CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-512

MEDICAL REVIEW(S)

DIVISION DIRECTOR'S MEMORANDUM

Date: June 24, 2004

To: NDA 21-512

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Loratadine Tablets 10 mg

Applicant: Perrigo Company

Administrative, Introduction, and Regulatory

The Perrigo Company submitted a 505(b)(2) new drug application (NDA 21-512) on June 28, 2002, for marketing loratadine 10 mg tablets over-the-counter (OTC) for use in patients 6 years of age and older with hay fever and other respiratory allergies. The application was based on bioequivalence studies using Claritin Tablets 10 mg as the reference drug and supporting safety data. The application was a (b)(2) because it was submitted prior to Schering-Plough receiving approval for its OTC switch supplement for the Claritin-brand of loratadine, and therefore no reference product was OTC. An approvable action was taken on May 1, 2003, primarily because of CMC deficiencies. At the time of that action the Division of Scientific Investigation's (DSI's) audit of — was not completed because of international travel restrictions. — conducted the bioequivalence studies. Perrigo submitted a complete response on May 9, 2003, responding to the deficiencies, and a request that the DSI audit be waived. The applicant's request to waive the DSI audit was not granted and an audit of — was conducted in July 2003. DSI identified that there were problems with the analyses of samples and recommended that the Agency not rely on the data for regulatory decision making. Specifically, there were cross-well contaminations of samples that made the results uncertain. The Division took an approvable action on July 11, 2003, noting the problem with analyses, and asked Perrigo to reanalyze all samples to demonstrate the accuracy of the assay. On December 22, 2003, Perrigo submitted a complete response with new data from the reanalysis. The Division finds Perrigo's response adequate and sufficient for approval. CMC and other deficiencies are also resolved. Of note, DSI audited the — site again in February 2004, and a memorandum dated April 20, 2004, was issued recommending the Agency not rely on the reanalysis results. Comments on DSI's concerns and our reasoning for not agreeing with DSI's recommendation are discussed in a subsequent section of this memorandum.

The active pharmaceutical ingredient loratadine was developed by Schering and is marketed by Schering under the brand name Claritin as various formulations, such as Claritin Tablets, Claritin Syrup, Claritin RediTabs, Claritin D-12 Hour Extended Release Tablets, and Claritin D-24 Extended Release Tablets, for treatment of symptoms of

allergic rhinitis and urticaria. These products were initially marked as prescription drugs and were later moved to OTC by Schering. The allergic rhinitis indication was approved for OTC marketing on November 27, 2002, and the urticaria indication was approved for OTC marketing on November 19, 2003. Various generic versions of loratadine have been subsequently approved as ANDA for OTC marketing in the United States. Of note, Perrigo also has a pending ANDA with the Office of Generic Drugs that relies on the same data.

There is a Citizen Petition submitted on behalf of Genpharm Inc., (Docket No. 03P-160/CP1 & RC1) on April 15, 2003, with supplemental comments dated May 12, 2003, asking the Agency not to approve this application. The petition argues that Perrigo's loratadine is a duplicate of a listed drug and is therefore ineligible for approval as a 505(b)(2), and could only be approved as an ANDA. The petition further argues that, even if it were eligible for 505(b)(2) approval, this would be prevented by a 30-month stay of approval in effect under 505(c)(3)(C). The Agency denied the Citizen Petition in a letter dated June 24, 2004. The current application by Perrigo is a 505(b)(2) because the application was filed by the Agency when loratadine was still marketed under prescription and before the expiry of Schering's patent and exclusivity on loratadine. The situation is similar to Wyeth Consumer Healthcare's (NDA was submitted by Whitehall-Robbins Healthcare) Alavert (loratadine 10 mg) Orally Disintegrating Tablets, which was also approved under the 505(b)(2) pathway. The 30-month stay is not an issue because that has been terminated by a court decision.

Perrigo has satisfied all scientific and regulatory requirements for approval of this application. The bioequivalence studies and the clinical safety data support approval and there are no chemistry and manufacturing issues. The 505(b)(2) regulatory pathway has also been determined to be appropriate. In subsequent sections of this document the submission is briefly reviewed. The reader is referred to discipline reviews for details. Note that the review of this application was a joint effort of the Division of Pulmonary and Allergy Drug Products and the Division of Over-the-Counter Drug Products (DOTCDP), the latter being primarily responsible for the labeling.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug product contains active drug substances loratadine and a number of commonly used excipients. Perrigo initially listed two suppliers of loratadine drug substance, but subsequently removed one of the two suppliers and settled on the drug substance supplier. The DMFs associated with the manufacture of drug substance is adequate. The drug product is manufactured by Perrigo Company at their facility in Michigan. All manufacturing sites and testing facilities related to this application have acceptable establishment evaluation status. The drug product will be marketed as 4 count, and 12 count blister packages, and as 10 count, 30 count, and 300 count bottles. There were several CMC deficiencies that were listed in previous CMC reviews and the first action letter. The applicant has resolved all the deficiencies. The applicant has proposed acceptance criteria for incoming drug substance and to reject lot based on preset

specifications that are acceptable. The CMC team has recommended an approval action on this application, and I concur with that recommendation.

Clinical Pharmacology and Biopharmaceutics

The applicant submitted results of two clinical pharmacology studies conducted in healthy male volunteers between the ages of 18 and 45 years. The studies were designed to show bioequivalence of Perrigo's loratadine to Claritin (loratadine) Tablets 10 mg as the reference product after a single dose in fasting condition (Study 003214) and after a standard high fat high calorie diet (Study 010177). Both studies were conducted at [redacted] Study 003214 was considered to be pivotal for this application and [redacted] was audited by DSI. As mentioned above, DSI identified problems with sample analysis due to cross-well contamination, which resulted in an approvable action in the previous review cycle. Perrigo has submitted a complete reanalysis of all samples with this application. The clinical pharmacology studies were reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) Reviewer Dr. Kim. The OCPB team concluded that the pharmacokinetic profile of Perrigo's loratadine is sufficiently similar to the reference listed drug to support approval, and I concur with that conclusion.

The Cmax and AUC data from the two studies are shown in Table 1. The pivotal bioequivalence study 003214 showed that Perrigo's loratadine and Claritin Tablets 10 mg were bioequivalent. The 90% confidence intervals for the ratio of the geometric means of AUC and Cmax of the test and reference formulations were within 80% to 125% for loratadine and its major active metabolite desloratadine. The food effect study showed that the bioavailability of Perrigo's loratadine was similar to Claritin Tablets 10 mg under fed condition.

Table 1. Ratio between test and reference product (test/reference) for log-transformed PK parameters of loratadine and desloratadine from the two studies

		Loratadine		**Desloratadine**	
	PK parameter	Point estimate	90% CI	Point estimate	90% CI
Study 003214 (Fasting state – original analyses) *					
	Cmax	103.1	94.2-112.8	98.8	94.1-103.8
	AUC inf	101.6	95.9-107.7	99.9	97.0-102.9
Study 003214 (Fasting state - reanalysis) *					
	Cmax	101.1	93.0-110.0	100.6	96.0-105.4
	AUC inf	100.5	94.9-106.5	98.6	95.5-101.9
Study 010177 (Fed state) *					
	Cmax	91.8	79.6-105.9	100.6	94.7-106.7
	AUC inf	92.2	83.8-101.4	101.2	96.8-105.8
* Reference drug: Claritin (loratadine) Tablets 10 mg					

Although the original analysis of Study 003214 established bioequivalence of Perrigo's loratadine to Claritin Tablets, the Agency did not rely on the data for regulatory action because DSI had identified problems with sample analysis due to cross-well contamination. A detailed review of resultant the data by the review staff also confirmed the problem, as there were several values in serial pharmacokinetic sampling that were

outside the range expected based on the value of previous and subsequent time points. Perrigo did not include those outliers in their analyses. Promoted by an Agency recommendation, Perrigo reanalyzed all samples with a validated assay and demonstrated that Perrigo's loratadine and the reference listed Claritin Tablets 10 mg were bioequivalent (Table 1).

DSI audited the site again in February 2004, to check the validity of the reanalysis, and in a memorandum dated April 20, 2004, DSI recommends that the data from reanalysis not be accepted. DSI's concern was that was not able to identify the problem that originally led to cross-well contamination. DSI also contended that the high concentration data from the original analysis and reanalysis should be similar because the effect of contamination should not affect the high concentration values. The OCBP team disagrees with DSI's recommendation and concludes that the reanalysis is acceptable, and I concur with OCBP's conclusion. The initial analysis was problematic and the Agency had decided not to accept that analysis. Given our concerns with the first analysis, it does not seem reasonable to suspect the results of the reanalysis because it does not show similar results to the original analysis for portion of the data points. The change in assay method, time lapse, and simply performing another run may result in slightly different values. Also there is no reason to believe that cross-well contamination will not affect the high concentration values. Furthermore, the reanalysis was done with a validated method with appropriate controls. Blank wells used during the reanalysis confirmed the absence of any cross-contamination. Finally, the CMC data and in vitro dissolution data do not suggest any problem with Perrigo's loratadine and therefore the prior probability of bioequivalence is reasonably good.

On June 23, 2004, the Division of Pulmonary and Allergy Drug Products and the Office of Generic Drugs met with the Office of Medical Policy to discuss the issues surrounding the findings of the DSI audit. The Office of Medical Policy expressed no objection to the proposed approval of this application.

Clinical and Statistical

There were no clinical studies submitted in support of this application. The applicant submitted safety data from their clinical pharmacology studies, and supported the safety of loratadine by a review of the published literature, and data from various publicly available databases including the Agency's Adverse Events Reporting System (AERS). Please see Dr. Charles Lee's review for detailed discussion of the safety database.

As with other recent loratadine applications the issue of hypospadias (mislocation of the urethral opening in the penis) came up during review. The applicant noted the 15 cases of hypospadias associated with loratadine use during pregnancy in Sweden that were reported previously. No similar finding was noted in the Agency review of US database. Furthermore, the preclinical data do not suggest a possibly mechanism of such an occurrence. The conclusion of the reviews of Office of Drug Safety and this Division remains that although there is a small signal of concern over hypospadias, the signal is

not sufficient to impact on the approvability decision on this application. The same issue was considered during OTC switch of Schering's loratadine and during review of Wyeth Consumer Healthcare's Alavert (loratadine 10 mg) Orally Disintegrating Tablets application. Both Schering and Wyeth were asked and agreed to provide periodic updates specifically related to hypospadias as a post-marketing phase 4 commitments. Perrigo has also agreed to a similar phase 4 commitment.

Pharmacology and Toxicology
The applicant did not conduct any new preclinical studies for this application because the active component and excipients have been studied before. Perrigo is referring to Agency's previous conclusion on these on the 505(b)(2) paradigm.

Data Quality, Integrity, and Financial Disclosure
As mentioned above DSI twice audited the site that conducted the bioequivalence studies and has recommended that the Agency do not rely on the data from the pivotal bioequivalence study. The OCPB team disagrees with DSI's recommendation and has concluded that the data are acceptable and I concur with OCPB's conclusion. The reasoning for accepting the data from the study in question is discussed above under the Clinical Pharmacology and Biopharmaceutics section of this memorandum.

The clinical pharmacology studies were conducted in accordance with accepted ethical standards. No financial disclosure issues are present. The applicant submitted acceptable financial disclosure statement and statements of good clinical practice.

Pediatric Considerations
Perrigo has asked for waiver of pediatric studies in children under the age of 6 years. Perrigo's justification for the waiver request was that the dosage form is not appropriate for children under the age of 6 years. This is acceptable because a tablet formulation at the proposed strength would not be suitable for younger children. Furthermore, loratadine is currently marketed by Schering as a syrup formulation that is appropriate for younger children.

Product Name
Perrigo is not proposing to use any trade name for this product. Generic name of the product, Loratadine Tablets 10 mg, will be used on the blister packages, blister cartons, and bottles.

Labeling
The labeling review is largely the purview of the DOTCDP. The reviewers of DOTCDP and this Division have worked with the applicant to achieve an appropriate labeling

Since the labeling is largely derived from the monograph labeling of antihistamines, no labeling comprehension studies were required of the applicant for the allergic rhinitis indication.

Action

Perrigo has submitted adequate data to support the approval of Loratadine Tablets 10 mg for over-the-counter use for temporary relief of symptoms of hay fever and other upper respiratory allergies in subjects 6 years of age and older. Therefore, the action on this application will be APPROVAL.

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/s/

Badrul Chowdhury
6/24/04 02:44:28 PM
MEDICAL OFFICER

Clinical Team Leader Review Memorandum

Memorandum to: NDA 21-512 file
Product: Loratadine
Memo Date: April 14, 2003
Memo From: Lydia I. Gilbert-McClain, MD, Clinical Team Leader (Actg)

This memorandum is to document the secondary review of Dr. Charles Lee's Primary Medical Review of the NDA 21-512 for loratadine 10–mg tablets. The application was submitted as a new NDA under Section 505 (b)(2) of the FD&C Act which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved reference product. The regulation allows for a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved reference product. The sponsor (Perrigo) used Claritin® Tablets 10 mg as the reference product. The application was submitted seeking an OTC indication for the temporary relief of symptoms due to hay fever allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat in adults and children 6 years of age and older. A brief overview of the application is presented below. For further details, please refer to Dr. Charles E. Lee's excellent review.

OVERVIEW

The reference product for this 505(b)(2) application is Claritin® (loratadine) Tablets 10 mg. Claritin® has an extensive marketing history having been in the US market since 1993 as a prescription product, and in Belgium since 1988. Claritin® has been marketed as an over-the-counter product in the U.S. since November 2002, however, the drug has had OTC status in several other countries including Canada for much longer.

Of relevance to the safety assessment of loratadine, is the fact that at a meeting held on May 11, 2001, of a joint Advisory committee on Non-Prescription and Pulmonary-Allergy drug products, it was determined that loratadine had a safety profile acceptable for OTC marketing. As part of the review leading to this Advisory Committee, a CDER OTC Switch Review Team reviewed the NDA databases of the Claritin ® products, the US AERS database, and reports from worldwide pharmacovigilance programs, and found no conclusive evidence to preclude the marketing of loratadine as an OTC product. In November and December, 2002, the Agency approved Claritin® [Schering-Plough] and Alavert™ an orally disintegrating tablet formulation of loratadine [Wyeth Consumer Healthcare] respectively, as an OTC product for the treatment of symptoms of allergic rhinitis.

Given that this application was submitted under Section 505(b)(2) of the FD&C act and the sponsor's reliance on the Agency's previous findings of efficacy and safety of the approved reference product, no clinical efficacy studies were required nor were any such studies submitted with the application.

The sponsor conducted two pharmacokinetic studies to compare the pharmacokinetic profile of Perrigo loratadine 10 mg (the test product) to Claritin® 10 mg (the reference product).

The 2 pivotal bioequivalence studies – study 003214 and study 010177, were both single-dose studies with 40 mg of the test (Perrigo loratadine 10–mg tablets) and reference (Claritin ® 10-mg tablet) product. Study 003214 compared the bioavailability of the two products under fasting conditions whereas, study 010177 compared the bioavailability of both products under fed conditions.

It is interesting to note that female subjects were excluded from both bioequivalence studies. The reason for this is unclear since Agency guidance advises against exclusion of subjects based solely on gender. The two studies were nonetheless acceptable for the stated purpose.

Study 003214 was an open-label, randomized, single dose four-way crossover bioavailability study conducted in 56 healthy male subjects under fasting conditions. In study 010177, an open-label, single-dose two –way crossover study, a total of 32 healthy male subjects were evaluated under fed conditions.

In the fasted state, the 90% confidence intervals for AUC_{0-inf} and C_{max} for Perrigo loratadine were within the limits for bioequivalence (80% - 125%) compared to the reference product (Claritin®) [AUC_{0-inf} 34.8 ng.hr/ml Perrigo loratadine vs. 34.1 ng.hr/ml Claritin, C_{max} 11.5 ng/ml Perrigo loratadine vs. 11.4 ng/ml Claritin®]. For Desloratadine (DCL), the 90% confidence intervals for AUC_{0-inf} and C_{max} were also within the limits for bioequivalence compared to the reference. In the opinion of our Biopharmaceutics reviewer, the products were not felt to be bioequivalent under fed conditions (90% confidence intervals for C_{max} 79.6 – 105.9) , but the food effects were similar for the test and the reference products.

Two subjects in study 003214 (one Black and one Caucasian) had an approximately 8 – fold higher AUC_{0-inf} and 4–fold higher value for T_{max} and were identified as slow metabolizers. It has been previously shown that approximately 20% of individuals of Black race and 7% of the general population are slow metabolizers of DCL, the major metabolite of loratadine. The median exposure (AUC) to DCL in the slow metabolizers is approximately 6-fold greater than in the subjects who are not slow metabolizers. However, this increase exposure has not been associated with a difference in the safety profile in the patient population proposed for use of this product.

