AEs

Both subjects who withdrew from the pivotal studies were from Study 99-104-MA, and both withdrew after receiving reference product [hpbio\bio\99104ma.pdf, pages 15, 18-22; N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 1-69]. Subject 5 dropped from the study prior to dosing in the second study period [hpbio\bio\99104ma.pdf, pages 14, 15]. This subject reported an AE for lightheadedness [hpbio\bio\99104ma.pdf, page 23]. Subject 126 dropped from the study prior to Phase 2 dosing [hpbio\bio\99104ma.pdf, pages 14, 18]. This subject reported AEs for skin rash, Strep throat, and sore throat [hpbio\bio\99104ma.pdf, page 25].

7.3.1.8. Vital signs

The sponsor integrated the vital signs data from this study with data from bioavailability study 99-105-MA. There were no clinically significant changes in mean values for vital signs [N21-375, 5/3/02, hpbio\biosum.pdf, page 1; N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 60]. There were 10 patients with a shift from baseline in HR from normal to high [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 61]. Maximum HR at study exit was 116 and the maximum change from baseline in HR was 48 [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 60].

Reviewer comment:
The significance of the 10 patients with a shift from baseline in HR from normal to high is unclear. As a second generation antihistamine, loratadine is much less likely to cause anticholinergic side effects. There were no increases in the frequency of urinary retention or dry mouth, which provides additional evidence that this shift is not likely to be due to anticholinergic activity [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 58-60].

7.3.1.9. Physical examination

Abnormalities in physical examinations were reported as adverse events, and are included in the "Adverse Events" section of the Integrated Review of Safety of this document [N21-375, 5/3/02, hpbio\biosum.pdf, page 1].

7.3.1.10. Laboratory studies

There were no clinically significant changes in mean values for laboratory studies [N21-375, 5/3/02, hpbio\biosum.pdf, page 1; N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 62-65]. There were 3 patients with a shift from baseline in % eosinophils from normal to high. The maximum % eosinophils at study exit was 7.6% and the maximum increase from baseline in % eosinophils was 4.7% [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 61, 67]. There were 4 patients with a shift from baseline in % lymphocytes from normal to high. The maximum % lymphocytes at study exit was 61.6% and the maximum increase from baseline in % lymphocytes was 28.4% [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 64, 68]. There were 4 patients with a shift from baseline in platelets from normal to high. The maximum platelet count at study exit was 500,000/mm^3 and the maximum increase from baseline in platelet count was 237,000/ mm^3 [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 64, 68].

7.3.1.11. ECGs

ECGs were performed at the start, but not at the end of the pivotal studies, and were not safety endpoints [hpbio\bio\99104ma.pdf, page 56; hpbio\bio\ma99105.pdf, page 51]

7.3.2. Supplemental safety data in the Integrated Summary of Safety

The sponsor provided supplemental safety data in their Integrated Summary of Safety that consisted of adverse event (AE) data from studies published in the medical literature, and from the FDA AERS, Canadian PMS, and American Association of Poison Control Center safety databases. The sponsor also reviewed safety data from controlled clinical studies published in the medical literature. These supplementary safety data are reviewed below.

7.3.2.1. Summary of published literature

The sponsor's analysis of safety data from published medical literature is reviewed below.

7.3.2.1.1. CNS effects

The sponsor reviewed the 25 published studies in the medical literature regarding CNS effects of loratadine. From their review of these of 25 clinical studies, the sponsor concludes that at the recommended dose of 10 mg once daily, loratadine is devoid of sedative effects and does not affect psychomotor performance [clinstat\iss\iss.pdf, pages 3-16].

These studies used both objective assessments, as well as patient assessments of CNS effects. Various aspects of CNS function were assessed in these studies, including measures of sedation such as somnolence, and wakefulness, as well as measures of psychomotor effects such as reaction times, driving skills and performance, flight simulator performance, visual motor integration, short-term memory, motivation and on-the-job performance.

As a whole, these studies indicate that at the proposed dose, loratadine was similar to placebo in effects on both sedation and psychomotor performance. Loratadine is associated with smaller effects on these measures than conventional sedating antihistamines, such as diphenhydramine, chlorpheniramine, triprolidine, promethazine, and clemastine. Regarding newer less sedating antihistamines, the sedative and psychomotor effects of loratadine were similar to those of fexofenadine and terfenadine, and in most studies, less than that of cetirizine. One study showed loratadine and cetirizine to be similar in their effects on sedation and psychomotor skills.[1] Decreases in psychomotor performance and driving skills were noted in some studies of loratadine at doses of 20 mg once daily and higher. It should be noted that these effects for loratadine occurred at doses are higher than that proposed in this application, and these effects were still less than those noted with conventional sedating antihistamines.

Reviewer comment:
The sponsor has supported their assertion that at the recommended dose of 10 mg once daily, loratadine is devoid of sedative effects and does not affect psychomotor performance.

7.3.2.1.2. Cardiovascular effects

Substantial prolongation of the QTc and QT intervals has been associated with two other previously FDA-approved second generation antihistamines that since have been withdrawn from the market—astemizole and terfenadine. QTc and QT prolongation occurs to a lesser extent with conventional antihistamines. QTc and QT prolongation are significant in their propensity to produce serious, life-threatening ventricular arrhythmias such as torsade des pointes, (TdP), as has been reported with astemizole and terfenadine. The sponsor provides evidence taken from preclinical, clinical, and epidemiologic studies that supports their position of the safety profile of loratadine with regard to cardiac conduction effects [clinstat\iss\iss.pdf, pages 16-20].

Nonclinical studies, including *in vitro* testing with myocardial cells and ion channel models have demonstrated no concerning signal for loratadine. The overwhelming majority of clinical trials and epidemiologic surveys have not evidence of QT effect for loratadine. The sponsor reports that exposure to loratadine in clinical trials has been extensive and is estimated to be 90,000 as of 1997. Some of these trials were designed specifically to look at cardiovascular events, such as arrhythmia and QT effects. Trials of loratadine in doses to 40 mg once daily for up to three months showed no evidence of a cardiac safety signal. The weight of evidence from epidemiologic studies suggests that the risk of ventricular arrhythmias and rhythm disturbances with loratadine is likely to be in the expected background range for the general population.

Reviewer comment:
There appears to be no cardiac safety signal for ventricular arrhythmia or TdP for loratadine. The safety profile of loratadine is clearly superior to that of astemizole and terfenadine. Parenthetically, it is likely that the cardiac safety profile of loratadine is also superior to that of the conventional antihistamines, as well.

7.3.2.1.3. Hepatic and renal effects

The sponsor included three case reports of hepatic failure and hepatic necrosis in patients who were taking loratadine. No conclusion is given regarding whether the sponsor considers these events to be evidence of a safety signal [clinstat\iss\iss.pdf, pages 20-21].

The sponsor provided evidence from a pharmacokinetics study that the clearance of loratadine is not significantly changed in patients in patients with renal insufficiency[2] [clinstat\iss\iss.pdf, pages 21-22].

Reviewer comment:
It is difficult to assess the significance of the three cases of hepatic failure given loratadine's extensive world-wide postmarketing history. It is appropriate to continue to

monitor for similar events, even if there is no strong evidence of a safety signal for hepatic injury.

