

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-891**

**MEDICAL REVIEW(S)**



MEMORANDUM

Department Of Health and Human Services  
Food and Drugs Administration  
Center for Drug Evaluation and Research  
**Division of Nonprescription Clinical Evaluation**

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**Date:** August 21, 2006  
**From:** Andrea Leonard-Segal, M.D.  
Director  
**Subject:** NDA 21-891  
Children's Claritin Chewable Grape Flavored 5 mg Tablets  
(loratadine HCl 5 mg)  
**Sponsor:** Schering-Plough HealthCare Products

**Background:**

Refer to my Division Director review dated May 31, 2006. This August 21, 2006 review focuses on the June 26, 2006 resubmission of NDA 21-891

On June 1, 2006 the Agency issued an approvable letter to Schering-Plough HealthCare Products for NDA 21-891, Children's Claritin Chewable Grape Flavored 5 mg Tablets. The proposed dosing for the 5 mg chewable loratadine formulation is one 5 mg tablet every 24 hours for children ages 2 years to < 6 years of age and two 5 mg tablets every 24 hours for adults and children  $\geq$  6 years of age.

Claritin® (loratadine) first became available as a nonprescription drug in the United States in 2002. Claritin® 10 mg tablets, Claritin® Reditabs orally disintegrating 10 mg tablets, and Claritin Children's 5 mg/ml syrup are approved as nonprescription drugs. One indication for nonprescription loratadine is the "temporary relief of symptoms of runny nose, itchy, watery eyes, and sneezing, and itching of the nose or throat, due to hay fever or other respiratory allergies. The proposed 5 mg product has this same indication and targets a population of adults and children 2 years of age and older. Schering-Plough also markets a nonprescription 10 mg Claritin® tablet, orally disintegrating tablet, and a syrup formulation for the relief of hives in adults and children 6 years of age and older.

The following deficiencies were cited in the June 1, 2006 approvable letter:

1. Based on the results of the audit of the bioequivalence study (CL2003-02), the Division of Scientific Investigations recommended that data from certain test subjects be excluded and that the data be reanalyzed without those subjects;
2. Labeling deficiencies for the 5- and 10-count carton, 2-count sachet, and the bi-fold card and bi-fold tray. (Refer to the June 1, 2006 action letter.)

On June 26, 2006, the sponsor submitted a complete, class I response to the June 1, 2006 action letter.

**Clinical Pharmacology:**

Refer to the July 26, 2006 review by Dr. Partha Roy.

The office of Clinical Pharmacology reviewed the resubmission reanalysis of the bioequivalence data excluding subjects 4 – 6 from the loratadine data and subjects 1-3, 13-15, and 22-24 from the desloratadine data. The reanalysis showed that the test product is bioequivalent to the reference product since the 90% confidence intervals around the ratio of mean values of AUC and C<sub>max</sub> for both loratadine and desloratadine fell within the 80 – 125% range. The reviewer recommended that the data was acceptable for approval of the NDA.

**Safety Update:**

See Dr. Osborne's review dated July 14, 2006.

The safety update data submitted with the complete response to the June action letter covered the time period from October 1, 2005 – March 31, 2006. The sources of the data were:

- Schering-Plough internal adverse event database
- World Health Organization database
- Toxic Exposure Surveillance System database
- Worldwide literature

The safety data update data did not suggest new safety signals for loratadine. As he did in his March 30, 2006 safety review, Dr. Osborne recommended that based upon the safety data, this application could be approved. I agree with his assessment.

**Labeling:**

Refer to the memo to the file by Elaine Abraham dated August 14, 2006 and the meeting minutes of a teleconference between FDA and Schering-Plough HealthCare Products on June 12, 2006.

At the June 12, 2006 meeting, FDA and the sponsor agreed that the established name could remain "loratadine tablets," and that any labeling changes required by FDA for this NDA could be made at the time of the next printing or after 180 days of marketing, whichever comes first. (Refer to the minutes of that meeting.) Subsequently, an internal meeting with the Division of Medication Errors and Technical Support staff was held to discuss the use of the term "allergy" on the label.

The outcome of both meetings was that the previously submitted (March 30, 2006) labeling could be approved as well as the labeling for the blister packages submitted August 2, 2005. Thus, the labeling issues for the NDA have been resolved.

**Conclusion:**

With this Class 1 complete response to the action letter, the sponsor has addressed the outstanding deficiencies for the NDA.

**Recommendation:**

NDA 21-891, Children's Claritin Chewable Grape Flavored 5 mg Tablets, should be approved. I do not recommend a Phase 4 commitment. The sponsor has fulfilled the pediatric study requirement for this NDA.

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MEDICAL OFFICER



MEMORANDUM

Department Of Health and Human Services  
Food and Drugs Administration  
Center for Drug Evaluation and Research  
**Division of Nonprescription Clinical Evaluation**

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**Date:** May 31, 2006  
**From:** Andrea Leonard-Segal, M.D.  
Director  
**Subject:** NDA 21-891  
Children's Claritin Chewable Grape Flavored 5 mg Tablets  
**Sponsor:** Schering-Plough HealthCare Products

**Background:**

Claritin® (loratadine) 10 mg tablets, Claritin® Reditabs orally disintegrating 10 mg tablets, and Claritin Children's 5 mg/ml syrup are approved as nonprescription drugs. Loratadine first became available as a nonprescription drug in the United States in 2002. The proposed product, Children's Claritin Chewable Grape Flavored Tablets contains 5 mg of loratadine per tablet.