Safety data in support of this application was provided from several sources including the U.S. AERS database, the worldwide pharmacovigilance reporting programs, the medical literature, and the safety data from the pivotal bioequivalence studies.

In the bioequivalence studies, there was one death that was not related to loratadine. One subject in study 003214 died in a — fire. Another subject had involuntary [myoclonic] limb movements which lasted less than one minute in association with a vasovagal fainting episode following a blood draw. The subject recovered completely

without sequelae. This event was not related to loratadine. There was no meaningful difference in the safety profile between the test and the reference product. AEs related to upper respiratory infections [nasal congestion] and gastroenteritis [loose stools] were reported more frequently in the reference product (4.6% and 10.3% respectively in the reference product compared to 1.1% each in the test product]. It is possibly that there could have been an outbreak of a viral illness during one of the study periods. There are no data to support a causal relationship of these AEs to Claritin.

Additional safety data from the published literature did not reveal any new safety signals. A total of 124 published articles were identified as containing sufficient data for AE evaluations and presented data from a total of 13, 348 patients.

It is noteworthy to mention that the sponsor noted a total of 10 reports of hypospadias in the AERS database. Of these reports, nine were associated with loratadine as the primary suspect drug. The European Medicines Evaluation Agency (EMEA) had been asked to review the safety of DCL after Swedish health authorities identified 15 cases of hypospadias in boys born to women who were taking loratadine during pregnancy and the possibility of an association with DCL was not ruled out by the Swedish authorities. A similar association of hypospadias with loratadine use during pregnancy was not seen in a previous review of the U.S. postmarking data by the Agency and there is no information in the medical literature that suggests that loratadine has anti-androgenic activity. However, the observation warrants further observation which could be undertaken post-approval as was requested for other loratadine products.

INTERDISCIPLINARY ISSUES

Chemistry, Manufacturing, and Controls

The sponsor has two manufacturing sites of loratadine drug substance – The drug product will be produced by L. Perrigo Company, Allegan, Michigan. Establishment Evaluation Requests (EER) from the drug manufacturing cites are pending and the drug product cannot be approved until an acceptable EER has been received. In addition several CMC deficiencies need to be addressed. Please see Dr. Chong Ho Kim's review for complete details.

Clinical Pharmacology and Biopharmaceutics

The study center that performed both pivotal clinical pharmacology studies is located in The Division of Scientific Investigations was consulted to conduct an audit of the study center. However, the audit is pending because of the limitations on international travel imposed because of the current terrorisim alert.

Non-clinical Pharmacology and Toxicology

The Agency did not require the sponsor to conduct nonclinical safety studies and none were submitted with this application.

SUMMARY/CONCULUSIONS

The sponsor has demonstrated bioequivalence of the test product loratadine 10–mg tablets with the innovator product Claritin® 10-mg tablets in the fasting state, and demonstrated a similar food effect between the two products. The safety profile was generally similar for the two products. In addition, the extensive safety databases, and marketing history of Claritin® which is currently marketed OTC in the U.S., all argue for the safety of the loratadine as an OTC product.

The proposed indication is for the temporary relief of symptoms due to hay fever ~~allergies: runny nose, sneezing, itch, watery eyes and itching of the nose or throat. The proposed dose for adults and children 6 years and older is one table (10 mg) daily. The product is not indicated for children under the age of 6 years.

There are no approvable issues from a clinical standpoint. However, the drug cannot be approved in this review cycle because of CMC deficiencies, and the outstanding audit of the study center.

RECOMMENDATIONS

From a clinical standpoint the drug can be approved, however, I recommend that the drug be given an APPROVABLE action pending satisfactory resolution of the CMC deficiencies and the completion of the DSI audit.

The sponsor must be informed that the proposed trade name ' ~~ will not be a suitable trade name. Final proposed labeling has not been negotiated with the sponsor at this time.

In view of the possibility of a causal relationship of loratadine to hypospadias, the sponsor will be asked to provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy as a phase 4 agreement similar to what has been requested of other sponsors of loratadine products.

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/s/

Lydia McClain
4/15/03 09:38:00 AM
MEDICAL OFFICER

Badrul Chowdhury
4/15/03 12:27:46 PM
MEDICAL OFFICER

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

APPLICATION:	NDA 21-512	TRADE NAME:	[redacted]
APPLICANT/SPONSOR:	Perrigo	USAN NAME:	Loratadine
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	CATEGORY:	Antihistamine
DATE:	1/13/04	ROUTE:	Oral, tablets

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
12/22/03	12/23/03	NDA 21-512 N000 SU	Safety update, one volume

RELATED APPLICATIONS

Document Date	Application Type	Comments
5/9/03	NDA 21-512 N000 BZ	Response to approvable letter, 5 volumes
6/28/02	NDA 21-512	Original submission, 74 volumes
1/25/02	NDA 19-658 SE6-018	NDA supplement, Claritin Tablets, allergic rhinitis, OTC

REVIEW SUMMARY:

The sponsor's NDA for loratadine 10-mg tablets was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act on June 28, 2002. The reference product is Claritin® Tablets, 10-mg. The sponsor's proposed indication is temporary relief of symptoms due to hay fever [redacted] allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat. The proposed dose for adults and children 6 years and older is one tablet (10 mg) daily, not to exceed more than one tablet daily. The product is not indicated for children under the age of 6 years. The Division took an approvable action on the application on May 1, 2003. The application had various chemistry, manufacturing, and controls (CMC) deficiencies. The sponsor submitted a response to approvable letter on May 9, 2003. A safety update provided at that time identified no evidence of a safety signal. The Division took a second approvable action on July 11, 2003 because additional bioequivalence data were needed. There were no clinical deficiencies. The current submission includes a safety update covering the time since the May 9, 2003 safety update. The additional bioequivalence data has been submitted under separate cover, and is under review by the Clinical Pharmacology and Biopharmaceutics review team. From a clinical standpoint, the current submission represents a complete response to the Division's second approvable letter. The sponsor's clinical safety update provides no new evidence of safety signal. This reviewer recommends an "approval" action. As recommended in the medical review of the original NDA application, the sponsor should provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy as a Phase 4 agreement.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	SAFE TO PROCEED	___	CLINICAL HOLD			
NDA/SUPPLEMENTS:	___	FILEABLE	___	NOT FILEABLE			
	X	APPROVAL	___	APPROVABLE	___	NOT APPROVABLE	
OTHER ACTION:	X—POST-MARKETING AGREEMENT						

1. BACKGROUND

The sponsor's NDA for loratadine 10-mg tablets was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act on June 28, 2002. The reference product is Claritin® Tablets, 10-mg. The sponsor's proposed indication is temporary relief of symptoms due to hay fever ——— allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat. The proposed dose for adults and children 6 years and older is one tablet (10 mg) daily, not to exceed more than one tablet daily. The product is not indicated for children under the age of 6 years.

The Division took an approvable action on the application on May 1, 2003. The application had various chemistry, manufacturing, and controls (CMC) deficiencies. The sponsor submitted a response to approvable letter on May 9, 2003. A safety update provided at that time identified no evidence of a safety signal. The Division took a second approvable action on July 11, 2003 because additional bioequivalence data were needed. There were no clinical deficiencies. The current submission includes a safety update covering the time since the May 9, 2003 safety update. The additional bioequivalence data has been submitted under separate cover, and is under review by the Clinical Pharmacology and Biopharmaceutics review team.

2. CONTENTS OF THE SUBMISSION

This submission represents the sponsor's response to the second approvable letter, dated July 11, 2003. This submission includes a clinical safety update. This review will not address the additional bioequivalence data that was submitted under separate cover.

3. SAFETY UPDATE

The clinical safety update is reviewed below.

3.1. Safety Update

The sponsor submitted information from the literature and postmarketing adverse event reports that were identified after completion of the safety update of May 9, 2003.

3.1.1. Literature review

The sponsor conducted a search of the nonclinical and clinical literature for safety information related to loratadine, covering the period from the completion of the previous safety update. The sponsor identified seven articles [NDA 21-512, N000 SU, page 1]. One was a nonclinical article that examined the offspring of pregnant rats following systemic exposure to loratadine up to 26 times the level of clinical exposure. No antiandrogen activity was observed and there were no malformations in androgen dependent reproductive tissues of male offspring.[1] There were six clinical articles describing clinical trials with desloratadine, loratadine's principal metabolite. There were no adverse events noted in three of the six clinical articles. Only nonserious and previously reported adverse events were noted in the other three clinical trials.

[1] McIntyre BS, et. al. Reprod Toxicol 2003; 17(6):691-697.

3.1.2. Postmarketing adverse event reports

The sponsor provided a summary of postmarketing adverse event reports from the US AERS database from July 1, 2002, the cut off date for the previous safety update through December 31, 2002.

The sponsor notes that their review did not identify conclusive evidence of a causal relationship between loratadine and any serious or life-threatening events and that there are no new adverse events that have not been previously been observed in other databases [NDA 21-512, N000, 12/22/03, page 2].

The sponsor's summary was reviewed. There were four additional reports of hypospadias since the previous safety update. The additional hypospadias cases may be in part due to reporter bias as a result media coverage of this issue. There were ten reports of ventricular arrhythmia and cardiac arrest, of which six were deaths. However, none of the deaths designated loratadine as a primary suspect agent. There were 19 new reports of seizures and seizure disorders. None of these were deaths. Loratadine was designated as the primary suspect drug in six of the 19 reports of seizure [NDA 21-512, N000, 12/22/03, page 2]. Reports of hepatic events occurred in similar proportions to those noted in the NDA review.

The CDER OTC Switch Review Team did not identify conclusive evidence of a causal relationship between the use of loratadine and serious adverse events in their review of the AERS database from 1993 to April 2000. They also noted that there was a possible association of seizure with loratadine use, but that the association may represent a class effect for antihistamines. Seizures were previously listed in the Claritin® prescription labeling. The proportions and types of adverse events noted in this safety update are similar to those noted in the original NDA submission and the previous safety update. This reviewer concurs with the sponsor that postmarketing adverse event reports summarized in this safety update do not identify any new safety signal.

4. SUMMARY AND RECOMMENDATIONS

The sponsor has provided a response to the Division's second approvable letter. From a clinical standpoint, the submission represents a complete response. The sponsor's safety update provides no new evidence of safety signal. This reviewer recommends an "approval" action. As recommended in the medical review of the original NDA application, as a Phase 4 agreement, the sponsor should provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy.

Reviewed by:

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

Lydia Gilbert McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/C. Kim/Chemistry, Manufacturing, and Controls Reviewer
HFD-870/S. Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-870/Fadiran/Clinical Pharmacology and Biopharmaceutics Team Leader
HFD-570/Zeccola/CSO
HFD-560/C. Martin
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Charles Lee
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Lydia McClain
1/14/04 02:55:35 PM
MEDICAL OFFICER

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

APPLICATION:	NDA 21-512	**TRADE NAME:**	___
APPLICANT/SPONSOR:	Perrigo	**USAN NAME:**	Loratadine
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	Antihistamine
DATE:	5/22/03	**ROUTE:**	Oral, tablets

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
5/9/03	5/12/03	NDA 21-512 N000 BZ	Response to approvable letter, 5 volumes

RELATED APPLICATIONS

Document Date	Application Type	Comments
6/28/02	NDA 21-512	Original submission, 74 volumes
1/25/02	NDA 19-658 SE6-018	NDA supplement, Claritin Tablets, allergic rhinitis, OTC

REVIEW SUMMARY:

The sponsor's NDA for loratadine 10-mg tablets was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The reference product is Claritin® Tablets, 10-mg. The sponsor's proposed indication is temporary relief of symptoms due to hay fever ___ allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat. The proposed dose for adults and children 6 years and older is one tablet (10 mg) daily, not to exceed more than one tablet daily. The product is not indicated for children under the age of 6 years. The Division took an approvable action on the application on May 1, 2003. The application had various chemistry, manufacturing, and controls (CMC) deficiencies. The sponsor was required to submit revised draft labeling and the sponsor was notified that a satisfactory Division of Scientific Information (DSI) inspection of the pivotal clinical pharmacology study site must be completed prior to approval of the application. The application had no clinical deficiencies. This submission represents the sponsor's response to the approvable letter. This submission addresses the CMC deficiencies. It also includes revised draft labeling, a request for waiver of the DSI inspection, and a clinical safety update. The CMC deficiencies and the request for DSI waiver are not addressed in this review. From a clinical standpoint, the sponsor has provided a complete response to the Division's approvable letter. The sponsor's clinical safety update provides no new evidence of safety signal. From the clinical perspective, the sponsor has acceptably addressed labeling comments in the approvable letter. This reviewer recommends an "approval" action. As recommended in the medical review of the original NDA application, the sponsor should provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy as a Phase 4 agreement.

OUTSTANDING ISSUES: DSI audit has not been conducted.

RECOMMENDED REGULATORY ACTION

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

1. BACKGROUND

The sponsor's NDA for loratadine 10-mg tablets was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The reference product is Claritin® Tablets, 10-mg. The sponsor's proposed indication is temporary relief of symptoms due to hay fever —— ——, allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat. The proposed dose for adults and children 6 years and older is one tablet (10 mg) daily, not to exceed more than one tablet daily. The product is not indicated for children under the age of 6 years.

The Division took an approvable action on the application on May 1, 2003. The application had various chemistry, manufacturing, and controls (CMC) deficiencies. The sponsor was required to submit revised draft labeling and was notified that a satisfactory Division of Scientific Information (DSI) inspection of the pivotal clinical pharmacology study site must be completed prior to approval of the application. The application had no clinical deficiencies.

2. CONTENTS OF THE SUBMISSION

This submission represents the sponsor's response to the approvable letter of May 1, 2003. This submission addresses the CMC deficiencies. It also includes revised draft labeling, a request for waiver of the DSI inspection, and a clinical safety update. This submission represents a complete response from the clinical standpoint because there were no clinical deficiencies in the original application and the required safety update has been included with this submission. This document will review the sponsor's safety update and briefly review the changes included in the revised draft labeling. It will not address the CMC deficiencies or the request for waiver of the DSI inspection.

3. SAFETY UPDATE

The sponsor provided a revised Integrated Summary of Safety and a Safety Update. They do not identify any new safety signals. The revised Integrated Summary of Safety and Safety Update are reviewed below.

3.1. Revised Integrated Summary of Safety

The sponsor's revised Integrated Summary of Safety includes a review of safety information related to loratadine from the medical literature and from postmarketing adverse event reports from the US AERS and worldwide databases. The bulk of this safety information has been previously examined in the original NDA review and will not be reviewed in depth in this document [Medical Officer Review, NDA 21-512, N000, 6/28/02, Charles E. Lee, M.D.]. The sponsor's revised Integrated Summary of Safety was reviewed. There was no information from the non-clinical and clinical literature that suggests a new safety signal. Postmarketing adverse event reports from the US AERS and worldwide databases do not provide evidence for new safety concerns [Volume 5, page 11]. This reviewer concurs with the sponsor's conclusion that there are no adverse medical event data or reports that indicate a problem with the continued OTC use of loratadine tablets in the United States.

3.2. Safety Update

Information from the literature and postmarketing adverse event reports identified after the cut-off date for the safety update of the original NDA submission are reviewed in this section of this review.

3.2.1. Literature review

The sponsor conducted a search of the clinical literature for safety information related to loratadine. The search covered the period from completion of the safety update for the original NDA submission, December 15, 2002, until May 5, 2003. The sponsor identified six articles [Volume 4, pages 4-10]. Four of the articles describe the results of controlled clinical trials of loratadine or desloratadine and do not provide evidence of new safety concerns. There were two articles of note. These are summarized below.

One article described the results of a prospective case control study of 161 women exposed to loratadine during their first trimester of the pregnancies.[1] There were a similar number of malformations in the exposed and control groups, with 5 malformations in the exposed group and 6 in the control group. The only malformation that occurred more than once in any group was hernia, which occurred twice in the control group. There were no cases of hypospadias in the treated group, and one in the control group. The article provides additional evidence that loratadine use in pregnancy is not associated with a large risk for major malformations. In the original NDA application, the sponsor noted a total of ten hypospadias reports in the AERS database and 15 cases of hypospadias reported by Swedish health authorities. The possible association of hypospadias with loratadine use during pregnancy have been previously discussed in depth [Medical Officer Review, NDA 21-512, N000, 6/28/02, Charles E. Lee, M.D.]. As previously noted, the potential safety benefits of drug, including lack of sedation, outweigh the potential risk for this weak signal. The sponsor will be asked to provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy. The sponsor's proposed labeling for consumers who are pregnant or who are breast-feeding is appropriate.