7.3.2.1.4. Drug-drug interaction

Co-administration of cimetidine, erythromycin, or ketoconazole with loratadine has been shown to result in increased levels of both loratadine and DCL. These interactions have not been associated with an increase in QTc or QT interval, as is seen with astemizole and terfenadine, even after increases in loratadine concentration of more than 300%. The sponsor reports one study in which an increase in loratadine (38%) and DCL (12%) levels were noted when loratadine was co-administered with nefazodone. Unlike other studies, an increase in QTc was noted (7.8 msec) with the increase in plasma loratadine and DCL levels[3] [clinstat\iss\iss.pdf, pages 22-25]. It is important to note that the results of this study have been questioned by one of its co-authors.[4]

Reviewer comment:
It is unclear why QTc prolongation was noted in this study where none was noted in other drug interaction studies where loratadine and DCL levels were much higher. The weight of the evidence from the other drug interaction and cardiac safety studies is that elevated loratadine and DCL levels do not produce QTc and QT interval prolongation.

7.3.2.1.5. Pregnancy and lactation

The sponsor also presents data from one prospective study of women exposed to loratadine in pregnancy and from a retrospective study of women exposed to newly marketed drugs used in the UK. These data do not suggest a safety signal for loratadine when used in pregnancy[5, 6] [clinstat\iss\iss.pdf, page 25-26].

Reviewer comment:
There recently has been an epidemiology study conducted in Sweden that noted an increased frequency of hypospadias in women who took loratadine during their pregnancy. This association has not been noted in US postmarketing data, and there is no scientific or toxicological evidence that suggests that loratadine has anti-androgenic activity [Memorandum to Robert Meyer MD from Carolyn A. McCloskey, MD, 5/3/02]. The innovator, Schering Laboratories, is disputing the data. The Agency has asked an independent teratology expert to review these data. The Division has discussed the Swedish data at a meeting with the Division of Drug Risk Assessment. There are no data to suggest that there is a similar increased frequency of this association in the US. It is unclear if this association represents a true signal. Similar associations of congenital defects have been noted for drugs that are currently marketed in the OTC setting, such as aspirin and nonsteroidal anti-inflammatory drugs (NDSAIDs). At this time, this does not appear to be an approvability issue. This possible association warrants further study and observation. Labeling will be changed accordingly if a signal is noted.

The sponsor provided evidence from the published literature that loratadine and DCL are excreted into breast milk and achieve concentrations in breast milk similar to those of plasma. In a study performed in women who took a single 40-mg dose of loratadine, the

amount of loratadine that would be ingested by a 4-kg infant is was estimated to be, at most, approximately 1% of the administered dose[7] [clinstat\iss\iss.pdf, pages 25-26].

7.3.2.1.6. Safety profile in children

The sponsor provides information from four studies relating to the safety profile of loratadine in children. Three of these studies evaluated ECGs. These studies included one study where loratadine co-administered with erythromycin. No effects on ECGs were noted in children from ages 5 to 12 years who received doses of loratadine of up to 10 mg per day for 14 days.[8] AEs, vital sign, physical examination, laboratory studies were also evaluated in one study of the tolerability of loratadine in this age group, with no effect noted in any of the safety endpoints[9] [clinstat\iss\iss.pdf, page 26-28].

7.3.2.1.7. General safety profile

The sponsor presents data from an article describing adverse events from 300 patients in post-approval controlled trials and 55,000 patients in post-approval open-label trials, and from published data based on spontaneous reports from 9 European countries. The most frequent adverse events noted in these data were similar to those noted in current labeling for the reference loratadine product.[10] These included somnolence, fatigue, headache, dry mouth, and GI upset. The labeling for the reference loratadine product notes that at 10 mg once daily, the frequencies of the most common AEs are similar to those of placebo. These include headache (12% loratadine, 11% placebo), somnolence (8% loratadine, 6% placebo), fatigue (4% loratadine, 3% placebo), and dry mouth (3% loratadine, 2% placebo) [clinstat\iss\iss.pdf, pages 28-29]

7.3.2.1.8. Abuse potential and overdose

The sponsor notes that data from the Drug Abuse Warning Network for the most recent five-year period does not include loratadine in the listing of most frequently cited drugs in connection with ER visits or by Medical Examiners [clinstat\iss\iss.pdf, page 29].

The sponsor also presents data from the published literature on overdoses. These data suggest that loratadine produces little toxicity after acute overdose. A retrospective survey of 71 cases, 83% of single ingestions were asymptomatic. Symptoms exhibited by patients included syncope, drowsiness, urticaria, vomiting, nausea, and headache. One patient had right bundle branch block and was discharged after a 6-hour observation period. Of 17 patients who had multiple exposures, 65% were asymptomatic, and the remaining patients had confusion, mydriasis, vomiting, lethargy, and headache. One patient had sinus tachycardia requiring hospitalization.[11] The sponsor presents a narrative of one 18 year-old female who ingested 300 mg of loratadine in a suicide attempt who developed respiratory alkalosis, but no cardiovascular or CNS effects[12] [clinstat\iss\iss.pdf, pages 29-30].

7.3.2.1.9. Commercial marketing experience and foreign regulatory actions, published literature

Loratadine was first marketed in Belgium in 1988. As of 1999, loratadine was marketed in 94 countries worldwide. Loratadine is now available as a non-prescription drug in 17

countries. The sponsor presents data from a published study that reviewed postmarketing data for 9 European countries from 1988 to 1991. There were 434 AEs reported. It is estimated that there were about 9 million patients exposed over this time period in these countries. The most common AEs reported were similar to those noted in current labeling, and included headache, fatigue, dizziness, nausea, and allergic symptoms[10] [clinstat\iss\iss.pdf, pages 49-50].

7.3.2.1.10. Safety data from published clinical trials

The sponsor provides a table summarizing data pertaining to loratadine from comparative clinical trials that were reported in the medical literature. Most of these studies were cited in the Citizen's Petition submitted by Blue Cross/Blue Shield (now WellPoint). The sponsor also updated the summary table to include additional more recent studies in their summary table.

Reviewer comment:
The safety profile of loratadine described in these controlled clinical studies is similar to that noted in the postmarketing database. Review of the sponsor's presentation of these data revealed no new safety signal.

7.3.2.2. American Association of Poison Control Centers Data

The sponsor summarized data for loratadine from the American Association of Poison Control Centers (AAPCC) over the period from 1993, the date of first approval in the US, to 2000. There were 35829 cases of exposure reported to the AAPCC over this period. Of these cases, 57% were exposure to loratadine alone, with no concomitant drugs. Most of the cases were unintentional exposures. The majority of cases (68%) resulted in no effect and 92% had either minor effect or no effect. There were three deaths reported, all of which were in patients ≥12 years of age, and were associated with concomitant drugs. In those with clinical effects, the predominant clinical effects were tachycardia and somnolence. These were the most prominent clinical effects for both children and adults, and tended to be more common in children than in adults [clinstat\iss\iss.pdf, pages 30-37].

7.3.2.3. Adverse Event Reporting System

The sponsor obtained data from the FDA's Adverse Event Reporting System (AERS) from the Period 11/1/97 to 9/30/00. These data included both US and foreign reports. There were 1128 serious and non-serious reports for loratadine. Most of these reports were for patients of unknown age (46%, 524/1128). Of those with age noted, 44% (491/1128) were in patients ≥12 years of age, 7% (79/1128) were in patients ≥6 years to <12 years of age, and 3% (34/1128) were in patients ≥2 years to <6 years of age.