One indication for nonprescription loratadine is the "temporary relief of symptoms of runny nose, itchy, watery eyes, and sneezing, and itching of the nose or throat, due to hay fever or other respiratory allergies. The proposed 5 mg product has this same indication and targets a population of adults and children 2 years of age and older. Schering-Plough also markets a nonprescription 10 mg Claritin® tablet for the relief of hives in adults and children 6 years of age and older.

Claritin D® Non-Drowsy 12 Hour Tablets (loratadine 5 mg /pseudoephedrine 120 mg) and Claritin D® Non-Drowsy 24 Hour Tablets (loratadine 10 mg/pseudoephedrine 240 mg) are also approved nonprescription drugs.

The proposed dosing for the 5 mg chewable loratadine formulation is one 5 mg tablet every 24 hours for children ages 2 years to < 6 years of age and two 5 mg tablets every 24 hours for adults and children ≥ 6 years of age.

**Review:**

**Chemistry**

The chemistry reviewer recommended that from the chemistry perspective this NDA could be approved. The chemists did not recommend a Phase IV commitment. (See the review dated May 30, 2006 by Dr. Tarun Mehta.)

**Pharmacology/Toxicology**

No new animal or toxicology data were submitted with this NDA.

**Clinical Pharmacology/Biopharmaceutics**

The sponsor submitted the results of one bioequivalence pharmacokinetic study (CL2003-02) to support this application. The purpose of the study was to determine the relative bioavailability/bioequivalence of the proposed loratadine formulation compared to the approved reference product (Claritin® 10 mg tablet) after a single dose under fasted conditions. The two-way crossover study in 48 healthy male and female

volunteers, ages 19 – 45 years, demonstrated that the new formulation (2 x 5 mg loratadine chewable tablets) was bioequivalent to the reference listed drug for loratadine and its pharmacologically active metabolite, desloratadine with regard to both C<sub>max</sub> and AUC.

In their review dated April 4, 2006 the Office of Clinical Pharmacology and Biopharmaceutics found this NDA acceptable from a clinical pharmacology standpoint pending favorable Division of Scientific Investigation (DSI) findings. (Refer to the review by Dr. Shinja Kim and by Dr. Emmanuel O. Fadiran.)

However, the DSI audit of the analytical portion of the study found that data from the study needed to be excluded. (See Dr. O'Shaughnessy's review dated May 23, 2006.) The Office of Clinical Pharmacology agreed with the DSI conclusions and updated their recommendation on this application. They now recommend that the sponsor exclude data from specific subjects and re-analyze the bioequivalence data. If bioequivalence is not demonstrated they recommend that the sponsor do a repeat assay of the samples for the specific study subjects. The sponsor should send the report of the re-analysis of the bioequivalence data as an amendment to the NDA and should send the analytical report to DSI to show that the issues in the Form 483 have been adequately addressed. (See the Memorandum from Dr. Fadiran dated May 25, 2006.)

No food effect study was conducted for the NDA, but the Clinical Pharmacology reviewers determined that in vitro dissolution data submitted by the sponsor could substitute for the absence of a food effect study because the food effect on Claritin drug products is well known.

**Clinical:**

(Refer to the review by Dr. Steven Osborne.)

**Efficacy**

No efficacy data were submitted with this NDA.

**Safety:**

An integrated review of safety was most recently conducted by the Agency at the time of the approval of Claritin® for hives relief on November 19, 2003. In NDA 21-891, the sponsor submitted safety data from the bioequivalence study, overdose and abuse data, post-marketing domestic and world-wide adverse event data and a literature review covering the period from December 1, 2002 through December 31, 2005.

I agree with Drs. Osborne and Shetty that the safety data reviewed did not raise new safety signals. I would reiterate that there are no data in this submission to causally link loratadine with cases of Torsade de Pointes, other ventricular arrhythmias, male congenital hypospadias, or seizure disorders. These adverse events have been raised as questionably associated with loratadine in past reviews.

**Pediatrics:**

In 1998, FDA issued a written request to Schering Plough for pediatric studies for loratadine.

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The Agency did not label the approved Claritin® products to allow use in children below 2 years of age.

In a May 23, 2006 e-mail communication, the Division of Pediatric Drug Development recommended that FDA waive studies for NDA 21-891 in children < 6 months of age and consider studies completed for those > 6 months of age. I agree with this recommendation.

**Labeling:**

The Agency submitted labeling comments to the sponsor on March 20, 2006 requesting revisions to the 2-count sachet, 5- and 10-count cartons, bi-fold card (with and without coupon), and the bi-fold card sample tray draft labeling. The sponsor submitted revised draft labeling which the reviewers found to be acceptable. (See the review by Cazemiro Martin dated April 7, 2006.) The Division of Medication Errors and Technical Support, in their review dated May 23, 2006 had no objections to the use of the proprietary name, Children's Claritin, for the chewable tablet formulation. However, upon considering other comments in the DMET's review, Cazemiro Martin wrote an NDA Addendum Labeling Review dated May

30, 2006, recommending that the statement "Allergy" that appears on the PDP of the 5- and 10-count SKU, 2-count sachet, and the bi-fold card and bi-fold card tray be relocated. He also recommended that the term "chewable" should appear as part of the statement of identity.

**Conclusion:**

The clinical pharmacology data submitted with this NDA is inadequate. The chemistry review did not reveal outstanding issues. There are no new safety signals noted for loratadine. The sponsor has additional labeling comments to address. No new pediatric studies are needed.

**Recommendations**

This NDA should be approvable. The sponsor needs to address the deficiencies noted by the DSI in the Clinical Pharmacology data. The additional labeling comments should be provided to the sponsor.