The second article of note described a case of prolonged QT interval and torsades de pointes in a patient who was taking amiodarone and loratadine.[2] The patient was a 73-year old woman with a history of hypertension, supraventricular tachycardia, and hyerplipidemia. She had been chronically taking amiodarone, pravastatin, and cilazapril. Her baseline QT interval was 400 msec. She was given loratadine 10 mg daily for a suspected allergic reaction. Several days later she was admitted to the hospital after a syncopal episode. She was found to have a QT interval of 720 msec and QTc interval of 688 msec with sinus bradycardia, multifocal ventricular premature beats, and episodes of torsades de pointes. Serum potassium was 4.05 mmol/L. Echocardiography showed normal left ventricular function, mild left ventricular hypertrophy, and significant diastolic dysfunction. Amiodarone and loratadine were discontinued, and the patient became asymptomatic with a return of the QT interval to normal over the next four days.

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[1] Moretti MM, et. al. J Allergy Clin Immunol 2003;111(3):479-483.
[2] Atar S, et.al. PACE 2003;26:785-786.

The authors suggest that this event a result of the concomitant use of amiodarone and loratadine. Both amiodarone and loratadine are metabolized by cytochrome P450 3A4 and loratadine is also metabolized by cytochrome P450 2D6 [PDR® Electronic Library, 2003]. Amiodarone is an inhibitor of both cytochromes P450 3A4 and 2D6 [www.drug-interaction.com]. As noted in the previous prescription labeling for Claritin®, loratadine has been shown to have no effects on QTc interval when administered with the potent cytochrome P450 inhibitor ketoconazole, despite increases in loratadine plasma concentrations of 307%. Labeling for amiodarone (Coradone®) notes that QTc prolongation and torsades de pointes may be associated with amiodarone use. It is possible that this patient's adverse event could be related to a drug interaction between amiodarone and loratadine. It should be noted however, that this patient clearly had pre-existing cardiac disease, which is a confounding factor. The weight of evidence from existing safety data suggests that the risk of ventricular arrhythmias with loratadine is likely to be in the background range for the general population. Although this single event is not likely to represent a safety signal, future safety data should be examined for additional similar cases.

3.2.2. Postmarketing adverse event reports

The sponsor provided a summary of postmarketing adverse event reports from the worldwide and US AERS databases, including those reported since the December, 2002 cut-off date for the safety update for the original NDA submission. The sponsor notes that their review does not identify conclusive evidence of a causal relationship between loratadine and any serious or life-threatening events and that there are no new adverse events that have not been previously been observed.

The sponsor's summaries were reviewed. There were seven additional reports of hypospadias since the previous safety update. The increase in hypospadias cases is likely to be due to reporter bias as a result media coverage of this issue. Otherwise, the proportions and types of adverse events noted in the safety update were similar to those noted in the original NDA submission and safety update. This reviewer concurs with the sponsor that postmarketing adverse event reports summarized in this safety update do not identify any new safety signal.

4. REVISED LABELING

The sponsor was advised in the approvable letter to revise their draft labeling. [redacted] From the clinical standpoint, the sponsor has acceptably addressed the Division's labeling comments in the approvable letter.

5. SUMMARY AND RECOMMENDATIONS

The sponsor has provided a response to the Division's approvable letter. From a clinical standpoint, the submission represents a complete response. The sponsor's safety update provides no new evidence of safety signal. From the clinical perspective, the sponsor has acceptably addressed labeling comments in the approvable letter. This reviewer recommends an "approval" action. As recommended in the medical review of the original NDA application, as a Phase 4 agreement, the sponsor should provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy.

Reviewed by:

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

Lydia Gilbert McClain, M.D.
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Gilbert-McClain/Acting Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/C. Kim/Chemistry, Manufacturing, and Controls Reviewer
HFD-870/S. Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-870/Fadiran/Clinical Pharmacology and Biopharmaceutics Team Leader
HFD-570/Zeccola/CSO
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/s/

Charles Lee
5/30/03 08:02:34 AM
MEDICAL OFFICER

Lydia McClain
6/4/03 03:58:56 PM
MEDICAL OFFICER

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

APPLICATION:	NDA 21-512	**TRADE NAME:**	[redacted]
APPLICANT/SPONSOR:	Perrigo	**USAN NAME:**	Loratadine
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	Antihistamine
DATE:	4/14/03	**ROUTE:**	Oral, tablets

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
6/28/02	7/1/02	NDA 21-512	Original submission, 74 volumes
1/22/03	1/24/03	NDA 21-512, N000 BM	Subpopulation analyses, ISS, 4 volumes
1/22/03	1/28/03	NDA 21-512, N000 SU	Safety update, 1 volume
3/04/03	3/05/03	NDA 21-512, N000 BZ	Revised labeling
3/04/03	3/05/03	NDA 21-512, N000 BL	Revised labeling
3/05/03	3/07/03	NDA 21-512, N000 BM	Information request response, AE

RELATED APPLICATIONS

Document Date	Application Type	Comments
1/25/02	N19-658 SE6-018	NDA supplement, Claritin Tablets, allergic rhinitis, OTC

REVIEW SUMMARY: This NDA is an application for loratadine, 10-mg tablets. The sponsor's application was submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved reference product and a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved reference product. The reference product is Claritin® Tablets, 10-mg. The sponsor's proposed indication is temporary relief of symptoms due to hay fever [redacted] allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat. The proposed dose for adults and children 6 years and older is one tablet (10 mg) daily, not to exceed more than one tablet daily. The product is not indicated for children under the age of 6 years. The sponsor's development plan consisted of two pivotal clinical pharmacology studies, Studies 003214 and 010177. The sponsor has succeeded in demonstrating that their 10-mg tablet formulation of loratadine is bioequivalent to the reference standard, Schering Claritin® Tablets, 10 mg. There were no meaningful differences between the test and reference products in adverse events (AEs), withdrawals due to AEs, or other safety endpoints in the pivotal clinical pharmacology studies. The sponsor's review of the published literature for loratadine-associated adverse events does not provide evidence of new safety concerns. The sponsor noted 15 cases of hypospadias associated with loratadine use during pregnancy in Sweden. A similar association of hypospadias with loratadine use during pregnancy was not noted in the Agency's previous review of US postmarketing data. The potential safety benefits of drug, including lack of sedation, outweigh the potential risk for this weak signal. This possible association warrants further study and observation. The sponsor's proposed labeling appropriately instructs pregnant consumers to ask a health professional before using the product. These data provide no evidence of a safety signal that has not been previously identified in the prescription labeling for Claritin, the literature, or the AERS database. As a Phase 4 agreement, the sponsor should provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy. From a clinical perspective, this reviewer recommends an approval action. However, the Clinical Pharmacology and Biopharmacuetics team has determined that the site must be audited and data must be found acceptable for use before an approval action may be considered.

OUTSTANDING ISSUES: DSI audit must be conducted.

RECOMMENDED REGULATORY ACTION

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

EXECUTIVE SUMMARY

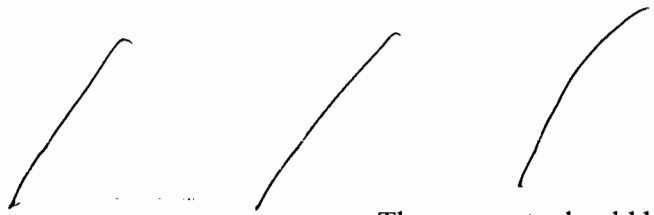
1. RECOMMENDATIONS

1.1. Recommendations on approvability

The sponsor has succeeded in demonstrating that their 10-mg tablet formulation of loratadine is bioequivalent to the reference standard Schering Claritin® Tablets. In addition, the sponsor has provided convincing evidence of safety of loratadine. From a clinical perspective, this reviewer recommends an approval action. However, the Clinical Pharmacology and Biopharmacuetics team has determined that the site must be audited and data must be found acceptable for use before an approval action may be considered.

1.2. Recommendations on Phase 4 studies and risk management steps

As a Phase 4 agreement, the sponsor should provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy.



These reports should be required for 3 years.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief overview of clinical program

This NDA is a 505(b)(2) application for loratadine, 10-mg tablets. The sponsor is Perrigo. The reference product is Claritin® tablets, 10-mg. The sponsor's proposed indication is temporary relief of symptoms due to hay fever allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat. The proposed dose for adults and children 6 years and older is one tablet (10 mg) daily, not to exceed more than one tablet daily. The product is not indicated for children under the age of 6 years. The sponsor's application was submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved reference product and a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved reference product.

The sponsor's development plan relied on two PK and bioavailability studies. One study was a single dose clinical pharmacology study that compared the bioavailability of Perrigo loratadine 10-mg tablets to Claritin® 10-mg loratadine tablets under fasting conditions. The second study was a single dose clinical pharmacology study that compared Perrigo loratadine 10-mg tablets to Claritin® 10-mg loratadine tablets under fed conditions.

The sponsor supported the safety of their product with data from their pivotal bioequivalence studies and an evaluation of safety information from the clinical literature, the US Adverse Event Reporting System (AERS) database, and worldwide pharmacovigilance reporting programs.

2.2. Efficacy

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

The reference product for this 505(b)(2) application, Claritin® Tablets (loratadine), 10 mg. Loratadine has been marketed since its approval in Belgium in 1988 and since 1993 in the US. The Claritin® line of products has been marketed as non-prescription drug products in the US since November 2002. The two clinical pharmacology studies in this application confirmed the bioequivalence of the new drug to the reference product, Claritin® Tablets, 10 mg, in the fasting state. Although not bioequivalent under fed conditions, food effects were similar for test and reference products.

2.3. Safety

The sponsor supported the safety of their product with data from their pivotal bioequivalence studies and an evaluation of safety information from the clinical literature, the US AERS database, and worldwide pharmacovigilance reporting programs.

There were no meaningful differences between the test and reference products in adverse events (AEs), withdrawals due to AEs, or other safety endpoints in the pivotal clinical pharmacology studies. The sponsor's review of the published literature for loratadine-associated adverse events did provide evidence of new safety concerns. Isolated cases of cardiac, hepatic, and CNS AEs are confounded and not likely to represent new safety signals.

The sponsor noted 15 cases of hypospadias in Sweden associated with loratadine use during pregnancy. These events represent a possible safety signal. The Division has previously reviewed these Swedish data and has discussed the data with the Division of Drug Risk Evaluation. A similar association of hypospadias with loratadine use during pregnancy was not noted in the Agency's previous review of US postmarketing data. There is no information in the medical literature that suggests that loratadine has anti-androgenic activity. The potential safety benefits of drug, including lack of sedation, outweigh the potential risk for this weak signal. This possible association warrants further study and observation. The sponsor will be asked to provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy. The sponsor's proposed labeling appropriately instructs pregnant consumers to ask a health professional before using the product. Otherwise, the AERS and worldwide safety databases do not provide evidence of new safety concerns.

In summary, there is no evidence of a safety signal that has not been previously identified in the prescription labeling for Claritin, the literature, or the AERS database. The sponsor's integrated review of safety supports the proposed indication and over-the-counter (OTC) marketing 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 label instructs the consumer not to use more than the recommended dose and that taking more than the recommended dose may cause drowsiness.

The reference drug product for this application, Claritin Tablets, 10 mg, was approved for OTC use in the US in November 2002 and now has OTC labeling in the "Drug Facts" format [21 CFR 201.66]. The previous prescription labeling for the reference drug product notes that food increases the systemic bioavailability of loratadine and its metabolite, descarboethoxyloratadine (DCL) by approximately 40% and 15%, respectively. However, there is no evidence that there is a change in the safety profile of loratadine at these increased exposures. The increased systemic exposures from the food effect are not likely to be clinically relevant.

2.5. Special populations

Geriatric subjects have AUC and C_{max} values for loratadine and descarboethoxyloratadine (DCL) that are approximately 50% greater than in younger subjects and have an increased elimination half-lives for loratadine. The literature suggests that the types and incidences of AEs in patients ≥65 years are similar to those in patients <65 years and that geriatric consumers might not experience somnolence even though they may experience higher systemic exposures. The sponsor's proposed labeling appropriately makes no special recommendations for dosing in the elderly.

The pharmacokinetics of loratadine in pediatric subjects is similar to that in healthy adults. The sponsor's review of the literature and safety databases identify no new safety signal specific to the pediatric subpopulation. The product is not proposed for use in children under 6 years of age. The sponsor's proposed labeling states that a doctor should be consulted before using the product in children under 6 years of age. The sponsor has requested a waiver of pediatric studies. The sponsor's request for a waiver of pediatric studies should be granted because a suitable pediatric dosage form currently exists and because the sponsor's formulation is an inappropriate dosage form and dose for children under the age of 6 years.

The sponsor identified one article that described the results of a study that compared the pharmacokinetics of DCL in men and women. The study found no clinically relevant differences in the pharmacokinetics of DCL between men and women. There is no evidence that there are gender-associated differences in the safety profile of loratadine.

Approximately 20% of individuals of Black race are slow metabolizers of DCL, the major metabolite of loratadine. Approximately 7% of the general patient population are slow metabolizers of DCL. The median exposure (AUC) to DCL in the slow metabolizers is approximately 6-fold greater than the subjects who are not slow metabolizers. The

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

Patients with liver impairment or kidney disease have increased AUC and C_{max} values for loratadine compared with normal subjects. The sponsor's search of the literature revealed no AEs related to patients with hepatic disease or renal impairment. The sponsor's proposed OTC labeling recommends that consumers with liver or kidney disease ask a doctor before using the product.

The sponsor noted a total of ten hypospadias reports in the AERS database of which nine were associated with loratadine as the primary suspect drug. The sponsor also reports that the European Medicines Evaluation Agency (EMEA) was asked to review the safety of DCL after Swedish health authorities identified 15 cases of hypospadias in boys born to women who were taking loratadine during pregnancy. The EMEA stated that they could not rule out the possibility that DCL might cause hypospadias, but also stated that the benefit/risk balance for DCL was favorable. The EMEA is conducting a similar review for loratadine.

This reviewer notes that the 15 cases of hypospadias reported by the EMEA are from a single country, Sweden. The Division has previously reviewed these Swedish data and has discussed the data with the Division of Drug Risk Evaluation. A similar association of hypospadias with loratadine use during pregnancy was not noted in the Agency's previous review of US postmarketing data. There is no information in the medical literature that suggests that loratadine has anti-androgenic activity. It is unclear if this association may be generalizable to the US population. 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 possible safety signal does not appear to be an approvability issue. The potential safety benefits of drug, including lack of sedation, outweigh the potential risk for this weak signal. This possible association warrants further study and observation and the sponsor will be asked to provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy.

The pharmacokinetics of loratadine and DCL in lactating women were similar to that in men. The concentration of loratadine and DCL in breast milk after a 40-mg dose of loratadine was similar to that in plasma. The amounts of loratadine and DCL excreted into breast milk after a 10 mg dose are very small and would represent only about 1% of the dose given to adults on a mg/kg basis. The sponsor's proposed labeling instructs consumers who are pregnant or who are breast-feeding to ask a health professional before using the product.

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1. Introduction

This NDA is a 505(b)(2) application for loratadine tablets, 10-mg. The sponsor is Perrigo. The reference product is Claritin® Tablets, 10 mg. The sponsor initially proposed [redacted]. At the time of the submission, the reference product was prescription only, however the innovator's application for an OTC switch of the reference product was approved on November 27, 2002. 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.

The sponsor's proposed indication is temporary relief of symptoms due to hay fever [redacted] allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat. The proposed dose for adults and children 6 years and older is one tablet (10 mg) daily, not to exceed more than one tablet daily. The product is not indicated for children under the age of 6 years [Volume 1, page 057].

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

1.2. Foreign marketing and regulatory history

Loratadine was first approved in Belgium in 1988 and is approved as a prescription or nonprescription drug product in 94 countries worldwide. Loratadine was approved for OTC use in the US in November 2002. Loratadine has not been withdrawn from marketing in any country for any reason related to safety or effectiveness or any other reasons. The sponsor plans to manufacture and market the product in the US only. The sponsor previously submitted an Abbreviated New Drug Application (ANDA 76-301) for loratadine tablets, 10 mg on 12/14/01 [Volume 1, page 062].

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 also 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, on May 11, 2001 at a combined meeting, the Nonprescription Drug Products Advisory Committee and the Pulmonary-Allergy Drug Products Advisory Committee 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].

A Pre-NDA meeting was held with the sponsor on 9/17/02 [FDA Meeting Minutes, 9/17/01 and Volume 1, pages 151-159]. The sponsor was advised that a 505(b)(2) filing was an acceptable means of switching the status of the drug to OTC from prescription, even without the sponsor first receiving approval for a prescription version of the product. Various other administrative and regulatory issues were discussed. The sponsor proposed to support their application with bioequivalence and label comprehension studies. The sponsor was advised that there would not be a possibility for exclusivity because no new clinical studies would be required for approval. The Division also confirmed that no pediatric studies would be required because a suitable pediatric dosage form existed as a prescription product.

The sponsor was advised that in addition to their proposed *in-vivo* bioequivalence studies, a comprehensive safety review would be required. The sponsor was also advised that the OTC monograph is the basis for labeling, and that any departure from monograph labeling must be supported. The Division recommended that the sponsor conduct a label comprehension study, but noted that this study was not required, and was not essential for approval of the application.