The most frequently reported events involved the cardiac (17%, 197/1128) and nervous systems (14%, 161/1128). There were 176 serious cardiac events. Loratadine was considered to be the primary suspect drug in 100 of these 176 serious cardiac events. These serious cardiac events included tachycardia (15 events), atrial fibrillation (15 events), TdP (9 events), arrhythmia (11 events), bradycardia, (11 events) and palpitations

(9 events). The sponsor states that a majority of these events were associated with confounding factors. There were 17 unique reports with death listed as the outcome. As noted above, concomitant medications and illnesses confound the interpretation of most of the deaths [clinstat\iss\iss.pdf, pages 39-43, 148-178].

Reviewer comment:
There were, as the sponsor states, confounding factors in the majority of these reports. Nonclinical studies and the overwhelming majority of clinical trials and epidemiologic surveys have not demonstrated evidence of QT effect for loratadine. These cardiovascular events are not likely to represent safety signals and are likely to be chance occurrences, or possibly may be the result of a rare susceptibility in an individual, not generalizable to the population at large.

7.3.2.4. FDA Review of loratadine, Advisory Committee, 5/11/01

The sponsor refers to the FDA's presentation at the Advisory Committee meeting held on 5/11/01 at which the safety profile of the newer less sedating antihistamines was discussed. The Executive Summary on Risk Issues reported that there was no conclusive evidence of a causal relationship between loratadine and SAEs. The conclusions from this FDA analysis of these events are similar to those of the sponsor [clinstat\iss\iss.pdf, pages 44-45; http://www.fda.gov/ohrms/dockets/ac/01/briefing/3737b1.htm].

7.3.2.5. Postmarketing surveillance, Canada

The sponsor presents a summary of postmarketing surveillance from Canada. Loratadine has been available as a non-prescription drug since 1989. Data from 1989 to 1999 was examined. There were 218 events reported for 105 individuals. Tachycardia and palpitations were most frequently reported, with 7 events each. No other event was reported more frequently. The Canadian regulatory authorities recommended that "tachycardia" should be added to labeling based on these cases [clinstat\iss\iss.pdf, pages 45-48].

7.4. Additional assessment of safety in certain subpopulations

This additional assessment included data from the summary basis of approval for Claritin®, the Claritin® package insert, published literature through 2001, and the FDA AERS data file for the period 11/1/97 through 9/30/00 [N21-375 N000 BM, 2/4/02, clinstat\other\responsetofdarequestforinformat.pdf, page 2]. The sponsor provided information on the elderly, those with renal impairment, and those with hepatic impairment. The sponsor examined both reports of the use of loratadine by patients with hepatic and renal impairment as well as the potential for the product to cause hepatic and renal impairment.

7.4.1. Geriatric population

The sponsor concludes that the data do not suggest an increased risk for elderly patients who use loratadine. Their review of the published medical literature revealed one study in which the T_{max} (1.5 hours) and $T_{1/2}$ (18.2 hours) for normal subjects 66 to 78 years of age were similar to those of healthy young volunteers [N21-375 N000 BM, 2/4/02,

clinstat\other\responsetofdarequestforinformat.pdf, page 3]. The sponsor also presented data from a two-week multicenter trial of loratadine in the treatment of SAR that examined AEs and laboratory values for patients stratified by age, <65 years versus ≥65 years. There were 2877 patients <65 years of age and 242 patients ≥65 years of age. Headache was slightly less frequent in patients ≥65 years (3%) than in patients <65 years (6%). Somnolence was slightly less frequent in patients ≥65 years (3%) than in patients <65 years (5%). Dry mouth was slightly less frequent in patients ≥65 years (<1%) than in patients <65 years (2%). Somnolence was slightly less frequent in patients ≥65 years (3%) than in patients <65 years (5%) [N21-375 N000 BM, 2/4/02, clinstat\pubs\lorber1994.pdf, page 1].

The sponsor noted 63 case reports for 59 patients ≥65 years of age in the AERS database. More than 50% of the reports were for cardiovascular events. Most patients were taking concomitant drugs and had concomitant medical conditions. There were two deaths noted. One was a 79-year old woman for which there was no other information and a 94-year old woman who was reported to have arrhythmia, tachycardia, and syncope [N21-375 N000 BM, 2/4/02, clinstat\other\responsetofdarequestforinformat.pdf, pages 4-10].

Reviewer comment:
The current Claritin® label notes that the AUC and C_{max} of both loratadine and DCL in 12 healthy patients 66 to 78 years of age were approximately 50% greater than those observed in younger subjects. The current Claritin® label does not recommend a dosage for those ≥65 years of age. The high proportion of cardiovascular events is not a surprise in the elderly subpopulation.

7.4.2. Hepatic impairment

The sponsor searched for reports of the use of loratadine by patients with hepatic impairment as well as the potential for the product to cause hepatic impairment. The sponsor notes that the current Claritin® label includes a summary of data from seven patients with chronic alcoholic liver disease whom were administered loratadine. AUC and C_{max} of loratadine were twice those of normal subjects. The elimination $T_{1/2}$ for loratadine was 24 hours and for DCL was 37 hours, and increased with increasing severity of liver disease. The sponsor's search of the literature revealed no reports of the use of loratadine by hepatically-compromised patients [N21-375 N000 BM, 2/4/02, clinstat\other\responsetofdarequestforinformat.pdf, page 4].

The sponsor's search of the AERS database revealed 29 reports of hepatic adverse events for loratadine. Of these 29 reports, loratadine was the primary suspect drug in 15. Five were taking concomitant drugs known to have hepatotoxic potential and one had Hepatitis C. The sponsor concludes that the AERS data suggest that patients my take loratadine without concern for drug-induced hepatotoxicity [N21-375 N000 BM, 2/4/02, clinstat\other\responsetofdarequestforinformat.pdf, pages 4-5].

The sponsor notes that the Claritin® label recommends a modified dosage schedule in patients with hepatic impairment, 10 mg every other day. The sponsor has therefore

proposed the text, "Ask a doctor before use if you have liver or kidney disease" for their labeling.

Reviewer comment:
Of the 15 patients who had loratadine as the primary suspect drug for their hepatic adverse events, five were 71 years or older. Review of the case reports reveals that three of these five patients (#3485449, #3502113, #3553792) had concomitant use of medications that can cause hepatotoxicity [N21-375 N000 BM, 2/4/02, clinstat\other\responsetofdarequestforinformat.pdf, pages 73-96]. The safety profile of loratadine was discussed at the joint Nonprescription Drugs Advisory Committee and Pulmonary-Allergy Drugs Advisory Committee meeting held on 5/11/01. The Executive Summary on Risk Issues summarized the report of the OTC Switch Review Team on the safety assessment of antihistamines and addressed the issue of hepatotoxicity with loratadine [http://www.fda.gov/ohrms/dockets/ac/01/briefing/3737b1.htm]. The committee, composed of members of the Division of Pulmonary and Allergy Drug Products and the Division of Drug Risk Evaluation, noted that the reporting rate for hepatotoxicity with loratadine was lower than the background rate, but that a potential safety signal could not be ruled out. Although these few cases do not represent a signal, future AE reports should be monitored closely for evidence of a safety signal for hepatotoxicity in the elderly.