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Andrea Segal  
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MEDICAL OFFICER

## Medical Officer's Review

NDA: 21-891

Product Name: Children's Claritin Chewable 5 mg

Use: Relief of hay fever and upper respiratory allergy symptoms

Type of Document: NDA Resubmission

Date Submitted: June 26, 2006

Date Reviewed: July 14, 2006

Reviewer: Steven Osborne, M.D.

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### Purpose

The purpose of this review is to evaluate the Sponsor's resubmission of data, following the June 2006 Approvable Letter, for Children's Claritin Chewable 5mg.

### Background

Schering-Plough, the Sponsor, currently markets loratadine formulations in the United States for the relief of hay fever and upper respiratory allergy symptoms in adults and children 6 years of age and older. The Sponsor markets Claritin Syrup (loratadine 5 mg per teaspoon) for the same indication in adults and children 2 years of age and older. In addition, the Sponsor markets an OTC 10-mg tablet for relief of hives in adults and children 6 years and older. These products, listed below, are available in the United States without a prescription since 2002-2003:

- Claritin 24 hour Allergy Tablets (10 mg loratadine)
- Claritin Hives Relief Tablets (10 mg loratadine)
- Claritin RediTabs Tablets (10 mg loratadine orally disintegrating tablets)
- Children's Claritin Allergy Oral Solution (5 mg loratadine/5 ml)

A separate nonprescription combination product with pseudoephedrine and loratadine, Claritin-D Non-Drowsy 12-Hour (and 24-Hour) Tablets, is available for the relief of hay fever and upper respiratory allergy symptoms in adults and children 6 years of age and older.

Loratadine has been shown in animals and in man to be an orally effective, long-acting antihistamine devoid of central nervous system effects. Following oral administration, loratadine is rapidly metabolized to desloratadine, a pharmacologically active metabolite. The half-life of loratadine is 8 to 15 hours and the half-life of desloratadine is 12 to 24 hours.

The Sponsor has developed a 5 mg loratadine tablet that is chewable, not buccal or sublingual. The proposed dosing regimen for this chewable tablet is one 5 mg tablet every 24 hours for children 2 to under 6 years of age or two 5 mg tablets every 24 hours for adults and children 6 years and older. To support this application, the Sponsor conducted one study designed to evaluate the bioequivalence of the test product (2 x 5 mg loratadine chewable tablets) and the reference product (1 x 10 mg loratadine tablet). In June 2006 the Agency issued an approvable letter citing a biopharmaceutical data deficiency following a Division of Scientific Investigations (DSI) inspection. The DSI recommended that 3 subjects be excluded from the loratadine data analysis and 9 subjects be excluded from the desloratadine data analysis. The Sponsor has addressed the deficiency with this resubmission and that data will be reviewed by the biopharmaceutics reviewer. In addition, the Sponsor updated the safety data, which is the subject of this review.

## **Review**

### Data Previously Reviewed for NDA 21-891, S-000:

An integrated review of safety was conducted at the time of the approval of Claritin for hives relief on November 19, 2003. Safety data previously submitted to the NDA for Children's Claritin Chewable 5 mg consisted of safety data from the current bioequivalence trial, postmarketing adverse event data, overdose and abuse data, and a literature review. The Sponsor submitted these data in three steps: with the submission in August 2005, with a four-month safety update through November 26, 2005, and in March 2006 in response to an FDA request for additional data. These data were previously reviewed by this reviewer. The data timeframes and a brief data summary are shown below to provide a context.

- Data from the current bioequivalence trial, CL#2003-02
- Schering-Plough internal summary of adverse events for the period December 1, 2002-September 30, 2005, later supplemented to November 26, 2005 by the Sponsor.
- World Health Organization (WHO) adverse events for the period November 27, 2002-September 30, 2005
- FDA AERS data for the period November 27, 2002-May 31, 2005, supplemented to January 31, 2005 by this reviewer.
- the Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers from January 1, 2002-December 31, 2005

- Worldwide human and pre-clinical peer-reviewed literature for the period December 1, 2002-December 31, 2005

(Note: some of these data were limited to a start date of November 19, 2003 since that is the date of the last Claritin approval--for hives relief).

Four different subjects reported adverse events (AEs) during the bioequivalence study #CL 2003-02. Only one event (headache) was considered treatment-related, and all AEs were mild. No deaths, other SAEs, AEs causing discontinuation or adjustment of study medication, or severe AEs were reported for any subjects in this study.

The Sponsor's Claritin product safety update, outlined above, did not show any new safety concerns during these data timeframes. Postmarketing data submitted to the Sponsor or FDA, and a review of the literature, did not reveal any new safety concerns. In particular there were no cases of Torsade de Pointes, severe cardiac arrhythmias, or male congenital hypospadias that could be clearly related to loratadine.

#### Sponsor's Current Safety Data Update:

The Sponsor now provides data in two formats:

- The US OTC postmarketing data previously reported in the Safety Update submitted on March 3, 2006 to NDA 21-891, S-000, Amendment 4 for the period December 1, 2002-September 30, 2005 was combined with international data from the same period. This provides a worldwide view of the safety of loratadine-only products for the time period originally submitted for the safety update report submitted to this NDA. These data were previously reviewed and will not be discussed further.
- Adverse events temporally associated with loratadine only products from all worldwide sources during the supplemental period October 1, 2005-March 31, 2006. This data is from the following four sources:
  1. Schering-Plough internal adverse event database
  2. World Health Organization (WHO) database
  3. Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers
  4. Worldwide human and pre-clinical peer-reviewed literature

During the update period of October 1, 2005-March 31, 2006, there were 1,738 worldwide AEs associated with 1,190 total worldwide loratadine-only cases. Of these, 47 AEs met the criteria for a serious event and 1,691 were nonserious AEs. One death temporal to a loratadine-only product was reported during this period.