Since the submission of this application the Agency has approved a Rx to OTC switch in November 2002 for the innovator's line of loratadine products, Claritin®. In December 2002, the Agency has also approved a 505(b)(2) application for an orally disintegrating tablet formulation of loratadine produced by Wyeth Consumer Healthcare.

The sponsor's development plan relied on two PK and bioavailability studies [Volume 1, page 083]:

- Study 003214, a single dose clinical pharmacology study that compared the bioavailability of Perrigo loratadine 10-mg tablets to Claritin® 10-mg loratadine tablets under fasting conditions after a 40-mg dose
- Study 010177, a single dose clinical pharmacology study that compared Perrigo loratadine 10-mg tablets to Claritin® 10-mg loratadine tablets under fed conditions after a 40-mg dose

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

2.1. Chemistry, Manufacturing, and Controls

The sponsor has two manufacturers of loratadine drug substance, [redacted]. Letters of authorization have been filed to allow reference to the respective DMFs [Volume 1, page 65].

The composition of the drug product is described in Table 2.1. Lactose, povidone, starch, — are excipients.

Table 2.1 Composition of loratadine drug product, Perrigo [Volume 1, pages 69-70].

	mg/tablet
Loratadine	
Lactose	
Povidone	
Starch	
Magnesium stearate	

The batch and lots used in both clinical pharmacology studies in this application were the same and the batch and lot numbers are displayed in Table 2.2. The sponsor indicates that the manufacturing process used to produce the clinical supplies was the same as that to be used for the to-be-marketed product. The drug substance for these studies was produced by — [Volume 1, pages 67, 70].

Table 2.2. Batch and lot numbers for study treatments, Studies 003214 and 010177 [Volume 29, page 55; Volume 41, page 6].

Proposed product	Loratadine, 10 mg tablet, Perrigo Batch #OC1868, expiration date 09/01
Reference product	Loratadine, 10 mg tablet (Claritin®), Schering Lot #9RXF559, expiration date 02/02

The drug product will be produced by L. Perrigo Company, Allegan, Michigan [Volume 1, page 70]. The sponsor initially proposed marketing 4 and — count blister cartons and 10 and 300 count bottles [Volume 1, page 17]. However, stability testing was performed on blister cartons —, and therefore was not acceptable. The . More details may be found in Dr. Chong-Ho Kim's CMC review of this NDA [Dr. C. Kim, CMC Review, NDA 21-512].

2.2. Nonclinical pharmacology and toxicology

The Agency did not require the sponsor to conduct nonclinical safety studies because of the extensive marketing experience with loratadine. Loratadine was an approved prescription drug and now is approved for OTC use in the US. Dr. Lawrence Sancilio's pharmacology/toxicology review notes that there are no safety issues for this drug [Dr. L. Sancilio, Pharmacology/Toxicology Review, NDA 21-512].

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

This submission refers to two clinical pharmacology studies, Studies 003214 and 010177. Study 003214 was a single dose study that compared the bioavailability of Perrigo loratadine 10-mg tablets to Claritin® 10-mg loratadine tablets under fasting conditions after a 40-mg dose. Study 010177 was a single dose study that compared Perrigo loratadine 10-mg tablets under fed conditions to Claritin® 10-mg loratadine tablets after a 40-mg dose [Volume 1, page 083].

Both of these studies were performed with single 40-mg doses of loratadine, instead of the proposed 10-mg dose. The Agency asked the sponsor to provide justification of this dose. The sponsor stated that if a lower dose of loratadine were to be used, that the PK of the drug would not have been characterized as robustly because concentrations would have been detectable only for 24 to 48 hours because of the limit of quantitation of their assay. The sponsor provided a literature reference to further support their justification [Volume 1, page 182]. The Agency agreed that the sponsor justified the use of the 40-mg dose in these studies [Volume 1, page 190].

Both of these studies were performed in males, aged 18 to 45 years, and both of these studies used gender as an inclusion criterion [Volume 29, page 086, Volume 41, page 028]. Current Agency guidance states that gender should not be an inclusion criterion. It should be noted that the protocols for these studies were reviewed by the Office of Generic Drugs, and gender of subjects was not addressed in comments provided for the sponsor [Review, S. P. Shrivastava, P-99-033, 8/17/99]. Although it would have been preferable to study a study population consisting of more varied demographics, the current studies are acceptable.

Statistical comparisons were performed to determine if the test product was bioequivalent to the reference product in the fasted and fed states. In the fasted state, 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 concluded that the results of this study demonstrate that the Perrigo and Schering Claritin® 10-mg loratadine tablets are bioequivalent under fasting conditions, following a 40-mg dose. In the fed state, loratadine, 90% confidence intervals for $AUC_{0\text{-}inf}$ and C_{max} were similar 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 concluded that the results of these studies demonstrate that the Perrigo and Schering (Claritin®) 10-mg loratadine tablets are bioequivalent under fasted and fed conditions, following a 40-mg dose [Volume 29, page 54; Volume 41, page 5]. Dr. S. Kim, the Clinical Pharmacology and Biopharmaceutics Reviewer concurred that the products were bioequivalent under fasted conditions. The products were not bioequivalent under fed conditions. Although not bioequivalent under fed conditions, food effects were similar for test and reference products [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-512].

Two subjects in Study 003214 were identified as slow metabolizers. One of the subjects was of Black race (#50) and the other was of Caucasian race (#25). These subjects had an approximately 8-fold higher value for $AUC_{0\text{-}inf}$ and 4-fold higher value for T_{max} for DCL. There was no difference in C_{max} values for the slow metabolizers. The Division's experience has been that there are no differences in safety profiles between slow and normal metabolizers. The increased exposure to DCL in slow metabolizers is not considered to be clinically relevant in the population proposed for use. More detail on the pharmacokinetics of the product may be found further below in the review of the individual studies (Section 11, Appendix, Clinical Studies) and in Dr. Kim's clinical

pharmacology and biopharmaceutics review [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-512].

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

This submission refers to two clinical pharmacology studies, Studies 003214 and 010177. Study 003214 was a single dose study that compared the bioavailability of Perrigo loratadine 10-mg tablets to Claritin® 10-mg loratadine tablets under fasting conditions after a 40-mg dose. Study 010177 was a single dose study that compared Perrigo loratadine 10-mg tablets under fed conditions to Claritin® 10-mg loratadine tablets after a 40-mg dose [Volume 1, page 083]. These studies are summarized in Table 4.1. More detailed descriptions of these studies follow below.

4.1. Study 003214

Study 003214 was a clinical pharmacology study that compared the bioavailability of Perrigo loratadine 10-mg tablets and Claritin® 10-mg loratadine tablets under fasted conditions after a 40-mg dose. The study was an open-label, randomized, single dose, four-way crossover bioavailability study conducted in 56 healthy male subjects. A total of 48 volunteers completed the clinical phase of the study and a total of 54 patients completed at least two periods of the study. 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, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours for plasma loratadine and descarboethoxyloratadine (DCL) levels. Patients were housed at the study site until after their 36-hour sample was drawn, and were discharged to return for remaining samples on an outpatient basis. A 21-day washout period separated the two treatment periods [Volume 29, pages 032, 056]. Safety endpoints reported included adverse events [Volume 30, pages 268-269]. Laboratory tests for hemoglobin and hematocrit were performed at screening and prior to dosing in Period 4 [Volume 30, page 269]. Three patients were withdrawn from the study because of AEs. None of these patients had a SAE. There was one death in the study, a subject who died in a — fire approximately 10 days after dosing. This was the only SAE in the study [Volume 30, page 268].

4.2. Study 010177

Study 010177 was a clinical pharmacology study that compared Perrigo loratadine 10-mg tablets under fed conditions to Claritin® 10-mg loratadine tablets after a 40-mg dose. The study was an open label, randomized, single dose, two-way crossover study. Thirty-two healthy male subjects were enrolled, and 31 subjects completed the study. Plasma samples were drawn 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, 5.5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours for loratadine and DCL levels. A 21-day washout period separated the two treatment periods [Volume 41, pages 005-006]. Safety endpoints included adverse events [Volume 41, page 252]. One patient withdrew from the study because of a toothache. There were no SAEs [Volume 41, pages 252, 255-256].

Table 4.1. Summary of studies, NDA 21-512 [Volume 1, page 086].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects	Materials submitted in this efficacy supplement
003214	Bioavailability, fasted state	Perrigo loratadine, 4 X 10-mg tablet Claritin®, 4 X 10-mg loratadine tablet	Single dose	Single center, randomized, open label, fasting, four-way crossover	56	Healthy males, 18-45 years	Protocol Tabulations Study report Case report forms
010177	Bioavailability, fed state	Perrigo loratadine, 4 X 10-mg tablet Claritin®, 4 X 10-mg loratadine tablet	Single dose	Single center, randomized, open label, fed, two-way crossover	32	Healthy males, 18-45 years	Protocol Tabulations Study report Case report forms

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.

The two pivotal clinical pharmacology studies were Study 003214, and Study 010177. These studies were individually reviewed, with a focus on safety findings. There was no Integrated Summary of Efficacy because there were no clinical studies necessary. 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 provided an evaluation of safety information from the clinical literature, the US AERS database, worldwide pharmacovigilance reporting programs, and a safety update.

5.2. Data quality

DSI audit of the study center that performed both pivotal clinical pharmacology studies was requested. Study 003214 was audited. There were no efficacy or safety studies included in the development program for this drug product. The study center was:

The DSI audit has been postponed because of restrictions on international travel due to heightened security concerns. The Clinical Pharmacology and Biopharmacuetics team has determined that the site must be audited and data must be found acceptable for use before an approval action may be considered.

5.2.1. Ethical standards and financial disclosure

The following items were included in this submission:

- Debarment certification [Volume 1, page 217]
- Financial disclosure statement [Volume 1, pages 220-232]
- Statements of Good Clinical Practice [Volume 29, page 047, Volume 41, page 248]

The sponsor certified that they did not use and would not use the services of any person debarred pursuant to 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.

6. INTEGRATED REVIEW OF EFFICACY

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

The reference product for this 505(b)(2) application, Claritin® (loratadine) Tablets, 10 mg. Loratadine has been marketed since its approval in Belgium in 1988 and since 1993 in the US. The Claritin® line of products has been marketed as non-prescription drug products in the US since November 2002. The two clinical pharmacology studies in this application confirmed the bioequivalence of the new drug to the reference product, Claritin® Tablets, 10 mg, in the fasted state. Although not bioequivalent under fed conditions, food effects were similar for test and reference products. No clinical studies of the efficacy of the product or integrated summary of efficacy were required for approval.

As the sponsor points out, efficacy and safety of loratadine has been reviewed by the Agency's OTC Switch Review Team and by the Joint Advisory Committee on Nonprescription and Pulmonary-Allergy Drug Products. These groups have found that evidence supports the safe OTC use of loratadine tablets [Volume 54, page 1].

7. INTEGRATED REVIEW OF SAFETY

At a joint meeting on May 11, 2001, 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]. As part of the review leading to this Advisory Committee, the CDER OTC Switch Review Team noted that there was no conclusive evidence in the NDA or AERS databases of a causal relationship between use of loratadine and serious adverse events (SAEs). Since then, on November 27, 2002, the Agency has approved the application submitted by the innovator, Schering, for a prescription drug to OTC switch of their loratadine products for the allergic rhinitis indication. OTC labeling superseded labeling for the prescription product at the time of approval. The Agency also approved Wyeth Consumer Healthcare's application of an orally disintegrating tablet formulation of loratadine for the OTC treatment of symptoms of allergic rhinitis on December 19, 2002.

The focus of this section of this review is on the case that the sponsor has made for the safety of loratadine, given this large background of existing safety information. A review sponsor's integrated review of safety data supporting this application follows below.

7.1. Summary and conclusions

The sponsor provided data from their pivotal bioequivalence studies and an evaluation of safety information from the clinical literature, the US AERS database, and worldwide pharmacovigilance reporting programs.

There were no meaningful differences between the test and reference products in AEs, withdrawals due to AEs, or other safety endpoints in the pivotal clinical pharmacology studies. The sponsor's review of the published literature for loratadine-associated adverse events did not provide evidence of new safety concerns. Isolated cases of cardiac, hepatic, and CNS AEs are confounded and not likely to represent new safety signals.

The sponsor noted 15 cases of hypospadias associated with loratadine use during pregnancy in Sweden that were reported by the EMEA. These events represent a possible safety signal. The Division of Pulmonary and Allergy Drug Products and the Division of Drug Risk Evaluation have previously reviewed and discussed these data. A similar association of hypospadias with loratadine use during pregnancy was not noted in the Agency's previous review of US postmarketing data. There is no information in the medical literature that suggests that loratadine has anti-androgenic activity. The potential safety benefits of drug, including lack of sedation, outweigh the potential risk for this weak signal. This possible association warrants further study and observation. The sponsor will be asked to provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy. The sponsor's proposed labeling appropriately instructs pregnant consumers to ask a health professional before using the product. Otherwise, the AERS and worldwide safety databases do not provide evidence of new safety concerns.

In summary, these data provide no evidence of a safety signal that has not been previously identified in the prescription labeling for Claritin, the literature, or the AERS database. The sponsor's integrated review of safety supports the proposed indication of their product.

7.2. Content

The following are reviewed in this Integrated Review of Safety:

- Integrated safety data from the sponsor's pivotal studies
- Sponsor's evaluation of safety information from the clinical literature
- Sponsor's evaluation of safety information from the US Adverse Event Reporting System (AERS) database
- Sponsor's evaluation of safety information from worldwide pharmacovigilance reporting programs
- Sponsor's safety update

7.3. Integrated safety data, pivotal studies

Integrated safety data from the sponsor's pivotal bioequivalence studies shows no evidence of safety signal. AEs were more frequent for the reference medication than with the test medication. AEs occurring more frequently with the test medication than with the reference medication included erythema at blood draw site, abdominal pain, back pain, constipation, and dizziness. There were no meaningful differences between the test and the reference products in AEs, withdrawals due to AEs, or other safety endpoints.

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

7.3.1. Description of pivotal studies

Study 003214 was an open-label, randomized, single dose, fully replicated, four-way crossover relative bioavailability study designed to compare the bioavailability of Perrigo and Schering (Claritin®) 10 mg loratadine tablets under fasting conditions following a 40 mg dose [Volume 29, pages 055, 84]. Each subject received study treatment and reference treatment twice in this four period study. There was a washout period of at least 21 days between study periods [Volume 29, pages 56, 85].

Study 010177 was an open-label, randomized, single dose, two-way crossover relative bioavailability study designed to compare the single dose bioavailability of Perrigo and Schering (Claritin®) 10 mg loratadine tablets under fasting conditions following a 40 mg dose. There was a washout period of at least 21 days between study periods [Volume 41, pages 7, 29].

7.3.2. Demographics

There were 92 subjects enrolled in the pivotal clinical pharmacology studies. The great majority of subjects were of Caucasian race (85/92, 92.4%). Small proportions of the study population were of Black (2/92, 2.2%) and Oriental (1/92, 1.1%) races. There were no subjects of Hispanic, American Indian, or other Asian races. All subjects were men. The mean age of subjects in these studies was 33.7 years, and subjects ranged from 20-45 years of age [from data, Volume 30, pages 271-272 and Volume 41, page 253].

Reviewer comment:
Non-Caucasian subjects were underrepresented in these studies and only males were enrolled. The Office of Generic Drugs (OGD) reviewed this protocol, and made no comment on the proposed study population [OGD Review, P#99-033, 8/17/99, S. P. Shrivastava, Ph.D.]. The pharmacologic and safety profiles for loratadine and DCL have previously been well established by the innovator, however.

7.3.3. Disposition

As noted above, there were 92 healthy adult males who were enrolled in these studies study. There were 13 subjects who did not complete the study. Of these 13 subjects, there were eight subjects who withdrew for personal reasons or other causes. There was one subject who died in a —— ire between study periods 1 and 2. Four subjects withdrew

because of AEs. [Volume 29, pages 55, 56; Volume 30, page 268; Volume 41, pages 6, 251, 252].

7.3.4. Exposure

Exposure to study medication is summarized in Table 7.1. A total of 91 subjects were exposed to at least one dose of 4 x 10 mg tablets of the sponsor's proposed drug product [from data, Volume 30, pages 271-272 and Volume 41, page 253].

Table 7.1. Exposure, pivotal studies, NDA 21-512 [from data, Volume 30, pages 271-272 and Volume 41, page 253].

Study	Drug tested	Subjects exposed	Doses taken
		n	
003214			
	Perrigo loratadine tablets, 4 x 10 mg (test product)	59	At least one dose
		48	Two doses
	Schering Claritin® Tablets 4 x 10 mg (reference product)	56	At least one dose
		50	Two doses
010177			
	Perrigo loratadine tablets, 4 x 10 mg (test product)	32	One dose
	Schering Claritin® Tablets, 4 x 10 mg (reference product)	31	One dose

7.3.5. Adverse events

Adverse events (AEs) occurring in the pivotal studies are integrated and presented in Table 7.2. AEs were more frequent for the reference medication than with the test medication. AEs occurring more frequently with the test medication than with the reference medication included erythema at blood draw site, abdominal pain, back pain, constipation, and dizziness.