The sponsor's proposed label instructs the patient with liver disease to contact a health care provider before using the product. In this reviewer's opinion, based on the sponsor's review of the literature and the AERS data, and the current Claritin® label, the sponsor's proposed text appropriately addresses use of the product in patients with hepatic impairment.

7.4.3. Renal impairment

The sponsor searched for reports of the use of loratadine by patients with renal impairment as well as the potential for the product to cause renal impairment. The sponsor notes that the current Claritin® label includes a summary of data from 12 patients with chronic renal impairment and creatinine clearance ≤30 mL/min who were administered loratadine. AUC and C_{max} of loratadine increased by 73% for loratadine and 120% for DCL. The elimination $T_{1/2}$ for loratadine was 7.6 hours and for DCL was 23.9 hours. The sponsor's search of the literature revealed no reports of the use of loratadine by renally-compromised patients [N21-375 N000 BM, 2/4/02, clinstat\other\responsetofdarequestforinformat.pdf, page 11].

The sponsor's search of the AERS database revealed 24 reports (15 initial and 9 follow-up) of renal adverse events for loratadine. Loratadine was the primary suspect drug in seven of these 24 reports. Concomitant drugs known to be associated with renal events were taken in three cases. The sponsor concludes that the AERS data do not suggest that patients are at risk for development of renal impairment when taking loratadine [N21-375 N000 BM, 2/4/02, clinstat\other\responsetofdarequestforinformat.pdf, pages 11-12].

The sponsor notes that the Claritin® label [redacted]

Reviewer comment:
These few cases of renal events do not appear to represent a safety signal. The sponsor's proposed label instructs the patient with kidney disease to contact a health care provider before using the product. In this reviewer's opinion, based on the sponsor's review of the literature and the AERS data, and the current Claritin label, the sponsor's proposed text appropriately addresses use of the product in patients with renal impairment.

7.5. Safety update

The sponsor provided as safety update to summarize new safety information since the submission of the NDA in August 2001. This safety update examined published articles identified by a search of the literature and a review of various postmarketing safety databases. Postmarketing safety databases were searched for exposures reported to the American Association of Poison Control Centers, reports of abuse and misuse from the Drug Abuse Warning Network, and spontaneous reports submitted to the FDA AERS database [N21-375 N000 SU, 5/23/02, update\iss\iss.pdf, page 2]. The sponsor's safety update revealed reports of 14 cases of hypospadias that were discussed earlier in this review in Section 7.3.2.1.5. As noted above, all of these cases were from a single country, Sweden, and there is no preclinical information that would suggest a mechanism for this association. The significance of these cases is unclear, and an independent teratology expert is reviewing these data. The Division has discussed the Swedish data at a meeting with the Division of Drug Risk Assessment. There are no data to suggest that there is a similar increased frequency of this association in the US. It is unclear if this association represents a true signal. Similar associations of congenital defects have been noted for drugs that are currently marketed in the OTC setting, such as aspirin and nonsteroidal anti-inflammatory drugs (NDSAIDs).

The sponsor's safety update identified no new clear safety signal, and supports the safety of loratadine for the proposed indication and dose in the OTC market. The safety update is reviewed below.

The sponsor searched the published literature from January 2001 to April 30, 2002 using the following databases:

- Medline
- Embase
- Biosis Previews
- Derwent Drug File
- PubMed
- SciSearch

Search terms included loratadine limited to human, and major descriptor or title, and any of the following as descriptors: tox, or safety, or poison, or overdose, or adverse reaction,

or affect, or effect. A second search was conducted using loratadine in title, and any of the following as descriptors or in title: tox, or safety, or poison, or overdose, or adverse reaction, or affect, or effect [N21-375 N000 SU, 5/23/02, update\iss\iss.pdf, page 2].

The sponsor's review of the literature revealed no evidence of new safety signal. The sponsor concludes that the literature continues to support the OTC availability of loratadine for the treatment of AR at the recommended dose of 10 mg once daily [N21-375 N000 SU, 5/23/02, update\iss\iss.pdf, page 7].

Reviewer comment:
The sponsor's review identified a single abstract describing a 46-year old woman who, after taking loratadine 5 mg plus pseudoephedrine (PSE) 120 mg for 5 days, experienced syncope and a prolonged QTc of 478 msec [N21-375 N000 SU, 5/23/02, update\pubs\hoffman2002.pdf, page 1]. She denied use of other medications. Prolonged QTc duration resolved within 24 hours of discontinuation of loratadine and pseudoephedrine. The next day her QTc was 398 msec. Laboratory studies were normal at admission to the hospital, including potassium levels. PSE, loratadine, and DCL levels were not in toxic levels. This report however, makes no mention of the frequency of dosing, whether there was any abnormal rhythm detected, and does not describe the details of the episode of syncope or her hospital course. The lack of detail in this report makes it difficult to firmly attribute the episode to the loratadine/PSE combination. As noted previously in this review, the weight of evidence from epidemiologic studies suggests that the risk of ventricular arrhythmias and rhythm disturbances with loratadine is likely to be in the expected background range for the general population. This reviewer concurs with the sponsor that the literature review reveals no new safety signal.

The sponsor's review of postmarketing safety databases identified one new item of interest. This sponsor's review identified a total of 14 cases of hypospadias associated with loratadine use during pregnancy. The sponsor points out that no literature articles were found that suggested that loratadine has an anti-androgenic effect or any proposed mechanism for the development of hypospadias. The sponsor also points out that there is no existing preclinical literature that points to an association between loratadine exposure or its metabolite with hypospadias. The sponsor has requested, but has not received, copies of MedWatch forms for these events. From the MedWatch forms, the sponsor plans to assess when the mothers ingested loratadine, as this malformation occurs between the ninth and twelfth week of pregnancy. The sponsor concludes that based on the existing information at this time, no definitive link can be made regarding loratadine exposure during pregnancy and the occurrence of hypospadias [N21-375 N000 SU, 5/23/02, update\iss\iss.pdf, pages 24-25].

Reviewer comment:
As noted previously in this review, all of these cases are from a single country, Sweden. The association of loratadine with hypospadias has not been noted in US postmarketing data. As the sponsor points out, there is no information in the medical literature that suggests that loratadine has anti-androgenic activity. The Agency has asked an independent teratology expert to review these data. The Division has discussed the

Swedish data at a meeting with the Division of Drug Risk Assessment. There are no data to suggest that there is a similar increased frequency of this association in the US. It is unclear if this association represents a true signal. Similar associations of congenital defects have been noted for drugs that are currently marketed in the OTC setting, such as aspirin and nonsteroidal anti-inflammatory drugs (NDSAIDs). At this time, this does not appear to be an approvability issue. This possible association warrants further study and observation. Labeling will be changed accordingly if a signal is noted.

7.6. References

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8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The proposed dose for adults and children ages 6 years and older is one 10-mg tablet once daily. The directions instruct the patient not to take more than one tablet in any 24-hour period. The directions note that the tablet [redacted] in the mouth, and that the product may be taken with or without water [labeling\proposed.pdf, page 2]. Current labeling of the reference product, Claritin® RediTabs® (loratadine 10 mg, orally disintegrating tablets) also notes that tablet disintegration occurs rapidly and that the product may be taken with or without water.