## Deaths

There were no reported deaths in study# CL2003-02. The proposed product is a new formulation and there are no reported deaths with its use. Worldwide, there was one death from October 1, 2005-March 31, 2006 associated with the oral solution. A consumer in the United Kingdom reported that her husband was receiving Clarityn Allergy Syrup (same dosage as the US OTC Children's Claritin Allergy Oral Solution) to reduce fluid secretions during his illness with lung cancer. He experienced a cough every time he took the Syrup. The family believed that his cough was due to the lung cancer. His cancer metastasized and he died of disease progression. Concomitant medications were unknown and were reported to change quickly because of the rapid progression of his disease. The consumer was being cared for at his home. The Sponsor notes that a quality analysis of the product did not reveal any reason for the cough or disease progression.

### *Comment:*

*1. The details of this case indicate that it is likely the product was not related to disease progression.*

Fatalities associated with the intentional overdose or abuses of the active ingredient, loratadine, are discussed in the section on Toxic Exposure Surveillance System (TESS) below (page 9).

### **Serious Worldwide AEs from October 1, 2005-March 31, 2006**

(From Schering-Plough internal adverse event database and World Health Organization database)

For reference, from December 1, 2002-September 30, 2005, there were few differences when comparing the serious adverse events by System, Organ, Class terminology (SOC) between the dosage forms. The oral solution (syrup) had a higher number of AEs related to Psychiatric Disorders (38 instances of crying, hallucinations or nightmares) than the other dosage forms of loratadine. Orally disintegrating tablets, although having a very low number of total serious AEs for both periods, had a higher rate of Hepatobiliary disorders (2 cases) that was not noted with other dosage forms. The Sponsor considered that neither one of these observations represents a safety signal but were related to the low absolute number of serious AEs with these two dosage forms (oral solution had 71 serious AEs, orally disintegrating tablets had 51).

In the follow up period of October 1, 2005- March 31, 2006, the trends for serious AEs (total of 47 SAEs) did not have marked differences among the products. The oral solution and orally disintegrating tablets had overall, a small number of serious AEs (9 AEs and 5 AEs, respectively). The most common SOC for serious AEs among all dosage forms was Nervous System Disorders and Psychiatric Disorders. Claritin Allergy Tablets also had Gastrointestinal and Immune System Disorders as a common SOC for serious AEs. It

should be noted that, for all dosage forms, the absolute number of serious AEs was very low for this period. Some examples of these serious cases are discussed below.

There were two reports of seizures temporally related to the use of Children's Claritin Allergy Oral Solution. One case involved a 6-year-old male who received 2 teaspoons of Children's Claritin Allergy Oral Solution for rhinorrhea, sneezing and nasal congestion on \_\_\_\_\_. Approximately 8 hours after ingestion, the child experienced a seizure that was characterized by loss of consciousness, foaming at the mouth, rigidity and a post-ictal state. The child was admitted to the hospital and underwent several diagnostic tests with no underlying cause for the event identified. The child was discharged from the hospital on \_\_\_\_\_. The product was discontinued. The second report of seizure was reported to occur in an 8-year-old male 14 hours after receiving 2 teaspoons of Children's Claritin Allergy Oral Solution. The child was transported to a hospital by ambulance and underwent medical testing. A Computed Tomography (CT) scan of his head revealed no abnormalities. A Magnetic Resonance Imaging (MRI) scan was to be performed and the child was scheduled to see a neurologist. The child was taking no other medications. No other information was available for this case.

There were two additional serious cases reported during this period for Children's Claritin Allergy Oral Solution. One case involved hallucinations reported to have occurred in an 83-year-old female after she received Children's Claritin Allergy Oral Solution as recommended by her physician for a rash. The 83-year-old also began to remove her clothes at the adult day care center. The reporter was the daughter who refused to provide additional information. The second case of hallucinations with Children's Claritin Allergy Oral Solution occurred in a 27-month old female who received one dose of Children's Claritin Allergy Oral Solution on February 15, 2006 for sneezing and rhinorrhea. The child's mother reported that her daughter experienced "psychotic episodes" in which she was hysterical and inconsolable as well as having hallucinations. The child received a second dose of Children's Claritin Allergy Oral Solution and experienced the same events. The events resolved once the product was discontinued. A quality investigation on the returned product did not reveal any quality issues or product variances.

For Claritin RediTabs Tablets, there was one report of seizure accompanied by monoplegia in an 11-year-old male. The child's father reported that he gave a Claritin RediTabs Tablet to his son. Approximately 5 hours after ingestion the child experienced a tonic-clonic seizure with myoclonic jerking. The father, who was a pharmacist, reported that his son did not have a change in mental status during the event and did not lose bowel or bladder function. The child was evaluated in an emergency department and medical tests for new onset seizure did not show any underlying cause for the seizure. The child experienced a similar event after receiving a Claritin RediTabs Tablet a second time. The cause of the event is unknown, but the product was discontinued.