Table 7.2. Adverse events occurring in more than one subject in Studies 003214 and 010177, integrated data. Events occurring more frequently in Perrigo loratadine than in Schering Claritin® are highlighted [compiled from Volume 30, pages 281-283 and Volume 41, pages 253, 255].

Adverse event	Perrigo loratadine tablets, 10 mg 4 x 10 mg Test Product (A) N = 91		Schering Claritin® Tablets, 10 mg 4 x 10 mg Reference product (B) N = 87	
	n	(%)	n	(%)
All adverse events	59	(64.8)	80	(92.0)
Headache	9	(9.9)	10	(11.5)
Erythema at blood draw site	**3**	**(3.3)**	**2**	**(2.3)**
Abdominal pain	**2**	**(2.2)**	**0**	**(0)**
Back pain	**3**	**(3.3)**	**2**	**(2.3)**
Constipation	**2**	**(2.2)**	**1**	**(1.1)**
Dizziness	**2**	**(2.2)**	**0**	**(0)**
Earache, ear pain	2	(2.2)	2	(2.3)
Nausea	2	(2.2)	5	(5.7)
Runny nose	3	(3.3)	5	(5.7)
Sore throat	2	(2.2)	4	(4.6)
Cough	2	(2.2)	5	(5.7)
Loose stool	1	(1.1)	9	(10.3)
Nasal congestion	1	(1.1)	4	(4.6)
Felt hot, feverish	0	(0)	3	(3.4)
Dizzy after blood draw	1	(1.1)	2	(2.3)

Adverse event	Perrigo loratadine tablets, 10 mg 4 x 10 mg Test Product (A) N = 91 n (%)	Schering Claritin® Tablets, 10 mg 4 x 10 mg Reference product (B) N = 87 n (%)
Felt weak	1 (1.1)	2 (2.3)
Pain at blood draw site	1 (1.1)	2 (2.3)
Toothache	1 (1.1)	2 (2.3)

Reviewer comment:
AEs were fairly common, and were more frequent with the reference treatment, Claritin®, than with the test treatment, Perrigo loratadine. The difference in frequency of AEs between the treatments appears to be related to AEs associated with viral upper respiratory tract infections or gastroenteritis in Study 003214. It appears that there may have been an outbreak of a viral illness during one of the study treatment periods. There are no meaningful differences between the test and reference products in AEs.

7.3.6. SAEs and deaths

There was one SAE in these studies. This SAE was an accidental death due to asphyxiation in a — fire. This SAE occurred in subject #19 in Study 003214. The SAE occurred after study period 1, approximately 10 days after dosing with treatment "A," Perrigo loratadine. The sponsor did not consider this SAE to be related to study treatment. The sponsor also reported one subject (#10) in Study 003214 who was treated with Perrigo loratadine and had convulsions. This AE was not considered by the sponsor to be serious and was considered not to be related to study treatment [Volume 30, page 282; Volume 33, page 5]. The sponsor provided no additional detail. The sponsor was asked to provide further detail and follow-up on this apparently previously healthy subject. The sponsor also was asked to explain why this AE was not considered to be a SAE and to provide the rationale for considering this event to be unrelated to study treatment. In their response to the request for additional information, the sponsor noted that the patient had involuntary movements of the limbs in association with a vasovagal fainting episode from a blood draw. The patient's involuntary movements lasted less than one minute and he recovered completely without any sequelae. The investigator considered this episode to not be a true convulsion. In the investigator's opinion, this event did not meet regulatory criteria for an SAE in that it was not life-threatening, did not result in death, hospitalization, or persistent disability, and was not medically important [NDA 21-512 N000 BM, 3/5/03, page 4].

Reviewer comment:
Myoclonic activity may be seen with vasovagal faints. The sponsor's response is acceptable.

7.3.7. Withdrawals due to AEs

There were three subjects who withdrew from Study 003214 because of AEs. Subject #23 withdrew 8 days into study period 2 (reference product) because of a toothache that began in study period 1 (test product). Subject #45 withdrew because of right ear pain that developed 20 days post-dose in study period 2 (test product). Subject #48 withdrew because of left ear pain that developed during study period 1 (reference product). All three subjects who withdrew required treatment with antibiotics. The three AEs resulting in withdrawal from the study were considered to be not related to study treatment [Volume 30, pages 268, 271-272]. There was one subject who withdrew from Study 010177 because of an AE. Subject #16 withdrew prior to dosing in study period 2 because of a toothache that began in study period 1 (test product). The subject required treatment with an antibiotic. This AE was considered to be not related to study treatment [Volume 41, pages 252, 253, 255].

Reviewer comment:
This reviewer concurs with the sponsor that these withdrawals due to AEs are not likely to be related to study treatment.

7.3.8. Vital signs

Vital signs were monitored for safety in both pivotal studies, but the sponsor did not analyze vital signs as a safety endpoint. This reviewer examined raw data for vital signs. There were no notable abnormalities in vital signs in either study [Volume 31, pages 67-126, 214-269; Volume 32, pages 46-97, 232-279; Volume 42, pages 45-76, 128-158].

7.3.9. Physical examination

Physical examination was not a safety endpoint in either pivotal study.

7.3.10. Laboratory studies

Hemoglobin and hematocrit studies were performed prior to dosing in study period 4 in Study 003214. There were no clinically significant abnormalities noted [Volume 30, page 269].

7.3.11. ECGs

ECGs were not a safety endpoint in either pivotal study.

7.4. Evaluation of safety information from the clinical literature

The sponsor conducted a search of the clinical literature for information relevant to the safety of loratadine. The sponsor concluded that the published literature did not provide evidence of safety concerns for loratadine-associated adverse events and did not identify new AEs that have not been previously observed. The sponsor concluded that the clinical literature supports the safe OTC marketing of their loratadine 10-mg tablets.

This reviewer concurs that the sponsor's review of the published literature for loratadine-associated adverse events does not provide evidence of new safety concerns. Isolated

cases of cardiac, hepatic, and CNS AEs are confounded and not likely to represent new safety signals. The literature review provided no evidence for AEs associated with population subgroups—the elderly, those with hepatic or renal impairment, the pediatric population, gender, or race. The literature review suggested that the pharmacokinetics of loratadine are similar in children and adults, in men and women, and in subjects of Black and Caucasian races. The sponsor did not note that that approximately 7% of the general patient population may be slow metabolizers of DCL, the major metabolite of loratadine and that approximately 20% of individuals of Black race are slow metabolizers. However, the Division's experience has been that there have been no differences in safety profiles between slow and normal metabolizers. This increased exposure to DCL in slow metabolizers is not considered to be clinically relevant in the population proposed for use. This reviewer concurs that the sponsor's review of the clinical literature supports the safe OTC marketing of their loratadine 10-mg tablets in the proposed population.

Detailed review of the sponsor's clinical literature review follows below.

7.4.1. Content of clinical literature review

The sponsor conducted a search of the clinical literature for information relevant to the safety of loratadine. The sponsor used PubMed to conduct the search for articles from 1986 until January 10, 2002. The search terms are listed in Table 7.3.

Table 7.3. Search terms used for PubMed literature search [Volume 46, page 6].

Search term
Claritin® and all other proprietary names
Loratadine
Prescription to OTC switch
Countries with OTC markets
Safety-related events
Adverse medical events
Ventricular arrhythmia and sudden death
Seizures
Hepatotoxicity
Renal impairment
Hepatic impairment
Post-marketing surveillance
Cardiac safety
Elderly-related events
Sudden cardiac deaths
Pharmacovigilance reports
Drug interactions
Special populations—elderly, renal impairment, and hepatic impairment

The sponsor identified approximately 400 articles. Of these articles, 124 were found to contain sufficient data for AE evaluations. Of these 124 articles, 64 provided data from double blind, placebo controlled studies. Thirty articles included data from studies of other designs. Thirty articles represented reviews, case reports, and postmarketing surveillance reports. There were safety data from 13,348 patients in the 124 articles [Volume 46, pages 7-8].

There were 984 AEs documented in the 124 articles. All but 60 of these AEs were noted in the US prescription labeling for Claritin® that preceded the OTC labeling. AEs not noted in current labeling included rhinitis (18 events), pharyngitis (31 events), epistaxis

(8 events), and unspecified ocular AEs (3 events). The sponsor notes that rhinitis AEs may represent treatment failures for the drug and that many of the reports of pharyngitis were also associated with use of albuterol or pseudoephedrine, both of which have been associated with pharyngitis. The sponsor concluded that these reports do not represent a new safety signal [Volume 46, pages 7-11].

Reviewer comment:
This reviewer concurs with the sponsor that these reports do not represent a new safety signal.

The sponsor also performed a review focused on articles related to loratadine and cardiac safety, seizures, and events in the elderly and patients with renal and/or hepatic impairment. These are described below.

The sponsor updated the literature search to include articles published until December 15, 2002 and to provide additional information on gender, race, and pediatric subgroups [NDA 21-512, N000 BM, 1/22/03, pages 5-9].

7.4.2. Cardiac events in the clinical literature

One case control study noted a single case of nonfatal ventricular arrhythmia in a population of 33,000 patients in the UK who received 73,000 prescriptions for loratadine. The author concluded that there was an increased risk of ventricular arrhythmias for nonsedating antihistamines, but the frequency of such events was quite low[1] [Volume 46, pages 8-10].

The sponsor noted one report of a 69 year-old male who had presyncopal episodes due to episodes of ventricular tachycardia after treatment with loratadine. The patient had a past medical history of atherosclerotic vascular disease with two recent percutaneous transluminal coronary angioplasties, hypertension, atrial fibrillation, and tobacco use. The ventricular arrhythmias ceased after discontinuation of loratadine and quinidine[2] [Volume 46, pages 8-10].

The sponsor's review identified 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]

Reviewer comment:
It is unlikely these two isolated cardiac cases represent a new safety signal for loratadine. The second case clearly is confounded by significant concomitant cardiovascular disease. The postmarketing experience in the US pointed to an association of cardiac arrhythmia with terfenadine and astemizole, but there has not been any clear association with loratadine. The Executive Summary on Risk Issues summarized the report of the OTC Switch Review Team on the safety assessment of antihistamines and addressed the cardiac safety of loratadine [Volume 51, pages 9-17 and http://www.fda.gov/ohrms/dockets/ac/01/briefing/3737b1.htm]. The OTC Switch

Review Team noted that there was no conclusive evidence of a causal relationship between use of loratadine and serious adverse events.

It is unclear why QTc prolongation was noted in the drug interaction study where none was noted in other drug interaction studies in which 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. It is important to note that the results of this study have been questioned by one of its co-authors.[4]

7.4.3. Hepatotoxicity

The sponsor's search identified two articles that reported three cases of hepatotoxicity associated with loratadine use. The first article included a report of a 42 year old woman who developed submassive hepatic necrosis and received a liver transplant one month after a cholecystectomy. She had been taking loratadine for 14 months until the time of the cholecystectomy, at which time its use was discontinued. She was a social drinker and there was no histologic evidence of chronic liver disease. The second patient in this article was a 33 year old man who developed clinical hepatitis with subacute areas of hepatic necrosis on biopsy. The patient had been taking loratadine for three weeks prior to the onset of symptoms. He had evidence of past infection with Hepatitis C, but the polymerase chain reaction test for Hepatitis C RNA was negative, indicating no active infection. The patient had a history of heavy alcohol use, but there was no evidence of alcohol-induced liver disease on biopsy.[5] The second article was a case report that described a 46 year old woman who developed hepatic necrosis and failure and required a liver transplant. She had been taking loratadine and cefprozil for allergic rhinitis and sinusitis for 10 days at the time of onset of symptoms[6] [Volume 46, page 9]. The sponsor notes that hepatic toxicity is a noted in the prescription labeling for Claritin® [Volume 54, page 4].

Reviewer comment:
Two of these cases are clearly confounded by use of medications, including anesthesia in the woman who had the cholecystectomy. The prior history of the patient who had a history of heavy alcohol use and prior Hepatitis C infection is also interesting. The OTC Switch Review Team evaluation could not exclude the possibility that loratadine use may rarely result in hepatic failure. However, they also noted that the reporting rate for hepatic failure in association with use of loratadine was several fold lower than the calculated background rate of hepatic failure [Volume 51, pages 9-17 and http://www.fda.gov/ohrms/dockets/ac/01/briefing/3737b1.htm].

7.4.4. Seizures

The sponsor's search identified a report of a clinical study of loratadine in which one patient experienced a seizure[7] [Volume 46, page 9].

7.4.5. Overdose

The sponsor identified one report of an attempted suicide. An 18 year old woman took 300 mg of loratadine. During her hospital stay she had normal ECGs and she remained alert and oriented. The patient had no cardiac or CNS events and was fully recovered at the time of discharge[8] [Volume 46, page 10].

7.4.6. Drug interaction

The sponsor notes that loratadine's safety profile was unaffected when co-administered with alcohol, hexobarbital, ketoconazole, cimetidine, and erythromycin. The sponsor points out that there were no increase in the number of AEs or clinically significant changes in ECGs in the drug interaction studies [Volume 50, page 374].

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

7.4.7. Special populations

The sponsor's search revealed no AEs related to the elderly or to those patients with renal or hepatic impairment [Volume 46, page 10]. The prescription label for Claritin® Tablets, 10 mg, notes that geriatric subjects have AUC and C_{max} values for loratadine and DCL that are approximately 50% greater than in younger subjects and have an increased elimination half-life for loratadine. Patients with renal impairment also had increased AUC and C_{max} values, but had an elimination half-life that was similar to those with normal renal function. Patients with liver impairment had increased AUC and C_{max} values and an increased elimination half-life compared with normal subjects.

Reviewer comment:
This reviewer notes a two-week multicenter trial of loratadine in the treatment of SAR in which AEs and laboratory values for patients stratified by age, <65 years versus ≥65 years, were examined. The types and incidences of AEs were similar in patients ≥65 years (3%) than in patients <65 years. Somnolence was slightly less frequent in patients ≥65 years (3%) than in patients <65 years (5%).[9] This article suggests that geriatric consumers might not experience somnolence even though they experience higher systemic exposures. The sponsor's proposed OTC labeling appropriately recommends that consumers with liver or kidney disease ask a doctor before using the product, and appropriately makes no special recommendations for dosing for healthy geriatric consumers [Volume 1, pages 31-49].

For the pediatric subpopulation, the sponsor's search identified 15 articles published between 1986 and December 15, 2002 with information pertinent to AEs for loratadine. Five of these articles described data from double blind, placebo controlled studies. Eight were described studies of other designs, and 3 included information from summary reviews. A total of 422 patients were represented in these articles [NDA 21-512, N000 BM, 1/22/03, page 5]. The sponsor's review of these articles identified no new safety signal [NDA 21-512, N000 BM, 1/22/03, pages 6-8].

The sponsor's search identified three studies in which the pharmacokinetics and pharmacodynamics of loratadine were studied. One study in children 8-12 years of age given a single 10-mg dose of loratadine found that C_{max} values for loratadine and descarboethoxyloratadine (DCL) were similar to those in adults. There were no significant laboratory or ECG abnormalities. The authors concluded that the pharmacokinetics of loratadine in pediatric subjects is similar to that in healthy adults.[10] Another study in children 2-5 years of age given a single 5 mg dose of loratadine syrup had exposures to loratadine and DCL that were similar to adults given 10 mg once daily. No ECG parameters were altered in the second portion of this study in which children were given 5 mg of loratadine once daily for 15 days.[11] One study showed no change in QT interval or QTc in children 5-12 years of age who received either 5 mg or 10 mg of loratadine once daily for 14 days, with and without co-administration of the CYP3A4 inhibitor, erythromycin. There were no AEs reported[12] [NDA 21-512, N000 BM, 1/22/03, pages 5-6].

The sponsor identified two articles published between 1986 and December 15, 2002 that contained information relevant to AEs for loratadine and gender subpopulations. Both articles described the results of open label studies and represented 54 patients. There was no evidence of gender-associated AEs in these reports [NDA 21-512, N000 BM, 1/22/03, pages 8, 23-24].

One article was identified which compared the pharmacokinetics of DCL in men and women. The study found no clinically relevant differences in the pharmacokinetics of DCL between men and women.[13]

The sponsor identified one study that investigated the pharmacokinetics of loratadine in lactating women. The pharmacokinetics of loratadine and DCL in lactating women were similar to that in men. The concentration of loratadine and DCL in breast milk after a 40-mg dose of loratadine was similar to that in plasma. The authors calculated that the amount of loratadine and DCL excreted into breast milk after a 10 mg dose would be very small and would represent only about 1% of the dose given to adults on a mg/kg basis[14] [NDA 21-512, N000 BM, 1/22/03, pages 18-12].