Reviewer comment:
The CMC reviewers note that the tablet disintegrates in the mouth, but does not necessarily dissolve in the mouth. The CMC reviewers will recommend appropriate language to describe the dosage form in product labeling.

9. USE IN SPECIAL POPULATIONS

The sponsor notes that the innovator's label recommends a modified dosage schedule in patients with hepatic impairment, 10 mg every other day. The sponsor also notes that the innovator's label recommends a modified dosage schedule in patients with pre-existing

renal disease, 10 mg every other day. The sponsor has therefore proposed the text, "Ask a doctor before use if you have liver or kidney disease" for their labeling.

There were 154 patients enrolled in the pivotal clinical pharmacology studies and the majority of subjects in the pivotal clinical pharmacology studies were of Caucasian race. Females represented 52.0% of subjects and males represented 48.0% of subjects in the pivotal clinical pharmacology studies[hpbio\bio\99104ma.pdf, pages 19-22; hpbio\bio\99105ma.pdf, page 17]. It not possible to draw conclusions regarding the safety of the product in special populations using data from these studies because of the small number of patients. There has been no particular ethnic signal from postmarketing or other studies. In addition, loratadine in overdose has not shown a strong correlation to SAEs, which provides additional evidence that any ethnic differences in drug metabolism would not be expected to lead to a substantially different AE profile.

There recently has been an epidemiology study conducted in Sweden that noted an increased frequency of hypospadias in women who took loratadine during their pregnancy. This association has not been noted in US postmarketing data, and there is no scientific or toxicological information that suggests that loratadine has anti-androgenic activity [Memorandum to Robert Meyer MD from Carolyn A. McCloskey, MD, 5/3/02]. The innovator, Schering Laboratories, is disputing the data. The Agency has asked an independent teratology expert to review these data. The Division has discussed the Swedish data at a meeting with the Division of Drug Risk Assessment. There are no data to suggest that there is a similar increased frequency of this association in the US. It is unclear if this association represents a true signal. Similar associations of congenital defects have been noted for drugs that are currently marketed in the OTC setting, such as aspirin and nonsteroidal anti-inflammatory drugs (NDSAIDs). At this time, this does not appear to be an approvability issue. This possible association warrants further study and observation. Labeling will be changed accordingly if a signal is noted.

The innovator's product labeling states that the recommended dose for children 6 years of age and older is one 10-mg RediTab® once daily. The sponsor proposes the same dose for children 6 years and older. The sponsor's proposed labeling states that a doctor should be consulted before using the product in children under 6 years of age [labeling\proposed.pdf, page 2, 5].

The sponsor has requested a partial waiver of pediatric studies in patients from birth to less than 6 years of age because the product contains 10 mg of loratadine, an inappropriate dose for children of this age group. The approved dose of loratadine in children from 2 to 5 years of age is 5 mg [N21-375 N-000 PW, 1/22/02, other\pediatricwaiver.pdf, page 1].

The sponsor's review of the literature and of the AERS database does not suggest an increased risk for the elderly patients who use loratadine. Although the current label for the innovator's product notes that the AUC and C_{max} of loratadine and DCL in 12 healthy patients greater than 65 years of age were approximately 50% greater than that observed in younger subjects, no dosage adjustment is recommended, and a wide safety margin

exists. The sponsor states that the T_{max} and $T_{1/2}$ were similar to those of healthy young volunteers [N21-375 N000 BM, 2/4/02, clinstat\other\responsetofdarequestforinformat.pdf, page 3].

Reviewer comment:
The sponsor's proposed text appropriately addresses use of the product in patients with hepatic and renal impairment. In this reviewer's opinion, and as noted earlier in the "Integrated Review of Safety" section of this document, the sponsor has adequately supported this portion of the proposed label, and appropriately addresses use of the product in patients with hepatic and renal impairment.

The sponsor's review of safety identifies no safety signal for use in children, and has appropriately addressed use in the pediatric population. The sponsor's request for partial waiver of pediatric studies is appropriate and should be granted. Safety data for children exist for loratadine, and the sponsor's product is not likely to result in a therapeutic meaningful benefit in children less than 6 years of age because an age-appropriate formulation of loratadine is currently approved and marketed. Loratadine is currently approved and marketed by Schering, Inc. for children ages 2 to <6 years in the form of Claritin® syrup, at the dose of 5 mg once daily. Schering has performed pediatric studies, and safety data exist for children from 6 months to 6 years of age. Substantial use of the proposed product would not be likely. [Medical Officer Review, N21-375 N-000 PW, 1/22/02]

Based on the data showing an increased C_{max} and AUC in those greater than 65 years of age, one might expect that an increased frequency of sedation might be observed. However, the sponsor's review identifies no safety signal for use in those greater than 65 years of age. The innovator's current label does not recommend a decreased dosage for those greater than 65 years of age. This reviewer concurs that no dosage adjustment is indicated in this population.

10. CONCLUSIONS AND RECOMMENDATIONS

This 505(b)2 application is based 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 the approved reference product. Because of the proposed switch from prescription to OTC status, the sponsor must provide convincing evidence of the safety of their product in the OTC setting.

The sponsor's development plan relied on two pivotal clinical pharmacology studies. The sponsor has succeeded in demonstrating that under both fasting and fed conditions, their loratadine 10-mg orally disintegrating tablet is bioequivalent to the reference standard Schering Claritin® RediTabs® 10-mg tablet. A greater degree of bioavailability for loratadine was noted when the proposed product was given under fed conditions compared with under fasting conditions. This has been previously demonstrated and is noted in labeling for the reference product, Claritin® RediTabs®. No food effect on bioavailability of DCL was noted.

The sponsor provided an integrated summary of safety that included data from their pivotal bioequivalence studies, review of the published literature, and from various safety databases, including AERS. The small amount of safety data from their pivotal bioequivalence studies reveals no new safety signal. There is no evidence that there is a potential for abuse, and there is a wide margin of safety in overdose. The sponsor's safety data identifies no special toxicity associated with loratadine. The incidence of QT prolongation, arrhythmia, appears to be similar to the background rates for these events. The safety profile for loratadine in large postmarketing safety databases is similar to that noted in labeling, and supports the proposed use in the intended population.

The sponsor has provided adequate and convincing data from their bioequivalence and bioavailability studies to support the differences between their product and the reference product, thereby meeting approvability criteria for a 505(b)2 application. In addition, the sponsor has provided convincing evidence of safety of their product and supports the proposed switch from prescription to OTC marketing status. From a clinical perspective, this reviewer recommends an approval action.

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11. APPENDIX, CLINICAL STUDIES

11.1. Study 99-104-MA

Title: A single-dose, randomized, crossover study comparing ESI Lederle loratadine 10 mg — dissolving tablets and Schering (Claritin® RediTabs®) in healthy male and female subjects under fasting conditions

Dosing dates, study group 1: 12/11/99, 1/8/00, 1/15/00
Dosing dates, study group 2: 12/18/99, 1/15/00
Date of study report: 2/29/00

Study 99-104-MA was a randomized, open-label, single dose, two-way crossover study designed to compare the bioavailability of ESI Lederle —-dissolving tables and Schering (Claritin® RediTabs®) 10 mg loratadine tablets under fasting conditions [hpbio\bio\99104ma.pdf, pages 1, 5]. There was a washout period of 28 days between study periods [hpbio\bio\99104ma.pdf, pages 1, 5, 8, 42]. The study was to enroll 130 healthy, non-smoking, male and female subjects, ages 18-65 years. Subjects checked into the study center at least 12 hours before drug administration and underwent an overnight supervised fast of at least 10 hours prior to dosing. Subjects were confined to the inpatient clinic through the 24-hour post-dose procedures in each study period. Blood samples were taken immediately before dosing (0 hours) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post-dose for measurement of loratadine and descarboethoxyloratadine (DCL) concentrations [hpbio\bio\99104ma.pdf, pages 8, 42].