For Claritin Allergy Tablets, the most common SOC for serious AEs was associated with Gastrointestinal (GI) Disorders and Investigations. Under the SOC Gastrointestinal Disorders, there were two reports of GI bleeding. In one case, a 61-year-old male

reported a previous bleeding from aspirin ingestion. He reported that he took Claritin Allergy Tablets for 5 days for allergy symptoms. The last dose was taken on December 28, 2005. On December 27, 2005, the consumer reported that he experienced abdominal pain and had one episode of diarrhea with bright red blood. He experienced a second episode of passing blood on December 28, 2005 and discontinued taking Claritin Allergy Tablets. There were no concomitant medications reported. The results of reserve sample testing indicated that all specifications were met at the time of release and there were no variances. The consumer did not return the product for evaluation.

In the second case of GI bleeding, a 51-year-old male reported that he passed blood in his stool after taking Claritin Allergy Tablets. He began taking the product on October 1, 2005 and discontinued the product on March 7, 2005. In February 2006 the consumer noticed an increasing amount of blood in his stool. He discontinued the Claritin Allergy Tablets and the event resolved. There was no other information reported by the consumer.

The reports of GI bleeding in these two cases were not confirmed by a health care professional and neither patient sought medical care. The frequency and rate of reports of gastrointestinal disorders do not indicate a trend suggestive of a relationship to exposure to loratadine.

Other serious AEs reported with the Claritin Allergy Tablet formulation included one report of a suicide gesture in which a 24-year-old female took an unknown amount of Claritin Allergy Tablets concomitantly with Tylenol Sinus Medication and Vick's Nyquil. The reporter refused to provide any additional information. There was one serious case in which a consumer with hypertension, NSAID use, hyperlipidemia, and thyroid disorder experienced a rise in blood pressure to a systolic of greater than 200 mmHg after taking Claritin Allergy Tablets. The consumer was intentionally taking more than the therapeutic dose of naproxen for arthritis pain. Her other concomitant medications at the time of the event included Benicar, Atenolol, Synthroid, Zetia, and Dyazide. She discontinued the use of naproxen and Claritin Allergy Tablets and her blood pressure normalized. Schering-Plough considered naproxen to be a co-suspect in the event.

There was one report of a 67-year-old female who experienced angioneurotic edema and anaphylaxis after taking Claritin Allergy Tablets and a pseudoephedrine product. The consumer did not have a positive allergic response when she subsequently underwent skin tests with sympathomimetic agents and oral challenge tests with increasing doses of loratadine. The cause of the reaction is unknown and the event resolved.

One serious Claritin Allergy Tablet case involved a 42-year-old female with underlying depression and anxiety as well as Gastro-Esophageal Reflux Disease (GERD) and hyperlipidemia who was hospitalized in \_\_\_\_\_ for an eye movement disorder and asthenopia after taking Claritin Allergy Tablets and Lexapro. Her diagnostic tests during the hospitalization did not reveal an underlying cause for the events. She discontinued both the Lexapro and Claritin Allergy Tablets and the events resolved. She experienced a

return of the symptoms after she began therapy with Lexapro in December 2005. Schering-Plough considered Lexapro to be a co-suspect for the event.

The majority of the remaining serious cases for Claritin Allergy tablets were reported in patients with multiple, chronic co-morbid conditions. There was one case of thrombocytopenia in an 81-year-old male with hypertension, deep vein thrombosis and chronic renal failure requiring dialysis. The patient was taking multiple medications, including loratadine tablets. The reporting health authority considered Clarityne (equivalent to Claritin Allergy Tablets) to be doubtfully related to the event.

There were several reports of allergic reactions, urticaria and one report of angioneurotic edema in patients taking multiple medications or having chronic disease states such as Chikungunya disease (a mosquito-borne viral infection involving fever and joint pains; the name comes from the Swahili for "that which bends up" that is a reference to the positions that victims take to relieve the joint pain). One case of hepatitis with eosinophilia was reported in a 48-year-old male who developed, on two separate occasions, elevated hepatic enzyme levels and eosinophilia, one event in 2001, and one in 2005. The patient was hospitalized and a liver biopsy showed acute hepatitis with eosinophils in the portal zones. Screens for hepatitis A, B and C were negative. The patient recovered without sequelae. The Health Authority coded the event as possibly related to Clarityn.

*Comment:*

*2. In the Sponsor's prior internal database review the cases of convulsions were mainly in patients with known seizure disorders, although in this resubmission the two patients did not have a seizure history. However, there is no control group for comparison, which precludes making any conclusion about seizure causality from loratadine. However, it is possible that loratadine could lower the seizure threshold, so these data bear further monitoring.*

**Non-Serious Adverse Events from the Schering-Plough AE Database**

In the period of October 1, 2005- March 31, 2006, Schering-Plough received 1,738 worldwide AEs associated with 1,190 total worldwide loratadine-only cases. Of these 1,691 were nonserious AEs in which loratadine was considered to be a suspect or co-suspect drug. Common nonserious adverse events are headache and drowsiness. There was no new information that suggests a substantial change in the incidence of common, less serious adverse events between the worldwide data for the previous reporting period December 1, 2002-September 30, 2005 and the period of October 1, 2005-March 31, 2006 presented in this Safety Update.

*Comment:*

*3. A review of these combined worldwide data (all loratadine-only formulations) as well as the data separated by Claritin dosage forms (tablet, oral solution, orally*

*disintegrating tablet) for the two reporting periods did not suggest any new safety trends or signals for loratadine-only products.*

#### **Toxic Exposure Surveillance System (TESS) Data:**

To evaluate overdose experience, the Sponsor analyzed data gathered from the Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers for the period December 1, 2005- May 31, 2006 for exposures to all loratadine-containing products.