The sponsor identified six articles in the literature between 1986 and December 15, 2002 with information pertinent to AEs for loratadine for subpopulations by race. Three of these articles described the results of double blind, placebo controlled studies and three described the results of studies of other designs. A total of 190 patients were represented [NDA 21-512, N000 BM, 1/22/03, page 11]. There were no association of AEs with any

subpopulation by race [NDA 21-512, N000 BM, 1/22/03, pages 12-13, 25-28]. One article was identified that compared the pharmacokinetics of DCL in subjects of Black and Caucasian races. The study found no clinically relevant differences in the pharmacokinetics of DCL between subjects in these subpopulations.[13] The sponsor noted that loratadine is well tolerated among racial subpopulations and that there are no racial differences in the pharmacokinetics and safety profile of loratadine [NDA 21-512, N000 BM, 1/22/03, pages 69-70].

Reviewer comment:
The current Clarinex® (descarboethoxyloratadine, DCL) label notes that approximately 7% of the general patient population may be slow metabolizers of DCL. DCL is the major metabolite of loratadine. The frequency of slow metabolizers is higher in individuals of Black race. Approximately 20% of individuals of Black race were slow metabolizers in pharmacokinetic studies. The median exposure (AUC) to DCL in the slow metabolizers was approximately 6-fold greater than the subjects who are not slow metabolizers. Similar proportion of the general population and of individuals of Black race would also be expected to be identified as slow metabolizers if they received loratadine. In fact, in one of the sponsor's pivotal clinical pharmacology studies in this NDA, Study 003214, two subjects were slow metabolizers. One of the subjects was of Black race and the other was of Caucasian race. These subjects had approximately 8-fold higher $AUC_{0\text{-}inf}$ values and 4-fold higher T_{max} values for DCL [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-512].

The Clarinex® label notes that patients who are slow metabolizers may be more susceptible to dose-related adverse events because of higher levels of DCL exposure. It should be noted that the Clarinex® label also notes that an increased frequency of adverse events was not seen in slow metabolizers participating in pharmacokinetic studies. The Division's experience has been that there are no differences in safety profiles between slow and normal metabolizers. This increased exposure to DCL in slow metabolizers is not considered to be clinically relevant in the population proposed for use.

7.5. Sponsor's evaluation of safety information from the US Adverse Event Reporting System (AERS) database

The sponsor reviewed AE reports for loratadine reported in the AERS database over the period 1993 to 2001 and also searched the AERS database for events that appeared to be related to gender or specific for the pediatric subpopulation.

The sponsor concluded that there was no conclusive evidence of a causal relationship between loratadine use and any serious or life-threatening AEs. The sponsor noted that the results of their analyses closely mirror those of the comprehensive review of the AERS database that was performed by the CDER OTC Switch Review Team. The sponsor concluded that there was no clear pattern of association of AEs with gender or the pediatric population and that their detailed analyses of the AERS database provide substantial evidence of loratadine's safety profile.

The sponsor noted 15 cases of hypospadias associated with loratadine use during pregnancy in Sweden that were reported by the EMEA. Contrary to the sponsor's conclusion, these events represent a possible safety signal. The Division has previously reviewed these Swedish data and has discussed the data with the Division of Drug Risk Evaluation. A similar association of hypospadias with loratadine use during pregnancy was not noted in the Agency's previous review of US postmarketing data. There is no information in the medical literature that suggests that loratadine has anti-androgenic activity. At this time, this possible safety signal does not appear to be an approvability issue. The potential safety benefits of drug, including lack of sedation, outweigh the potential risk for this weak signal. This possible association warrants further study and observation. The sponsor will be asked to provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy. The sponsor's proposed labeling appropriately instructs pregnant consumers to ask a health professional before using the product. Labeling will be changed accordingly if a signal is noted. Otherwise, this reviewer concurs with the sponsor's conclusion that the AERS database does not provide evidence of new safety concerns and supports the safe OTC marketing of their product in the proposed population.

A detailed review of the sponsor's analysis of the AERS database follows below.

7.5.1. Content

The sponsor reviewed AE reports for loratadine reported over the period 1993 to 2001 in the AERS database. The sponsor filed to identify AEs that were not included in the Claritin® prescription labeling, in publicly available databases, or the published clinical literature [Volume 46, page 96]. The CDER OTC Switch Review Team reviewed the AERS database for events associated with loratadine over the period 1993 to April 2000. The review team did not identify conclusive evidence of a causal relationship between the use of loratadine and serious AEs [Volume 51, pages 9-17 and http://www.fda.gov/ohrms/dockets/ac/01/briefing/3737b1.htm].

As the Agency recommended, the sponsor also performed a focused review of loratadine AEs related to deaths, seizures, and cardiac, hepatic, and renal events occurring after the cut-off date of the CDER OTC Switch Review Team, April 2000. The sponsor's focused review covered events in the AERS database over the period of May 2000 to the submission of the NDA, May 2001 [Volume 46, page 96]. The sponsor also searched the AERS database for events that appeared to be related to gender or specific for the pediatric subpopulation, as recommended by the Division.

7.5.2. Deaths in the AERS database, May 2000 to May 2001

There was one AE report of death and there were 13 other deaths reported as outcomes for AEs for cardiac, hepatic, renal, and seizure-related events.

7.5.3. Cardiac events in the AERS database, May 2000 to May 2001

The sponsor's review identified 212 cardiac events in the AERS database over this period of time. The most common cardiac events included palpitations, tachycardia, chest pain,

and hypotension. The sponsor notes that these events are noted in the Claritin® prescription labeling. The sponsor's review of less frequent cardiac events did not identify new AEs that were not observed in other databases. The sponsor reports that these data are consistent with the findings of the OTC Switch Review Team's analysis [Volume 46, page 96]. This reviewer's examination of the sponsor's summaries of individual cardiac AEs over this period reveals that the great majority of AEs list loratadine as a concomitant medication and not the primary suspect drug [Volume 46, pages 126-131].

Reviewer comment:
As noted above and as the sponsor notes, the CDER OTC Switch Review Team did not identify conclusive evidence of a causal relationship between the use of loratadine and serious AEs in their review of the AERS database from 1993 to April 2000. The sponsor's review and conclusion is consistent with the CDER Switch Review Team's findings.

7.5.4. Hepatic events in the AERS database, May 2000 to May 2001

There were 41 hepatic events identified in the sponsor's review of the AERS database over this period of time. The most frequent hepatic events were abnormal liver function test, jaundice, and hepatitis. The sponsor notes that these AEs are noted in the Claritin® prescription labeling. The sponsor's review of less frequent hepatic events did not identify new AEs that were not observed in other databases. The sponsor notes that the CDER Switch Review Team noted that the reporting rate for hepatic failure associated with loratadine use was lower than the calculated background rate in the general population [Volume 46, pages 96-97]. This reviewer notes that many of these hepatic events and all hepatic events resulting in death listed loratadine as a concomitant drug and not the primary suspect drug [Volume 46, pages 133-134].

Reviewer comment:
These data do not suggest a new safety signal.

7.5.5. Renal events in the AERS database, May 2000 to May 2001

The sponsor reports that of the 23 renal AEs noted in their review of the AERS database over this period of time, urinary discoloration, urinary incontinence, and urinary retention are noted in the Claritin® prescription labeling. The sponsor notes that other renal AEs did not identify any new safety signal. The sponsor notes that the one renal AE with death as an outcome had loratadine listed as a concomitant drug and not the primary suspect drug [Volume 46, page 97].

Reviewer comment:
These data do not suggest a new safety signal.

7.5.6. Seizure events in the AERS database, May 2000 to May 2001

The sponsor identified 19 AEs for seizure in their review of the AERS database over this period of time. The sponsor notes that the OTC Switch Review Team concluded that there was a possible association of seizure with loratadine use, but that this is may

represent a class effect for antihistamines. Seizures are listed in the Claritin® prescription labeling [Volume 46, page 97].

Reviewer comment:
These data do not suggest a new safety signal.

7.5.7. Special populations

The sponsor also searched the AERS database for events that appeared to be related to gender or specific for the pediatric subpopulation. The sponsor could not perform an analysis of the AERS database for race or ethnicity-related effects because the database does not capture this information. A review of the sponsor's presentation of these analyses follows.

The sponsor found that hepatobiliary disorders, psychiatric disorders, renal disorders, and coronary artery disorders were more frequently represented in men than in women. General disorders such as malaise, weakness, infections such as bronchitis, and alopecia were represented more frequently in women than in men. The sponsor also found reports of torsades de pointes to be more frequent in women than in men [NDA 21-512, N000 BM, 1/22/03, pages 32-34].

The sponsor noted that for children 2 to 5 years of age, the most significant AEs were tachycardia and convulsions and that these AEs appeared to be more frequent in this population than in adults. For children 6 to 12 years of age, headache and abdominal pain were most frequently reported. It appeared that convulsions were represented in children 6 to 12 years of age more frequently than in adults. In adolescents 13 to 17 years of age, headache, dyspnea, dizziness, vomiting, and syncope were the most frequently reported AEs. It appeared that syncope, depression, and convulsions were more frequent in adolescents 13 to 17 years of age than in adults [NDA 21-512, N000 BM, 1/22/03, pages 35-36].

The sponsor identified a total of ten hypospadias reports in the AERS database, of which nine were associated with loratadine as the primary suspect drug. The sponsor reported that the European Medicines Evaluation Agency (EMEA) was asked to review the safety of DCL after Swedish health authorities identified 15 cases of hypospadias in boys born to women who were taking loratadine during pregnancy. In April 2002, the EMEA issued a press release stating that it could not rule out the possibility that DCL might cause hypospadias. The EMEA stated that it could not confirm or exclude a causal relationship between DCL and hypospadias, that the benefit/risk balance for DCL was favorable. The sponsor notes that the EMEA is conducting a similar review for loratadine [NDA 21-512, N000 BM, 1/22/03, page 33].

The sponsor concluded that these data did not suggest any clear patterns of gender or age differences in AEs.

Reviewer comment:
The significance of these of the gender-associated AEs is not clear. There is no evidence that the gender effects are related to loratadine. For example, in the population at large, coronary artery disorders would be expected to more frequently represented in men than in women, and malaise and weakness might be more frequently represented in women than in men. Clearly, we know that the risk of torsades de pointes is more frequent in women than in men in the general population.

Similarly, it is difficult to draw conclusions from the AE data for the pediatric subpopulation. Convulsions appeared to be represented more frequently in each of the pediatric age groups than in adults. However, it should be noted that the incidence of seizures is highest in infancy and decreases with increasing age through childhood. The incidence of seizures is higher in children than in adults. The annual incidence of seizures is 86/100,000 in the first year of life, 62/100,000 at ages 1-5 years, 50/100,000 at ages 5-9 years, and 39/100,00 at ages 10 to 14 years[15]. It is likely that the higher frequency of seizures in the pediatric subpopulation taking loratadine is not related to use of the drug.

The 15 cases of hypospadias reported by the EMEA are from a single country, Sweden. Both the Division of Pulmonary and Allergy Drug Products and the Division of Drug Risk Evaluation have previously reviewed and discussed the Swedish data. A similar association of hypospadias with loratadine use during pregnancy was not noted in the Agency's previous review of US postmarketing data [Medical Officer Review, PID# D020137, Carolyn McCloskey, M.D, 5/3/02]. There is no information in the medical literature that suggests that loratadine has anti-androgenic activity.

This reviewer examined the AERS database in March 2003 for cases of hypospadias associated with loratadine use during pregnancy. There were 32 reports. Of these 32 reports, only 13 were reported before the EMEA's announcement that they were investigating this possible association. All of these 13 cases are from Sweden. There are no US cases reported before the date of the press release and its subsequent publicity. Since the press release, there have been 14 cases from the US and 5 cases from other countries. The cases in the AERS database that were reported after the EMEA's press release, including all of the US cases, are likely to be affected by reporting bias.

It is unclear at this time if this association may be generalizable to the US population. 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 possible safety signal does not appear to be an approvability issue. The potential safety benefits of drug, including lack of sedation, outweigh the potential risk for this weak signal. This possible association warrants further study and observation and the sponsor will be asked to provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy. The sponsor's proposed labeling instructs pregnant consumers to ask a health professional before using the product. Labeling will be changed accordingly if a signal is noted.

7.6. Sponsor's evaluation of safety information from worldwide pharmacovigilance reporting programs

The sponsor contacted various agencies worldwide to collect adverse event data for loratadine. These agencies are responsible for postmarketing surveillance programs for the World Health Organization (WHO), the European Medicines Evaluation Agency (EMEA), as well as 45 individual countries. The WHO and 10 individual countries provided postmarketing data for loratadine [Volume 49, pages 2-4; Volume 50, pages 152-357]. The sponsor concludes that these data do not provide evidence for new safety concern and concludes that the foreign marketing experience supports the safe OTC marketing of 10 mg loratadine tablets.

This reviewer concurs with the sponsor. These data provide no evidence of a safety signal that has not been identified in the prescription labeling for Claritin, the literature, or the AERS database.

The sponsor's summary and conclusions of these data are reviewed below.

7.6.1. Adverse event data from WHO

The sponsor reports that approximately 80% of the WHO database was composed of the same events in the US AERS database [NDA 21-512, N000 BM, 1/22/03]. The most frequent AEs in the WHO database included rash (193 events), therapeutic response decreased (190 events), vision abnormal (81 events), convulsions (73 events), face edema (68 events), aggressive reaction (65 events), condition aggravated (65 events), term not accepted in database (64 events), arrhythmia (60 events) [Volume 49, pages 13-19]. Cardiac, hepatic, renal, and seizure AEs were noted in this database. The sponsor notes that there were no AEs related to the elderly or patients with hepatic or renal impairment [Volume 49, page 5].

7.6.2. Adverse event data from individual countries

The sponsor received AE data from 10 individual countries—the United Kingdom, Canada, Australia, Ireland, France, Germany, New Zealand, Switzerland, Norway, Sweden [Volume 50, pages 152-357]. Cardiac, hepatic, renal, and seizure AEs were noted in these data from these countries. The sponsor noted that the AEs noted have been documented in the US experience with loratadine. The sponsor concludes that these data do not provide evidence for new safety concern and concludes that the foreign marketing experience supports the safe OTC marketing of 10 mg loratadine tablets [Volume 49, pages 4-10].

7.7. Safety update

The sponsor provided a safety update that included a review of the clinical literature from January 1, 2002, the sponsor's cut-off date for the NDA submission, until December 15, 2002. The sponsor also reanalyzed AEs associated with loratadine and listed in the AERS database over the period January 1993 until March 2002, the most recent date available at the cut-off for the safety update.

The sponsor concluded that the safety update did not identify any new safety concerns and did not identify any AEs not previously observed with loratadine [NDA 21-512, N000 SU, 1/22/03, page 219].

This reviewer concurs with the sponsor's conclusion that the safety update database does not provide evidence of new safety concerns and supports the safe OTC marketing of their product in the proposed population.

The safety update is reviewed below.

7.7.1. Updated literature review

The sponsor used PubMed to conduct the search for articles relevant to the safety of loratadine from January 1, 2002 until December 15, 2002. The sponsor identified 16 articles. Of these 16 articles, six had data from double blind, placebo controlled studies, five from studies of other designs, and five had data from reviews, commentaries, and case presentations. Pharyngitis and influenza-like symptoms were noted in one study[16]. The sponsor identified on case of ventricular arrhythmia reported in an Australian case study. The patient was a 43-year old woman who had a an episode of presyncope, interrupted by a spontaneous automatic implantable defibrillator (IED) shock approximately 90 minutes after taking a 10 mg loratadine tablet. She had a history of an identical twin sister that died suddenly from a possible cardiac arrhythmia and a history of mitral valve prolapse. She had been asymptomatic previously but had the IED placed prophylactically approximately 2 years prior to this event. The IED record revealed that there was a rapid ventricular rhythm prior to the shock[17].

There were a number of articles that were in response to a paper by Abernethy that noted QTc increase when loratadine was co-administered with nefazodone[3]. This article was previously addressed in the earlier in this review, Section 7.4.2. The study noted an increase in loratadine (38%) and DCL (12%) levels 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] Importantly, as the sponsor points out, the findings of this paper have been questioned by one of the co-authors.[4]

The sponsor's review identified one article that indicated that there is no QTc prolongation with the co-administration of DCL with erythromycin[18]. Another article noted no change in QTc interval, ECG parameters, or AE profile when ketoconazole is co-administered with DCL[19].

The sponsor concluded that the literature review did not identify any new safety concerns and that the data provide evidence to support use of the product in the OTC market.

Reviewer comment:
This reviewer concurs that the literature review identifies no new safety signal. The Abernethy paper has been questioned by one of its co-authors. The Australian case report 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 the patient's

hospital course. The lack of detail in this report makes it difficult to firmly attribute the episode to loratadine. 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.