The formulations studied are displayed in Table 11.1.1. The formulation used in the study was representative of the proposed to-be-marketed formulation, and was created in a batch size considered to be "full-scale" [cmc\invest.pdf, pages 1-2].

Table 11.1.1. Study treatments, Study 99-104-MA [hpbio\bio\99104ma.pdf, page 8].

Proposed product	Loratadine, 10 mg tablet, ESI Lederle Lot #990043
Reference product	Claritin® RediTabs®, 10 mg tablet, Schering Lot #9EBT-88

Each subject received a complete medical history, vital signs, physical examination, 12-lead ECG, and clinical laboratory tests on blood and urine. Vital signs, physical examination, and clinical laboratory tests were repeated at the end of the study [hpbio\bio\99104ma.pdf, pages 56]. Subjects were monitored for the occurrence of reported or observed adverse events. Subjects were released on Day 2 and returned to the clinic on an outpatient basis for the remaining blood draws [hpbio\bio\99104ma.pdf, page 46].

A total of 65 subjects were randomized to each treatment group [hpbio\bio\99104ma.pdf, pages 14, 42-43]. Of the 130 subjects enrolled, 128 completed the study. One subject, #5,

withdrew during the first study period, and one subject, #126, withdrew prior to dosing in the second study period. One subject, #3, was removed from the PK analysis for not receiving the complete dose in the first study period [hpbio\bio\99104ma.pdf, page 14]. Therefore, there were 127 subjects included in the analysis of data.

Review of demographic data revealed that the majority of subjects were Caucasian (78%). Hispanic subjects represented 16% of the study population, followed by subjects of Black (3%), American Indian (1.5%), and Asian (1.5%) races. Males represented 45% of subjects and females represented 55% of subjects. The mean age for subjects in this study was 34.2 years. Subjects ranged from 18 to 65 years of age [summary\summary.pdf, pages 15-16].

11.1.1. Clinical pharmacology outcomes

Assays for loratadine and DCL were performed using a LC/MS/MS technique valid over concentrations of [redacted] for loratadine and [redacted] for DCL [hpbio\bio\99104ma.pdf, pages 887, 905-906; summary\summary.pdf, page 14].

PK analyses were based on the data for the 127 subjects who completed the study and received complete doses of study treatment. PK results are presented in Table 11.1.2 comparing the proposed product and the reference product when given under fasting conditions. Please see Dr. Kim's clinical pharmacology and biopharmaceutics review for additional information [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-375].

$AUC_{0\text{-}inf}$ for loratadine was similar for the test (11.56 ng.hr/mL) and reference (11.58 ng.hr/mL) products. $AUC_{0\text{-}inf}$ for DCL was similar for the test (56.50 ng.hr/mL) and reference (56.59 ng.hr/mL) products. C_{max} for loratadine was similar for the test (3.66 ng/mL) and reference (3.60 ng/mL) products. C_{max} for DCL was similar for the test (3.75 ng/mL) and reference (3.83 ng/mL) products. $T_{1/2}$ and T_{max} for loratadine and DCL were also similar for test and reference products [hpbio\bio\99104ma.pdf, pages 14, 42-43].

Table 11.1.2. Mean PK parameters for loratadine and DCL, least-squares means, Study 99-104-MA [hpbio\bio\99104ma.pdf, pages 14, 42-43].

PK Parameter	Loratadine Orally Disintegrating Tablet, 10 mg (A) Test Product (A) N = 127	Schering Claritin® RediTab®, 10 mg Reference Product (B) N =127	Ratio, A/B	90% C I
Loratadine				
$AUC_{(0\text{-}inf)}$, ng.hr/mL	11.56	11.58	0.998	93.38 – 106.30
C_{max}, ng/mL	3.66	3.60	1.016	92.34 – 110.94
$T_{1/2}$, hr	23.78	23.66	1.005	93.47 – 107.49
T_{max}, hr	1.04	1.13	0.915	83.46 – 99.59
DCL				
$AUC_{(0\text{-}inf)}$, ng.hr/mL	56.50	56.59	0.998	96.70 – 102.97
C_{max}, ng/mL	3.75	3.83	0.980	94.25 – 101.68
$T_{1/2}$, hr	24.91	25.00	0.997	97.58 – 101.75
T_{max}, hr	1.94	1.76	1.104	100.76 – 120.02

Statistical comparisons were performed to determine if the test product was bioequivalent to the reference product. For loratadine, 90% confidence intervals for $AUC_{0\text{-}inf}$ and C_{max} were within limits for bioequivalence compared to the reference standard. For DCL, 90% confidence intervals for $AUC_{0\text{-}inf}$ and C_{max} were within limits for bioequivalence compared to the reference standard. The sponsor concludes that the results of this study demonstrates that the loratadine 10 mg orally disintegrating tablet is bioequivalent to the reference standard Schering Claritin® RediTabs® 10 mg tablet [hpbio\bio\99104ma.pdf, pages 11-12; summary\summary, pages 15-16].

Two females of a total of 21 subjects of Hispanic race and one male of a total of four subjects of Black race were identified as poor metabolizers. Systemic exposure (AUC, but not C_{max}) was increased approximately 5-fold compared to the mean values [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-375].

11.1.2. Safety outcomes

Safety endpoints included adverse events, vital signs, physical examination, and laboratory tests on blood and urine [hpbio\bio\99104ma.pdf, page 56]. Abnormalities in physical examinations were reported as adverse events [N21-375, 5/3/02, hpbio\biosum.pdf, page 1].

There were 76 adverse events (AEs) that occurred in this study. Of these 76 AEs, 53 resolved spontaneously and 23 resolved with treatment. All AEs were mild or moderate in severity.

The sponsor integrated AE data from this study with data from bioavailability Study 99-105-MA. AEs occurring more frequently with test medication than with reference medication included nasal congestion, dysmenorrhea, pharyngeolaryngeal pain, URI, and cough [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 58-60]. These data are summarized in Table 11.1.3.

Table 11.1.3. Adverse events occurring in more than one patient and more frequently in loratadine orally disintegrating tablet, 10 mg than for reference, Schering Claritin® RediTab®, 10 mg, Studies 99-104-MA and 99-105-MA, integrated data [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 58-60].