During this period US Poison Control Centers received 3,300 reports of cases in which patients ingested loratadine in an overdose event. Two thirds involved exposure to loratadine alone. About 80% were unintentional and 20% intentional, with 70% of all cases in children 12 years of age or younger. There were 67 patients admitted to a critical care setting and 86 admitted to a non-critical care bed or a psychiatric inpatient facility. The range of estimated or confirmed tablets ingested was 0.25-300. The range of patient age was 1 month to 95 years old. About 90% of the patients in the reported cases had minimal or no symptoms. The most common treatment in those requiring intervention was gastric decontamination performed was oral activated charcoal followed by gastric lavage or a cathartic. Ten patients, ingesting an average of 6.6 substances, exhibited major clinical effects (defined as life threatening). There was one death, which occurred as a result of an intentional multi-drug overdose. No deaths occurred with loratadine-only exposure.

#### *Comments:*

*4. One month of the current time period reviewed overlaps with the previously reviewed time period, January 1, 2002- December 31, 2005. The Sponsor did not stratify the data to show only those cases reported in this one month overlap period. However the rate of case reports per month from December 1, 2005- May 31, 2006 (3,300/6 months or 650 per month) is slightly lower than that of 2005 (8,455/12 months or 704 per month).*

*5. In the original NDA submission of Children's Claritin the TESS data showed that the number of overdose reports in which loratadine was ingested increased each year from 2003-2005; however, only about 9% (2,000 of 22,000) of the reports involved loratadine as the sole overdose drug. The current rate of overdose cases is slightly lower and has no other worrisome data. Thus, the Sponsor concluded that the overdose data do not show a safety signal or trend that indicates that loratadine is unsafe, even in an overdose. This conclusion appears to be correct.*

#### **Literature Review**

The Sponsor reviewed the worldwide literature relevant to the safety of loratadine from January 2006 to April 2006. In addition they included any literature references of human exposure from 2005 that were not previously reported to FDA. This literature review yielded six references. Three of these (Ruiz-Montero et al., Heller, and Patriarca et al.)

were case reports, two were clinical trials (Hyo et al, Pineyro et al.), and one was an epidemiology report (reference 6, Kallen). These are discussed below.

#### Case Reports:

In a study designed to improve the detection of hepatotoxic adverse drug reactions among hospitalized patient, Ruiz-Montero et al. (2005) used clinical chemistry "alert signals" to investigated potential hepatotoxicity among 519,381 patients treated in a university, urban teaching hospital over a 12-month period. The alert signals included the following: >76 U/L of SGPT, or >0.6 mg/dL of conjugated bilirubin, or >80 U/L SGOT, >2 mg/dL total bilirubin, and 516 U/L of alkaline phosphatase (simultaneously). In this study, the presence of a single alert signal was sufficient to generate an investigation of the patient's case. The authors reported 2 subjects (a 52-year old female and a 43-year old male) having mild hepatocellular toxicity potentially attributed to loratadine. No additional case information surrounding these subjects was reported by the authors.

Heller (2005) reported a case study of a 34-year old male treated with multiple therapies for hypopigmented macules (Bier spots). Loratadine (10 mg daily) was administered for an unspecified duration as a treatment, but was discontinued, due to drowsiness.

As part of a desensitization protocol for a patient with peanut allergy, Patriarca et al. (2006) instructed the patient (38-year old female) to use loratadine (10 mg/day) and ranitidine (300 mg/day) during the rush phase and for 2 weeks during the maintenance therapy. The authors reported that she did not manifest side effects.

#### Clinical Trials:

Hyo et al. (2005) conducted a randomized, double blind, placebo-controlled trial in 113 participants with Japanese cedar pollinosis for two days. Participants were divided into four groups that included daily doses of loratadine, cetirizine, fexofenadine, or placebo. The authors noted that all study medications were well tolerated. No serious adverse events were reported. The most frequent adverse event was drowsiness, which was seen in two subjects in the loratadine arm and one subject in the placebo arm. No other adverse events were reported.

Pineyro-Lopez et al. (2006) conducted an open-label, randomized, 2-period crossover study in 32 subjects to evaluate the comparative bioavailability and tolerability of two different loratadine formulations used in Mexico. Subjects were given 400 mg of ketoconazole one day before the test period. On the test day they were given 200 mg of ketoconazole and two 10 mg tablets (a 20 mg total dose) of loratadine. They assessed tolerability via vital signs and a subject interview during the study and one week after the study. A two week washout period separated the crossover period. The investigators found that the test formulation of loratadine was bioequivalent to the reference formulation and that no adverse events were reported.

*Comment:*

*6. Other than saying that ketoconazole has been shown to increase loratadine levels, the investigators do not mention why they included dosing with ketoconazole in this bioequivalence trial. While the trial was small (32 subjects) and not designed to assess safety, and electrocardiograms were not reported, it appears that a single dose of loratadine 20 mg total might be safe with ketoconazole dosed for 2 days.*

Additional Information from Worldwide Literature:

The Sponsor refers to the Worldwide Literature for the loratadine section of the 4-month safety update submitted March 3, 2006 to NDA 21-952, S-000, Amendment 4. In a discussion of prenatal exposure and risk of hypospadias in male infants, a preliminary epidemiology report by Kallen et al. was referenced (reference 6, Kallen and Olausson 2001). The March 3, 2006 submission also included a discussion of a followup, short research communication confirming that the initial signal for hypospadias has not been confirmed upon continuing review of available data. This research communication was published in the International Journal of Medical Sciences (reference 7, Kallen and Olausson 2006).