7.7.2. Updated evaluation of the US Adverse Event Reporting System (AERS) database

The sponsor reanalyzed AEs associated with loratadine and listed in the AERS database over the period January 1993 until March 31, 2002, the most recent date available at the cut-off for the safety update. The sponsor focused on reports of cardiac, hepatic, renal, and seizure events. The sponsor did not identify significant differences from the prior earlier focused evaluation in reports of these events. The sponsor reports that there were 10 cases of hypospadias identified in this updated evaluation of the AERS database, and that Swedish authorities have noted 15 cases of hypospadias. The sponsor notes that the EMEA could not rule out the possibility that DCL might be associated with hypospadias [NDA 21-512, N000 SU, 1/22/03, pages 29-33].

The sponsor concluded that the updated evaluation of the AERS database review did not identify any new safety concerns and did not identify any AEs not previously observed with loratadine [NDA 21-512, N000 SU, 1/22/03, page 32].

Reviewer comment:
The safety update identifies no new safety issues that have arisen since submission of the application.

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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 label instructs the consumer not to use more than the recommended dose and that taking more than the recommended dose may cause drowsiness.

Dosing for consumers with liver or kidney diseases is discussed in Section 9 of this review, "Use in Special Populations."

The reference drug product for this application, Claritin Tablets, 10 mg, was approved for OTC use in the US in November 2002 and now has OTC labeling in the "Drug Facts" format [21 CFR 201.66]. The previous prescription labeling for the reference drug product notes that food increases the systemic bioavailability (AUC) of loratadine and DCL by approximately 40% and 15%, respectively. The time to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine was delayed by 1 hour. Peak plasma concentrations (C_{max}) were not affected by food. The previous prescription labeling notes that systemic exposures greater than these were obtained in drug interaction studies. These drug interaction studies showed no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and adverse events. The sponsor's pivotal clinical pharmacology studies demonstrated that food effects for the proposed product and the reference product, Claritin® Tablets were similar.

Reviewer comment:
The increased systemic exposures from the food effect are not likely to be clinically relevant. The sponsor's proposed labeling appropriately makes no recommendations relevant to administering the drug with food.

9. USE IN SPECIAL POPULATIONS

Use in special populations is discussed below.

9.1. Elderly

The sponsor identified no AEs related to the elderly [Volume 46, page 10]. The prescription label for Claritin® noted that geriatric subjects have AUC and C_{max} values for loratadine and DCL that are approximately 50% greater than in younger subjects and have an increased elimination half-life for loratadine. However, OTC labeling for the innovator makes no special recommendations for dosing in the elderly. The sponsor's proposed labeling appropriately makes no special recommendations for dosing in the elderly [Volume 1, pages 31-49].

Reviewer comment:
As discussed in Section 7.4.7 of this review, the literature suggests that the types and incidences of AEs are similar in patients ≥65 years to those in patients <65 years and

that geriatric consumers might not experience somnolence even though they may experience higher systemic exposures. The sponsor's proposed OTC labeling appropriately makes no special recommendations for dosing for healthy geriatric consumers.

9.2. Pediatric population

As noted earlier in this review, the pharmacokinetics of loratadine in pediatric subjects is similar to that in healthy adults. The sponsor's review of the literature and safety databases identify no new safety signal specific to the pediatric subpopulation, as previously noted in Sections 7.4.7 and 7.5.7 of this review [NDA 21-512, N000 BM, 1/22/03, pages 6-8]. The innovator's product labeling states that the recommended dose for children 6 years of age and older is one 10-mg loratadine tablet once daily. The sponsor proposes the same dose for children 6 years and older. The product is not proposed for use in children under 6 years of age. The sponsor's proposed labeling states that a doctor should be consulted before using the product in children under 6 years of age [Volume 1, pages 17-49].

The sponsor has requested a waiver of pediatric studies for patients 6-17 years of age because a suitable pediatric dosage from currently exists [Volume 1, page 233].

Reviewer comment:
This product is also an inappropriate dosage form and dose for children under the age of 6 years. A waiver of pediatric studies should be granted.

9.3. Gender

DCL is the major metabolite of loratadine. The sponsor identified one article that described the results of a study that compared the pharmacokinetics of DCL in men and women. The study found no clinically relevant differences in the pharmacokinetics of DCL between men and women. The sponsor found that hepatobiliary disorders, psychiatric disorders, renal disorders, and coronary artery disorders were more frequently represented in men than in women. General disorders such as malaise, weakness, infections such as bronchitis, and alopecia were represented more frequently in women than in men. The sponsor also found reports of torsades de pointes to be more frequent in women than in men [NDA 21-512, N000 BM, 1/22/03, pages 32-34].

Reviewer comment:
The significance of these of the gender-associated AEs is not clear. For example, in the population at large, coronary artery disorders would be expected to more frequently represented in men than in women, and malaise and weakness might be more frequently represented in women than in men. Clearly, we know that the risk of torsades de pointes is more frequent in women than in men in the general population. There is no evidence that these gender effects are related to loratadine.

9.4. Race

The sponsor notes that loratadine is well tolerated among racial subpopulations and that there are no racial differences in the pharmacokinetics and safety profile of loratadine [NDA 21-512, N000 BM, 1/22/03, pages 69-70].

Reviewer comment:
Contrary to the sponsors statement, there are differences among races in the pharmacokinetics of loratadine. The current Clarinex® (descarboethoxyloratadine, DCL) label notes that approximately 7% of the general patient population may be slow metabolizers of DCL, the major metabolite of loratadine. The frequency of slow metabolizers is higher in individuals of Black race. Approximately 20% of individuals of Black race were slow metabolizers in pharmacokinetic studies. The median exposure (AUC) to DCL in the slow metabolizers was approximately 6-fold greater than the subjects who are not slow metabolizers. Similar proportion of the general population and of individuals of Black race would also be expected to be identified as slow metabolizers if they received loratadine. In fact, in Study 003214, one of the sponsor's pivotal clinical pharmacology studies in this NDA, two subjects were slow metabolizers. One of the subjects was of Black race and the other was of Caucasian race. These subjects had approximately 8-fold higher $AUC_{0\text{-}inf}$ values and 4-fold higher T_{max} values for DCL [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-512].

The Clarinex® label notes that patients who are slow metabolizers may be more susceptible to dose-related adverse events because of higher levels of DCL exposure. It should be noted that the Clarinex® label also notes that an increased frequency of adverse events was not seen in slow metabolizers participating in pharmacokinetic studies. The Division's experience has been that there are no differences in safety profiles between slow and normal metabolizers. This increased exposure to DCL in slow metabolizers is not considered to be clinically relevant in the population proposed for use.

9.5. Hepatic disease

As noted in the previous prescription labeling for the reference drug product for this application, Claritin®, patients with liver impairment have increased AUC and C_{max} values for loratadine but have similar AUC and C_{max} values for DCL to normal subjects. The elimination half-life values for loratadine and DCL in patients with liver impairment are increased compared with normal subjects. The sponsor's search of the literature revealed no AEs related to the elderly or to those patients with renal or hepatic impairment [Volume 46, page 10]. The sponsor's proposed OTC labeling recommends that consumers with liver disease ask a doctor before using the product [Volume 1, pages 31-49].

Reviewer comment:
The sponsor's proposed OTC labeling instructions are appropriate for consumers with liver disease.

9.6. Kidney disease

The previous prescription labeling for the reference drug product for this application, Claritin®, patients with kidney disease have increased AUC and C_{max} values for loratadine and DCL compared to normal subjects. The elimination half-life values for loratadine and DCL in patients with kidney disease are similar to those in normal subjects. The sponsor's search of the literature revealed no AEs related to the elderly or to those patients with renal impairment [Volume 46, page 10]. The sponsor's proposed OTC labeling recommends that consumers with kidney disease ask a doctor before using the product [Volume 1, pages 31-49].

Reviewer comment:
The sponsor's proposed OTC labeling instructions are appropriate for consumers with kidney disease.

9.7. Pregnancy and lactation

The sponsor noted a total of ten hypospadias reports in the AERS database, of which nine were associated with loratadine as the primary suspect drug. The sponsor also reports that the European Medicines Evaluation Agency (EMEA) was asked to review the safety of DCL after Swedish health authorities identified 15 cases of hypospadias in boys born to women who were taking loratadine during pregnancy. The EMEA issued a press release stating that it could not rule out the possibility that DCL might cause hypospadias but also stated that the benefit/risk balance for DCL was favorable. The sponsor notes that the EMEA is conducting a similar review for loratadine [NDA 21-512, N000 BM, 1/22/03, page 33].

The sponsor identified one study that investigated the pharmacokinetics of loratadine in lactating women. The pharmacokinetics of loratadine and DCL in lactating women is similar to that in men. The concentration of loratadine and DCL in breast milk after a 40 mg dose of loratadine was similar to that in plasma. The authors calculated that the amounts of loratadine and DCL excreted into breast milk are very small and would represent only about 1% of the dose given to adults on a mg/kg basis[14] [NDA 21-512, N000 BM, 1/22/03, pages 18-12].

The sponsor's proposed labeling instructs consumers who are pregnant or who are breast-feeding to ask a health professional before using the product [Volume 1, pages 17-49].

Reviewer comment:
The possible association of hypospadias with loratadine use during pregnancy is discussed in depth in Section 7.5.7 of this review. The potential safety benefits of drug, including lack of sedation, outweigh the potential risk for this weak signal. This possible association warrants further study and observation and the sponsor will be asked to provide post-approval updates on the possible association of hypospadias with loratadine

use in pregnancy. The sponsor's proposed labeling for consumers who are pregnant or who are breast-feeding is appropriate.

10. CONCLUSIONS AND RECOMMENDATIONS

This NDA is an application for loratadine tablets, 10-mg. The sponsor's application was submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved reference product and a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved reference product. The reference product is Claritin® Tablets, 10-mg. The sponsor's proposed indication is temporary relief of symptoms due to hay fever [redacted] allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat. The proposed dose for adults and children 6 years and older is one tablet (10 mg) daily, not to exceed more than one tablet daily. The product is not indicated for children under the age of 6 years.

The sponsor's development plan consisted of two pivotal clinical pharmacology studies, Studies 003214 and 010177. The sponsor has succeeded in demonstrating that under fasting conditions, their 10-mg tablet formulation of loratadine is bioequivalent to the reference standard Schering Claritin® Tablets. Although not bioequivalent under fed conditions, food effects were similar for test and reference products.

The sponsor provided data from their pivotal bioequivalence studies and an evaluation of safety information from the clinical literature, the US AERS database, and worldwide pharmacovigilance reporting programs. There were no meaningful differences between the test and reference products in AEs, withdrawals due to AEs, or other safety endpoints in the pivotal clinical pharmacology studies. The sponsor's review of the published literature for loratadine-associated adverse events did not provide evidence of new safety concerns. Isolated cases of cardiac, hepatic, and CNS AEs are confounded and not likely to represent new safety signals.

The sponsor identified 15 cases of hypospadias associated with loratadine use during pregnancy in Sweden that were reported by the EMEA. A similar association of hypospadias with loratadine use during pregnancy was not noted in the Agency's previous review of US postmarketing data. There is no information in the medical literature that suggests that loratadine has anti-androgenic activity. The potential safety benefits of drug, including lack of sedation, outweigh the potential risk for this weak signal. This possible association warrants further study and observation. The sponsor's proposed labeling appropriately instructs pregnant consumers to ask a health professional before using the product. Otherwise, the AERS and worldwide safety databases do not provide evidence of new safety concerns. These data provide no evidence of a safety signal that has not been previously identified in the prescription labeling for Claritin, the literature, or the AERS database. The sponsor's integrated review of safety supports the proposed indication of their product.

The sponsor has succeeded in demonstrating that their 10-mg tablet formulation of loratadine is bioequivalent to the reference standard Schering Claritin® Tablets. In

addition, the sponsor has provided convincing evidence of safety of loratadine. From a clinical perspective, this reviewer recommends an approval action. However, the Clinical Pharmacology and Biopharmacuetics team has determined that the site must be audited and data must be found acceptable for use before an approval action may be considered.

APPEARS THIS WAY
ON ORIGINAL

11. APPENDIX, CLINICAL STUDIES

11.1. Study 003214

Title: Comparative, randomized, single-dose, four-way crossover, fully-replicated, bioavailability study of Perrigo and Schering (Claritin®) 10 mg loratadine tablets in healthy adult males under fasting conditions following a 40 mg dose

Date of protocol: 2/20/01
Date of study report: 8/21/01

Study 003214 was an open-label, randomized, single dose, fully replicated , four-way crossover relative bioavailability study designed to compare the bioavailability of Perrigo and Schering (Claritin®) 10 mg loratadine tablets under fasting conditions following a 40 mg dose [Volume 29, pages 055, 84]. The study was conducted at

Each subject received study treatment and reference treatment twice in this four period study. There was a washout period of at least 21 days between study periods [Volume 29, pages 56, 85]. The study was to enroll 56 healthy, adult male subjects, ages 18-45 years of age and at least 52 kg and within 15% of ideal weight. Four subjects were to be enrolled as alternates [Volume 29, page 86]. Sixty healthy adult male subjects were actually enrolled in the study [Volume 29, page 55].

Subjects were confined to the study center from the evening before dose administration until after the final blood draw, 36 hours after dosing. Subjects returned to the study center at 48 hours after dosing and for subsequent blood draws. Subjects fasted overnight before dosing and for at least 4 hours afterwards. Water was not permitted for one hour before dosing and one hour after dosing, but was allowed at other times. Standard meals were provided approximately 4 hours and 9 hours after administration of study treatment and at appropriate times thereafter. The meal plans during the confinement period were identical for all study periods [Volume 29, page 56].

Blood samples were collected prior to dosing with study treatment (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, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post-dose for measurement of loratadine and descarboethoxyloratadine (DCL) concentrations [Volume 29, pages 56, 84]. The total number of blood draws during the study was 100 for each subject and a total volume of blood drawn per subject was 716 mL [Volume 29, page 84].

The formulations studied are displayed in Table 11.1.1. The sponsor indicates that the manufacturing process used to produce the clinical supplies was the same as that to be used for the to-be-marketed product. The drug substance for this study was produced by [Volume 1, pages 67, 70]. This study was performed with a single dose of 40 mg of loratadine in each treatment period, instead of the proposed 10-mg dose.

Table 11.1.1. Study treatments, Study 003214 [Volume 29, page 55].

Proposed product	Loratadine, 10 mg tablet, Perrigo Batch #OC1868, expiration date 09/01
Reference product	Loratadine, 10 mg tablet (Claritin®), Schering Lot #9RXF559, expiration date 02/02

Reviewer comment:
The Agency asked the sponsor to provide justification for using a 40 mg dose of loratadine instead of the proposed labeled dose, 10 mg. The sponsor stated the PK of the drug would not have been characterized as robustly if a lower dose of loratadine were to be used. Concentrations would have been detectable only for 24 to 48 hours because of the limit of quantitation of the sponsor's assay. The sponsor provided a literature reference to further support their justification [Volume 1, page 182]. The Agency agreed that the sponsor justified the use of the 40-mg dose in these studies [Volume 1, page 190].

Each subject received a medical history, vital signs, physical examination, and clinical laboratory tests on blood and urine at screening. Vital signs were also measured before dosing and at approximately 2 hours after dosing. [Volume 29, pages 85-86; Volume 30, page 267]. Subjects were monitored throughout confinement for adverse events (AEs). Subjects were questioned concerning unusual symptoms that may have occurred after the previous administration of study treatment at the beginning of the second, third, and fourth study periods [Volume 29, page 88; Volume 30, page 268].

There were 60 healthy adult males who were enrolled in this study. Of these 60 subjects, 48 completed the clinical phase of the study. There were 12 subjects who did not complete the study. Of these 12 subjects, there were seven subjects who withdrew for personal reasons. There was one subject who died in a — fire between study periods 1 and 2. Three subjects withdrew because of AEs. One subject was discontinued because of the inability to draw blood samples. There were 54 subjects who completed at least two of the study periods, and the pharmacologic and statistical analyses were performed on data from these subjects [Volume 29, pages 55, 56 Volume 30, page 268].

The majority of subjects enrolled in this study were Caucasian (57/60, 95%). The remaining subjects were of Black race (3%, 2/60) and Oriental race (2%, 1/60). The study enrolled only males. The mean age for subjects in this study was 32.8 years. Subjects ranged from 20 to 45 years of age [Volume 30, pages 271-272].

Reviewer comment:
Non-Caucasian subjects were underrepresented in this study, and only males were enrolled. This is less than ideal. However, the Office of Generic Drugs (OGD) reviewed this protocol, and made no comment on the proposed study population [OGD Review, P#99-033, 8/17/99, S. P. Shrivastava, Ph.D.]. Even though the subject population in this study is not ideal, it must be acknowledged that the pharmacologic and safety profiles of loratadine and DCL have previously been well established by the innovator.