Adverse event	Loratadine Orally Disintegrating Tablet, 10 mg Test Product (A) N = 154		Schering Claritin® RediTab®, 10 mg Reference Product (B) N =154	
	n	(%)	n	(%)
All adverse events	42	(27.3)	49	(31.8)
Nasal congestion	4	(2.6)	0	(0)
Dysmenorrhea	3	(1.9)	2	(1.3)
Pharyngeolaryngeal pain	2	(1.3)	1	(0.6)
URI, not otherwise specified	2	(1.3)	0	(0)
Cough	2	(1.3)	1	(0.6)

There were no serious adverse events (SAEs) or deaths in the study [hpbio\bio\99104ma.pdf, pages 14, 23-26]. There were two patients who withdrew for the study because of AEs. Subject 5 withdrew due to lightheadedness and subject 126 withdrew because of Strep throat, sore throat, and rash. Both were received reference

treatment [hpbio\bio\99104ma.pdf, pages 14, 15, 18-23, 25; N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 1-69].

The sponsor integrated vital signs data from this study with data from bioavailability study 99-105-MA. There were no clinically significant changes in mean values for vital signs [N21-375, 5/3/02, hpbio\biosum.pdf, page 1; N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 60]. There were 10 patients with a shift from baseline in HR from normal to high [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 61]. Maximum HR at study exit was 116 and the maximum change from baseline in HR was 48 [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 60].

There were no clinically significant changes in mean values for laboratory studies [N21-375, 5/3/02, hpbio\biosum.pdf, page 1; N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 62-65]. There were 3 patients with a shift from baseline in % eosinophils from normal to high. The maximum % eosinophils at study exit was 7.6% and the maximum increase from baseline in % eosinophils was 4.7% [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 61, 67]. There were 4 patients with a shift from baseline in % lymphocytes from normal to high. The maximum % lymphocytes at study exit was 61.6% and the maximum increase from baseline in % lymphocytes was 28.4% [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 64, 68]. There were 4 patients with a shift from baseline in platelets from normal to high. The maximum platelet count at study exit was 500,000/mm^3 and the maximum increase from baseline in platelet count was 237,000/ mm^3 [N21-375, 5/3/02, hpbio\bio\ma99104.pdf, pages 64, 68].

Reviewer comment:
It is difficult to draw conclusions based on these data because of the single dose nature of these trials and the small number of patients. There were a small number of AEs, and it appears that there is no safety signal. There were no significant changes in laboratory studies. There were no differences between the test and reference products for AEs or for other safety variables. There are no concerning safety signals noted.

11.2. Study 99-105-MA

Title: A comparative, randomized, 3-way crossover study comparing ESI Lederle loratadine 10 mg [redacted] tablets and Schering (Claritin® RediTabs®) in healthy male and female subjects under fed and fasting conditions

Date, start of study period 1: 12/11/99
Date, start of study period 2: 1/8/00
Date, start of study period 3: 1/29/00
Date of study report: 2/29/00

Study 99-105-MA was a randomized, open-label, single dose, 3-way crossover study designed to compare the bioavailability of the ESI Lederle product under fed and fasting conditions. In addition, the bioavailability of the proposed loratadine product was compared with the reference loratadine product in the fed condition [hpbio\bio\99105ma.pdf, page 1].

There was a washout period of 21 days between study periods. The study was to enroll 24 healthy, non-smoking, male and female subjects, ages 18-65 years. Subjects checked into the study center at least 12 hours before drug administration. Patients assigned to fasting treatment were dosed after a 10-hour fast. Patients randomized to fed treatment received study treatment after a high-fat meal consisting of a buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, 8 ounces of whole milk, and 6 ounces of orange juice. Subjects were confined to the inpatient clinic through the 24-hour post-dose procedures in each study period. Blood samples were taken immediately before dosing (0 hours) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post-dose for measurement of loratadine and descarboethoxyloratadine (DCL) concentrations [hpbio\bio\99105ma.pdf, pages 6-8, 37, 38].

The formulations studied are displayed in Table 11.2.1. The formulation used in the study was representative of the proposed to-be-marketed formulation, and was created in a batch size considered to be "full-scale" [cmc\invest.pdf, pages 1-2].

Table 11.2.1. Study treatments, Study 99-105-MA [hpbio\bio\99105ma.pdf, pages 9-10].

Treatment A	Fasted Loratadine, 10 mg tablet, ESI Lederle Lot #990043
Treatment B	Fed Loratadine, 10 mg tablet, ESI Lederle Lot #990043
Treatment C	Fed Claritin® RediTabs®, 10 mg tablet, Schering Lot #9EBT-88

Each subject received a complete medical history, vital signs, physical examination, 12-lead ECG, and clinical laboratory tests on blood and urine. Vital signs, physical examination, and clinical laboratory tests were repeated at the end of the study [hpbio\bio\99105ma.pdf, page 51]. Subjects were monitored for the occurrence of

reported or observed adverse events. Subjects were released on Day 2 and returned to the clinic on an outpatient basis for the remaining blood draws [hpbio\bio\99105ma.pdf, page 42].

A total of 24 subjects were randomized to each treatment group. All subjects that were enrolled completed the study [hpbio\bio\99105ma.pdf, pages 11, 14]. Review of demographic data revealed that the majority of subjects were Caucasian (71%). Subjects of Black race represented 25% of the study population, followed by subjects of Asian (4%) race. Males represented 63% of subjects and females represented 38% of subjects. The mean age for subjects in this study was 34.7 years. Subjects ranged from 18 to 60 years of age [summary\summary.pdf, pages 18-19].

11.2.1. Clinical pharmacology outcomes

PK analyses were based on the data for the 24 subjects who completed the all treatment periods. PK results from this study are presented in Tables 11.2.2. and 11.2.3. Please see Dr. Kim's clinical pharmacology and biopharmaceutics review for additional information [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-375].

Assays for loratadine and DCL were performed using a LC/MS/MS technique valid over concentrations of _____ for loratadine and _____ for DCL [hpbio\bio\99105ma.pdf, pages 11, 403, 404; summary\summary.pdf page 14].

PK results for the proposed product under fed and fasted conditions are presented in Table 11.2.2.

$AUC_{0\text{-}inf}$ for loratadine for the proposed product was higher under fed (17.66 ng.hr/mL) than under fasting (11.15 ng.hr/mL) conditions. $AUC_{0\text{-}inf}$ for DCL for the proposed product was similar under fed (85.90 ng.hr/mL) and fasting (84.98 ng.hr/mL) conditions. C_{max} for loratadine for the proposed product was similar under fed (3.17 ng/mL) and fasting conditions (3.18 ng/mL) products. C_{max} for DCL for the proposed product was similar under fed (3.95 ng/mL) and fasting (3.98 ng/mL) conditions. $T_{1/2}$ and T_{max} for loratadine under fed conditions were longer than under fasting conditions. $T_{1/2}$ for DCL for the proposed product was similar under fed and fasting conditions, but T_{max} for DCL for the proposed product was longer under fed than under fasting conditions [hpbio\bio\99105ma.pdf, pages 21-24]. These data indicate a food effect that results in a higher $AUC_{0\text{-}inf}$, and longer $T_{1/2}$ and T_{max} for loratadine when the proposed product is given under fed conditions. These data indicate a smaller food effect for DCL with a longer T_{max} under fed conditions than under fasting conditions. No food effect was noted for DCL for $AUC_{0\text{-}inf}$, C_{max}, and $T_{1/2}$.

Table 11.2.2. Mean PK parameters for loratadine and DCL, fed and fasted states for proposed product, least-squares means, Study 99-105-MA [hpbio\bio\99105ma.pdf, pages 21, 23].