**Summary**

The Sponsor resubmitted an analysis of biopharmaceutical data which is being reviewed by the biopharmaceutics reviewer. With this resubmission the Sponsor included an update of safety data from October 1, 2005-March 31, 2006 from the following sources:

- Schering-Plough internal adverse event database
- World Health Organization (WHO) database
- Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers
- Worldwide human and pre-clinical peer-reviewed literature

The Sponsor's and the WHO internal adverse event database showed 1738 adverse events of which 47 were serious. The TESS database showed 3,300 cases of overdose in which loratadine was ingested, a monthly rate of cases that was slightly lower than in the previously reviewed period from January 1, 2002-December 31, 2005. The literature review included a total of 7 articles. One article discussed hypospadias and reported no definite association of hypospadias in the male offspring of women exposed to loratadine during pregnancy.

**Conclusions**

The Sponsor's update of Claritin product safety did not show any new safety concerns during the period October 1, 2005-March 31, 2006. Postmarketing data submitted to the Sponsor or FDA, and a review of the literature, did not reveal any new safety concerns. In particular there were no cases of Torsade de Pointes, severe cardiac arrhythmias, or

male congenital hypospadias that could be clearly related to loratadine. These had been areas of interest with loratadine products.

The proposed 5-mg loratadine chewable tablet for the indication of the relief of upper respiratory allergy symptoms in adults and children 2 years of age and older has an acceptable safety profile for OTC marketing. Therefore, this application is approvable from the safety standpoint. Final approvability depends on the outcome of the re-analysis of the biopharmaceutical equivalence study #CL2003-02, which the biopharmaceutics reviewer is reviewing.

#### **Recommendations**

1. This application should be approved from the safety standpoint.
2. Since it is possible that loratadine could lower the seizure threshold, the post marketing data bear further monitoring.

Steven F. Osborne, M.D.  
Medical Officer, HFD-560

Concurrence

## References

1. Heller M.. Diffuse Bier spots. *Dermatology Online J.* 2005;11(4):2005.
2. Hyo S, Fujieda S, Kawada R, Kitazawa S, Takenaka H. The efficacy of short-term administration of 3 antihistamines vs placebo under natural exposure to Japanese cedar pollen. *Ann Allergy Asthma Immunol.* 2005; 94: 457-464.
3. Patriarca G, Nucera E, Pollanstrini E, de Pasquale T, et al. Oral rush desensitization in peanut allergy: a case report. *Digest. Dis. Sci.* 2006; 51: 471-473.
4. Pineyro-Lopez , A, Pineyro-Garza E, Torres- Alanis O, et al. Bioavailability of two oral formulations of loratadine 20 mg with concomitant ketoconazole: An open-label, randomized, two-period crossover comparison in healthy Mexican adult volunteers. *Clin Therap* 2006; 28: 110-115.
5. Montero A Ruiz, Quintana JA, and Saenz MJ et al.,. A strategy to improve the detection of drug- induced hepatotoxicity. *Rev Esp Enferm Dig (Madrid)* 2005; 155-160.
6. Kallen B and Olausson PO. (2001) Monitoring of maternal drug use and infant congenital malformations. Does loratadine cause hypospadias? *Int. J. Risk Safety in Med.* 14: 115-119.
7. Kallen B and Olausson PO. No increased risk of infant hypospadias after maternal use of loratadine in early pregnancy. *Int J Med Sciences* 2006; 3: 106-107.

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## CLINICAL REVIEW

Application Type NDA  
Submission Number 21-891  
Submission Code N-000

Letter Date August 3, 2005  
Stamp Date August 3, 2005  
PDUFA Goal Date June 3, 2006

Reviewer Name Steven F. Osborne, M.D.  
Review Completion Date March 24, 2006

Established Name loratadine  
(Proposed) Trade Name Claritin chewable tablets  
Therapeutic Class antihistamine  
Applicant Schering Plough Healthcare  
Products

Priority Designation Standard  
Formulation Chewable tablet

Dosing Regimen for children age 2 to under 6, one  
5-mg tablet daily; for adults and  
children 6 years of age and older,  
two 5-mg tablets daily

Indication Temporary relief of symptoms of  
runny nose, itchy, watery eyes,  
sneezing, and itching of the nose  
or throat, due to hay fever or other  
respiratory allergies

Intended Population age 2 years and older

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

The proposed 5-mg loratadine chewable tablet for the indication of the relief of upper respiratory allergy symptoms in adults and children 2 years of age and older has an acceptable safety profile for OTC marketing. Therefore, this application is approvable from the safety standpoint. Final approvability depends on the outcome of the biopharmaceutical equivalence study #CL2003-02, which the biopharmaceutics reviewer is reviewing.

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

No special post-marketing risk management activities are recommended.

#### 1.2.2 Required Phase 4

No special Phase 4 commitments are recommended.

#### 1.2.3 Other Phase 4 Requests

None.

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

Schering Plough Healthcare Products is seeking approval to market an immediate release chewable solid oral dosage form (tablet) containing 5 mg of loratadine for the indication of relief of hay fever and upper respiratory allergy symptoms in adults and children 2 years of age and older. The Sponsor currently markets an over-the-counter (OTC) 10-mg loratadine tablet and a 10-mg loratadine orally disintegrating tablet for adults and children 6 years and older for the same indication. The Sponsor also markets a 5-mg loratadine per teaspoon syrup for use in adults and children 2 years and older for the same indication.

#### 1.3.2 Efficacy

No controlled clinical efficacy trials were conducted. In support of efficacy, the Sponsor conducted a pharmacokinetic study comparing two formulations of loratadine (2 x 5 mg

chewable tablets and 1 x 10 mg tablet. The biopharmaceutical reviewer is reviewing the results of this bioequivalence trial.