11.1.1. Clinical pharmacology outcomes

Plasma loratadine and descarboethoxyloratadine (DCL) were analyzed using a validated LC/MC/MS method developed at —. The validated analytical ranges used were 20.0-50049.9 pg/mL for loratadine and 20.0-29934.2 pg/mL for DCL [Volume 29, page 56].

The pharmacokinetic and statistical analyses were conducted on data from the 54 subjects who completed at least two periods of the study. One subject (#50) was not included in the main analyses because of non-zero pre-dose values for DCL that were greater than 5% of the C_{max} in the affected period [Volume 29, page 56]. There were two other subjects with non-zero values for DCL, subjects #25 and #49. Both subjects #25 and #50 were identified as poor metabolizers. Subject #49 was not a poor metabolizer. He had a non-zero dose prior to Period 1, but not before any of the other three study periods.

PK results comparing the proposed product and the reference product when given under fasting conditions are presented in Table 11.1.2. Please see Dr. Kim's clinical pharmacology and biopharmaceutics review for additional information [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-512].

$AUC_{0\text{-}inf}$ for loratadine was similar for the test (34.8 ng.hr/mL) and reference (34.1 ng.hr/mL) products. $AUC_{0\text{-}inf}$ for DCL was similar for the test (172.3 ng.hr/mL) and reference (173.4 ng.hr/mL) products. C_{max} for loratadine was similar for the test (11.5 ng/mL) and reference (11.4 ng/mL) products. C_{max} for DCL was similar for the test (11.0 ng/mL) and reference (11.2 ng/mL) products. $T_{1/2}$ and T_{max} for loratadine and DCL were also similar for test and reference products [Volume 29, pages 68, 70].

Table 11.1.2. Mean PK parameters for loratadine and DCL, fasting conditions, Study 003214 [Volume 29, pages 68, 70].

PK Parameter	Perrigo Loratadine Tablet Fasting conditions 4 x 10 mg Test Product (A) N = 53	Schering Claritin® Tablet Fasting conditions 4 x 10 mg Reference Product (B) N = 53	Ratio, A/B %	90% C I %
Loratadine				
$AUC_{(0\text{-}inf)}$, ng.hr/mL	34.8	34.1	101.6	95.9 – 107.7
C_{max}, ng/mL	11.5	11.4	103.1	94.2 – 112.8
$T_{1/2}$, hr	24.4	24.4	--	--
T_{max}, hr	1.25	1.27	--	--
DCL				
$AUC_{(0\text{-}inf)}$, ng.hr/mL	172.3	173.4	99.9	97.0 – 102.9
C_{max}, ng/mL	11.0	11.2	98.8	94.1 – 103.8
$T_{1/2}$, hr	29.37	29.18	--	--
T_{max}, hr	2.37	2.17	--	--

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 demonstrate that the Perrigo and Schering (Claritin®) 10 mg loratadine tablets are bioequivalent under fasting conditions, following a 40 mg dose [Volume 29, page 65].

Two subjects in this study were poor metabolizers. One of the subjects was of Black race (#50) and the other was of Caucasian race (#25). These subjects had approximately 8-fold higher $AUC_{0\text{-}inf}$ values and 4-fold higher T_{max} values for DCL. Dr. S. Kim, the Clinical Pharmacology and Biopharmaceutics Reviewer concurred that the products were bioequivalent under fasting conditions. There was no difference in C_{max} values for the slow metabolizers [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-512].

Reviewer comment:
The Clarinex® (descarboethoxyloratadine) label notes that patients who are slow metabolizers may be more susceptible to dose-related adverse events because of higher levels of DCL exposure. However, it should be noted that the Clarinex® label also notes that an increased frequency of adverse events was not seen in slow metabolizers participating in pharmacokinetic studies. The Division's experience has been that there are no differences in safety profiles between slow and normal metabolizers. The increased exposure to DCL in slow metabolizers is not considered to be clinically relevant in the population proposed for use.

11.1.2. Safety outcomes

Safety endpoints included adverse events. Vital signs were monitored for safety, but an analysis of vital signs was not provided as a safety endpoint. Laboratory tests for hemoglobin and hematocrit were repeated prior to dosing in Period 4 [Volume 29, pages 58-87; Volume 30, page 269].

There were 127 post-dose adverse events (AEs) that occurred in this study. There were 59 subjects who were exposed to at least one dose of test product and 56 subjects who were exposed to at least one dose of reference product. The sponsor reported one SAE. This SAE was an accidental death that occurred in subject #19 due to asphyxiation in a fire [Volume 30, page 268]. SAEs are discussed in greater detail below.

AEs occurring more frequently with test medication than with reference medication included erythema at the blood draw site, constipation, abdominal pain, dizziness, and runny nose [Volume 30, pages 281-283]. There was a higher frequency of AEs in reference treated subjects (132.1%, 74/56) than in test product treated subjects (89.8%, 53/59). These data are summarized in Table 11.1.3.

Table 11.1.3. Adverse events occurring in more than one subject in Study 003214. Events occurring more frequently in Perrigo loratadine than in Schering Claritin® are highlighted [compiled from Volume 30, pages 281-283].

Adverse event	Perrigo loratadine tablets, 10 mg 4 x 10 mg Test Product (A) N = 59		Schering Claritin® Tablets, 10 mg 4 x 10 mg Reference product (B) N = 56	
	n	(%)	n	(%)
All adverse events	53	(89.8)	74	(132.1)
Headache	9	(15.3)	10	(17.9)
Erythema at blood draw site	**3**	**(5.1)**	**2**	**(3.6)**
Nausea	2	(3.4)	5	(8.9)
Sore throat	2	(3.4)	4	(7.1)
Back pain	2	(3.4)	2	(3.6)
Earache, ear pain	2	(3.4)	2	(3.6)
Constipation	**2**	**(3.4)**	**1**	**(1.8)**
Abdominal pain	**2**	**(3.4)**	**0**	**(0)**
Dizziness	**2**	**(3.4)**	**0**	**(0)**
Runny nose	2	(3.4)	5	(8.9)
Loose stool	1	(1.7)	9	(16.1)
Nasal congestion	1	(1.7)	4	(7.1)
Cough	1	(1.7)	3	(5.4)
Felt hot, feverish	0	(0)	3	(5.4)
Dizzy with blood draw	1	(1.7)	2	(3.6)
Pain at blood draw site	1	(1.7)	2	(3.6)
Feel tired	0	(0)	2	(3.6)
Toothache	0	(0)	2	(3.6)

As noted above, the sponsor reported one SAE. This SAE was an accidental death that occurred in subject #19 due to asphyxiation in a — fire. The SAE occurred after study period 1, approximately 10 days after dosing with treatment "A," Perrigo loratadine. This SAE was considered not to be related to study treatment. The sponsor also reported one subject (#10) who was treated with Perrigo loratadine who had convulsions. This AE was not considered to be serious and was considered not to be related to study treatment [Volume 30, page 282; a Volume 33, page 5]. The sponsor provided no additional detail. The sponsor was asked to provide further detail and follow-up on this apparently previously healthy subject. The sponsor also was asked to explain why this AE was not considered to be a SAE and to provide the rationale for considering this event to be unrelated to study treatment. In their response to the request for additional information, the sponsor noted that the patient had involuntary movements of the limbs in association with a vasovagal fainting episode from a blood draw. The patient's involuntary movements lasted less than one minute and he recovered completely without any sequelae. The investigator considered this episode to not be a true convulsion. In the investigator's opinion, this event did not meet regulatory criteria for an SAE in that it was not life-threatening, did not result in death, hospitalization, or persistent disability, and was not medically important [NDA 21-512 N000 BM, 3/5/03, page 4].

Reviewer comment:
Myoclonic activity may be seen with vasovagal faints. The sponsor's response is acceptable.

There were three subjects who withdrew from the study because of AEs. Subject #23 withdrew 8 days into study period 2 (reference product) because of a toothache that began in study period 1 (test product). Subject #45 withdrew because of right ear pain that developed 20 days post-dose in study period 2 (test product). Subject #48 withdrew because of left ear pain that developed during study period 1 (reference product). All three subjects who withdrew required treatment with antibiotics. The three AEs resulting in withdrawal from the study were considered to be not related to study treatment [Volume 30, pages 268, 271-272].

Vital signs were monitored for safety, but the sponsor did not analyze vital signs as a safety endpoint. This reviewer examined raw data for vital signs. There were no notable abnormalities in vital signs [Volume 31, pages 67-126, 214-269; Volume 32, pages 46-97, 232-279].

There were no clinically significant abnormalities for hemoglobin and hematocrit studies performed prior to dosing in study period 4 [Volume 30, page 269].

Reviewer comment:
AEs were fairly common, and were more frequent with the reference treatment, Claritin® than with the test treatment, Perrigo loratadine. The difference in frequency of AEs between the treatments appears to be related to AEs associated with viral upper respiratory tract infections or gastroenteritis. It appears that there may have been an outbreak of a viral illness during one of the study treatment periods. It is tragic that one of the subjects in this study was killed in a — fire, however, this tragedy does not appear to be related to study treatment. There appears to be no safety signal. There are no meaningful differences between the test and reference products in AEs or for other safety variables. There are no concerning safety signals noted in this study.

11.2. Study 010177

Title: Comparative, randomized, single dose, two-way crossover relative bioavailability study of Perrigo and Schering (Claritin®) 10 mg loratadine tablets in healthy adult males under fed conditions following a 40 mg dose

Date of protocol: 6/27/01
Date of study report: 9/24/01, amended 11/21/01

Study 010177 was an open-label, randomized, single dose, two-way crossover relative bioavailability study designed to compare the single dose bioavailability of Perrigo and Schering (Claritin®) 10 mg loratadine tablets under fasting conditions following a 40 mg dose. The study was conducted at [Volume 41, pages 6, 28].

There was a washout period of at least 21 days between study periods [Volume 41, pages 7, 29]. The study was to enroll 30 healthy, adult male subjects, ages 18-45 years of age and at least 52 kg and within 15% of ideal weight. two subjects were to be enrolled as alternates [Volume 41, pages 28-30]. Thirty-two healthy adult male subjects were actually enrolled in the study [Volume 41, page 6].

Subjects were confined to the study center from the evening before dose administration until after the final blood draw, 36 hours after dosing. Subjects returned to the study center at 48 hours after dosing and for subsequent blood draws. Subjects fasted overnight until 30 minutes before dosing, at which time they received a breakfast that consisted of a buttered English muffin, one fried egg, one slice of cheese, 1 slice of Canadian bacon, one serving of hash brown potatoes, 180 mL of orange juice, and 240 mL of whole milk. Subjects were fasted for at least 4 hours after dosing. Water was not permitted for one hour before dosing and one hour after dosing, but was allowed at other times. Standard meals were provided approximately 4 hours and 9 hours after administration of study treatment and at appropriate times thereafter. The meal plans during the confinement period were identical for all study periods [Volume 41, pages 6-7, 49, 251].

Blood samples were collected prior to dosing with study treatment (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, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post-dose for measurement of loratadine and descarboethoxyloratadine (DCL) concentrations [Volume 41, pages 6, 28]. The total number of blood draws during the study was 52 for each subject and a total volume of blood drawn per subjects was 376 mL [Volume 41, page 28].

The formulations studied are displayed in Table 11.2.1. The sponsor indicates that the manufacturing process used to produce the clinical supplies was the same as that to be used for the to-be-marketed product. The drug substance for this study was produced by , Volume 1, pages 67, 70]. This study were performed with a single dose of 40 mg of loratadine, instead of the proposed 10-mg dose.

used were 20.2-50549.4 pg/mL for loratadine and 19.9-29786.4 pg/mL for DCL [Volume 41, page 7].

PK results for the proposed product under fed and fasted conditions are presented in Table 11.2.2. $AUC_{0\text{-}inf}$ for loratadine was similar for the test (73.8 ng.hr/mL) and reference (81.1 ng.hr/mL) products. $AUC_{0\text{-}inf}$ for DCL was similar for the test (187.8 ng.hr/mL) and reference (185.6 ng.hr/mL) products. C_{max} for loratadine was similar for the test (17.6 ng/mL) and reference (19.2 ng/mL) products. C_{max} for DCL was the same for the test (12.2 ng/mL) and reference (12.2 ng/mL) products. $T_{1/2}$ and T_{max} for loratadine and DCL were similar for test and reference products [Volume 41, pages 13, 14].

Table 11.2.2 Mean PK parameters for loratadine and DCL, fed conditions, Study 010177 [Volume 1, page 102; Volume 41, pages 13, 14].

PK Parameter	Perrigo Loratadine Tablet (A) Fed conditions 4 x 10 mg Test Product (A) N = 30	Schering Claritin® Tablet Fed conditions 4 x 10 mg Reference Product (B) N = 30	Ratio, A/B %	90% C I %
Loratadine				
$AUC_{(0\text{-}inf)}$, ng.hr/mL	73.8	81.1	92.2	83.8—101.4
C_{max}, ng/mL	17.6	19.2	91.8	79.6—105.9
$T_{1/2}$, hr	29.0	31.3	--	--
T_{max}, hr	2.2	1.97	--	--
DCL				
$AUC_{(0\text{-}inf)}$, ng.hr/mL	187.8	185.6	101.2	96.8—105.8
C_{max}, ng/mL	12.2	12.2	100.6	94.7—106.7
$T_{1/2}$, hr	25.5	24.7	--	--
T_{max}, hr	2.80	2.70	--	--

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 similar 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 demonstrate that the Perrigo and Schering (Claritin®) 10 mg loratadine tablets are bioequivalent under fed conditions, following a 40 mg dose [Volume 41, page 5]. Dr. S. Kim, the Clinical Pharmacology and Biopharmaceutics Reviewer noted that the test and reference products were not bioequivalent under fed conditions, but that the food effects were similar. There were no slow metabolizers identified in this study [Dr. S. Kim, Clinical Pharmacology and Biopharmaceutics Review, NDA 21-512].

11.2.2. Safety outcomes

Safety endpoints included adverse events. Vital signs were monitored for safety, but an analysis of vital signs was not provided as a safety endpoint [Volume 41, pages 7, 28, 32, 252].

There were 12 post-dose adverse events (AEs) that occurred in this study. There were 32 subjects who were exposed to at least one dose of test product and 31 subjects who were exposed to at least one dose of reference product. There were few AEs in this study. AEs occurred at similar frequencies in the test and reference treatments. There were no AEs that occurred more than once in the test treatment [Volume 41, page 255]. These data are summarized in Table 11.2.3. One subject, #26 developed mild left anterior chest pain shortly after lunch during study period 2. An ECG was normal. The pain resolved within 5 hours and no treatment was needed. The pain was attributed to dyspepsia [Volume 42, pages 199-201].

Table 11.2.3. Adverse events occurring in Study 010177 [compiled from Volume 41, pages 253, 255].

Adverse event	Perrigo loratadine tablets, 10 mg 4 x 10 mg Test Product (A) N = 32		Schering Claritin® Tablets, 10 mg 4 x 10 mg Reference product (B) N = 31	
	n	(%)	n	(%)
All adverse events	6	(18.8)	6	(19.4)
Lower back pain	1	(3.1)	0	(0)
Runny nose	1	(3.1)	0	(0)
Tiredness in joints	1	(3.1)	0	(0)
Cough	1	(3.1)	2	(6.5)
Tiredness of legs	1	(3.1)	1	(3.2)
Toothache	1	(3.1)	0	(0)
Bruise at blood draw site	0	(0)	1	(3.2)
Chest pain	0	(0)	1	(3.2)
Tiredness of back	0	(0)	1	(3.2)

There were no SAEs or deaths in this study [Volume 41, page 252]. There was one subject who withdrew from the study because of an AE. Subject #16 withdrew prior to dosing in study period 2 because of a toothache that began in study period 1 (test product). The subject required treatment with an antibiotic. This AE was considered to be not related to study treatment [Volume 41, pages 252, 253, 255].

Vital signs were monitored for safety, but the sponsor did not analyze vital signs as a safety endpoint. This reviewer examined raw data for vital signs. There were no notable abnormalities in vital signs [Volume 42, pages 45-76, 128-158].

Reviewer comment:
AEs were uncommon in this study and occurred at similar frequencies in test and reference treatments. There are no meaningful differences between the test and reference products in AEs or for other safety variables. There are no concerning safety signals noted in this study.

1 Page(s) Withheld

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1 Draft Labeling

_____ Deliberative Process

13. COMMENTS FOR THE SPONSOR

The following comments should be communicated to the sponsor:

As a Phase 4 agreement, you should provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy.

These reports should be required for 3 years.

Reviewed by:

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

Lydia Gilbert McClain, M.D.
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Gilbert-McClain/Acting Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/C. Kim/Chemistry, Manufacturing, and Controls Reviewer
HFD-870/S. Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-570/Zeccola/CSO

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/s/

Charles Lee
4/15/03 10:44:29 AM
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