PK Parameter	Loratadine Orally Disintegrating Tablet, 10 mg Fed (A) N = 24	Loratadine Orally Disintegrating Tablet, 10 mg Fasted (B) N =24	Ratio, B/A	90% C I
Loratadine				
$AUC_{(0-inf)}$, ng.hr/mL	17.66	11.15	1.583	109.89 – 206.80
C_{max}, ng/mL	3.17	3.18	0.997	64.08 – 135.30
$T_{1/2}$, hr	36.00	22.81	1.578	129.98 – 185.67
T_{max}, hr	3.73	1.21	3.092	271.62 – 346.72
DCL				
$AUC_{(0-inf)}$, ng.hr/mL	85.90	84.98	1.011	92.37 – 109.80
C_{max}, ng/mL	3.95	3.98	0.993	89.44 – 109.22
$T_{1/2}$, hr	28.39	29.93	0.949	85.38 – 104.36
T_{max}, hr	4.90	2.14	2.292	195.37 – 263.11

PK results are presented in Table 11.2.3. comparing the proposed product and the reference product when given under fed conditions. AUC_{0-inf} for loratadine was higher for the test product (17.66 ng.hr/mL) than the reference product (14.08 ng.hr/mL) under fed conditions. AUC_{0-inf} for DCL was similar for the test (85.90 ng.hr/mL) and reference (85.82 ng.hr/mL) products. C_{max} for loratadine was higher for the test (3.17 ng/mL) than for the reference (2.38 ng/mL) product. C_{max} for DCL was similar for the test (3.95 ng/mL) and reference (3.98 ng/mL) products under fed conditions. $T_{1/2}$ was slightly higher for loratadine for the proposed product than for the reference product under fed conditions. $T_{1/2}$ for DCL and T_{max} for loratadine and DCL were similar for test and reference products [hpbio\bio\99104ma.pdf, pages 21-24].

Table 11.2.3. Mean PK parameters for loratadine and DCL, fed and fasted states for proposed product, least-squares means, Study 99-105-MA [hpbio\bio\99105ma.pdf, pages 21, 23].

PK Parameter	Loratadine Orally Disintegrating Tablet, 10 mg Test Product (A) Fed N = 24	Schering Claritin® RediTab®, 10 mg Reference Product (C) Fed N =24	Ratio, B/C	90% C I
Loratadine				
$AUC_{(0-inf)}$, ng.hr/mL	17.66	14.08	1.254	87.06 – 163.83
C_{max}, ng/mL	3.17	2.38	1.334	85.75 – 181.06
$T_{1/2}$, hr	36.00	32.96	1.092	89.97 – 128.52
T_{max}, hr	3.73	3.90	0.958	84.20 – 107.48
DCL				
$AUC_{(0-inf)}$, ng.hr/mL	85.90	85.82	1.001	91.46 – 108.72
C_{max}, ng/mL	3.95	3.98	0.994	89.47 – 109.26
$T_{1/2}$, hr	28.39	28.33	1.002	90.19 – 110.23
T_{max}, hr	4.90	4.992	0.981	83.64 – 112.65

Statistical comparisons were performed to determine if the test product was bioequivalent to the reference product. For loratadine, 90% confidence intervals for AUC_{0-inf} and C_{max} were within limits for bioequivalence compared to the reference standard. For DCL, 90% confidence intervals for AUC_{0-inf} and C_{max} were within limits for bioequivalence compared to the reference standard. The sponsor concludes that the results of this study demonstrates that the loratadine 10-mg orally disintegrating tablet is bioequivalent to the

reference standard Schering Claritin® RediTabs® 10 mg tablet, when given under fed conditions [hpbio\bio\99105ma.pdf, page 15; summary\summary, pages 19-20].

One female of 6 subjects of Black race was identified as a poor metabolizer. As noted in 99-104-MA, AUCs of poor metabolizers were increased approximately 5-fold compared to the mean values [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-375].

11.2.2. Safety outcomes

Safety endpoints included adverse events, vital signs, physical examination [hpbio\bio\99105ma.pdf, page 51]. Abnormalities in physical examinations were reported as adverse events. Laboratory studies and ECGs were performed only at baseline and were not safety endpoints in this study [hpbio\bio\99105ma.pdf, page 51; N21-375, 5/3/02, hpbio\biosum.pdf, pages 1-2].

There were 17 adverse events (AEs) that occurred in this study. Of these 17 AEs, 14 resolved spontaneously, one resolved with treatment and two did not resolve by the end of the study. Subject #20 had edema and bruising due to a fall that was still present at the end of the study. All AEs were mild in severity [hpbio\bio\99105ma.pdf, pages 14, 18]. The sponsor integrated AE data from this study with data from bioavailability study 99-104-MA. These data are summarized in Table 11.1.3 and discussed in Section 11.1.2 of this document, "Safety outcomes." There were no serious adverse events (SAEs) or deaths in the study. There were no patients who withdrew from the study because of AEs [hpbio\bio\99105ma.pdf, page 14].

The sponsor integrated vital signs data from this study with data from bioavailability study 99-104-MA. There were no clinically significant changes in mean values for vital signs [N21-375, 5/3/02, hpbio\biosum.pdf, page 1; N21-375, 5/3/02, hpbio\bio\ma99104.pdf, page 60]. These data are discussed in Section 11.1.2 of this document, "Safety outcomes."

Reviewer comment:
It is difficult to draw conclusions based on these data because of the single dose nature of these trials and the small number of patients. There were a small number of AEs, and it appears that there is no safety signal. There were no differences between the two products in AEs or for other safety variables. As in study 99-104-MA, there are no concerning safety signals noted.

12. APPENDIX, BRIEF LABEL REVIEW

Brief comments on proposed labeling follow. Detailed comments on proposed labeling will be incorporated in the final labeling.

1. The sponsor has proposed two trade names: Alavert™ Allergy and Dimetapp® Allergy. In this reviewer's opinion, Dimetapp Allergy will not be acceptable because of confusion with other Dimetapp products containing other drugs that have an allergy indication.

2. The statement "Non-Drowsy Allergy Relief" occurs on each face of the package, and the back panel makes the statement that the product does not cause drowsiness. The Drug Facts lists the purpose as "non-sedating antihistamine." The language referring to non-sedating claims will need to be examined closely by DPADP and the Division of Over-the-Counter Drug Products, in consultation with the Office of Medical Policy.

3. The back panel also makes the statement that the product contains [redacted] loratadine. This statement is not appropriate, [redacted]

4. The back panel implies the [redacted] nature of the tablet results in [redacted] onset of action. This claim will not be suitable, as the sponsor has not provided evidence that the [redacted] character of the tablet results in a [redacted] onset of action. Furthermore, the product actually is a orally disintegrating tablet that does not necessarily [redacted] in the mouth. The CMC reviewers will recommend appropriate language to describe the dosage form in product labeling.

APPEARS THIS WAY
ON ORIGINAL

Reviewed by:

/S/

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

/S/

Mary Purucker, M.D., Ph.D.
Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Purucker/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-570/Zeccola/CSO
HFD-560/Hu/Medical Reviewer

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/s/

Charles Lee
6/7/02 06:12:09 PM
MEDICAL OFFICER

Mary Purucker
6/10/02 03:19:47 PM
MEDICAL OFFICER
Concur with Dr. Lee's review