Briefly, this was a randomized, open-label, single-dose, two-way crossover bioequivalence study in 48 healthy adult subjects. Subjects were randomly assigned to one of two treatment sequences (2 x 5 mg loratadine chewable tablets, followed by 1 x 10 mg loratadine tablet; or 1 x 10 mg loratadine tablet, followed by 2 x 5 mg loratadine chewable tablets), with single dose administration in each period. A 14-day washout period separated the two doses of study medication. For 120 hours following study drug administration the investigators collected blood for pharmacokinetic and safety monitoring, including plasma loratadine and desloratadine levels (metabolite). The test product (2 x 5 mg loratadine chewable tablets) was considered bioequivalent to the reference product (1 x 10 mg loratadine tablet) with 90% confidence intervals around the ratio of the least squares means for the  $C_{max}$  and AUC for loratadine and desloratadine all falling within the bioequivalence interval of 0.8 to 1.25.

### 1.3.3 Safety

An integrated review of safety was conducted at the time of the approval of Claritin for hives relief on November 19, 2003. Safety data submitted to this application consists of safety data from the current bioequivalence trial, overdose and abuse data, postmarketing adverse event data, and a literature review.

Four different subjects reported adverse events (AEs) during the bioequivalence study (1/48, 2.1% for the 2 x 5 mg group and 3/47, 6.4% for the 1 x 10 mg group. Only one event (headache) was considered treatment-related, and all AEs were mild. No deaths, other SAEs, AEs causing discontinuation or adjustment of study medication, or severe AEs were reported for any subjects in this study.

The Sponsor's 2005 Claritin product safety update did not show any new safety concerns during the period November 27, 2004-November 26, 2005. Postmarketing data submitted to the Sponsor or FDA, and a review of the literature, did not reveal any new safety concerns. In particular there were no cases of Torsade de Pointes, severe cardiac arrhythmias, or male congenital hypospadias that could be clearly related to loratadine.

### 1.3.4 Dosing Regimen and Administration

The proposed dosing regimen for this chewable tablet is one 5 mg tablet every 24 hours for children 2 to under 6 years of age, or two 5 mg tablets every 24 hours for adults and children 6 years and older.

### 1.3.5 Drug-Drug Interactions

No drug-drug interactions were evaluated in this safety update or in the current trial, Protocol # CL2003-02. However, in a FDA safety assessment for the OTC switch (May 12, 2000, reference 5) the potential interaction between loratadine with erythromycin, cimetidine, and ketoconazole

was reviewed. The latter three drugs combined with loratadine were not associated with adverse events, though an increase was noted in the area under the curve (AUC) values for loratadine and the active metabolite, descarboethoxyloratadine (desloratadine).

### 1.3.6 Special Populations

## 2 INTRODUCTION AND BACKGROUND

Claritin Tablets (loratadine 10 mg) are marketed for the relief of hay fever and upper respiratory allergy symptoms in adults and children 6 years of age and older and are available in the United States without a prescription since 2002. The Sponsor also markets Claritin Syrup (loratadine 5 mg per teaspoon) for the same indication in adults and children 2 years of age and older. In addition, the Sponsor markets an OTC 10-mg tablet for relief of hives in adults and children 6 years and older. A separate combination product with pseudoephedrine and loratadine, Claritin-D Non-Drowsy 12-Hour (and 24-Hour) Tablets, is available for the same indication.

Loratadine has been shown in animals and in man to be an orally effective, long-acting antihistamine devoid of central nervous system effects. Following oral administration, loratadine is rapidly metabolized to desloratadine, a pharmacologically active metabolite. The half-life of loratadine is 8 to 15 hours and the half-life of desloratadine is 12 to 24 hours.

The sponsor has developed a 5 mg loratadine tablet that is chewable, not buccal or sublingual. The proposed dosing regimen for this chewable tablet is one 5 mg tablet every 24 hours for children 2 to under 6 years of age or two 5 mg tablets every 24 hours for adults and children 6 years and older. To support this application, the Sponsor conducted one study designed to evaluate the bioequivalence of the test product (2 x 5 mg loratadine chewable tablets) and the reference product (1 x 10 mg loratadine tablet).

### 2.1 Product Information

Schering Plough Healthcare Products is seeking approval to market a 5-mg loratadine chewable tablet for the indication of the temporary relief of symptoms of runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat, due to hay fever or other upper respiratory allergies in adults and children 2 years of age and older. The proposed dosing directions are:

- adults and children 6 years and over: chew 2 tablets daily; not more than 2 tablets in 24 hours
- children 2 to under 6 years of age: chew 1 tablet daily; not more than 1 tablets in 24 hours
- consumers with liver or kidney disease: ask a doctor

## 2.2 Currently Available Treatment for Indications

Loratadine is available OTC in a 10-mg tablet, a 10-mg orally disintegrating tablet, and a 5-mg/teaspoon syrup for the relief of upper respiratory allergy symptoms. In addition, other antihistamines, both sedating and non-sedating, are available for the indication of the relief of upper respiratory allergy symptoms in adults and children 2 years of age and older.

## 2.3 Availability of Proposed Active Ingredient in the United States

See section 2.1 and 2.2.

## 2.4 Important Issues With Pharmacologically Related Products

Two other non-sedating antihistamines, terfenadine and astemizole, have been removed from the market due to the occurrence of a cardiac arrhythmia (Torsade de Pointes) that can occur when the blood level of terfenadine or astemizole is elevated. The blood level can become elevated beyond the therapeutic range when the respective drug is co-administered with another drug such as ketoconazole or erythromycin. To date, there have not been reports of the Torsade de Pointes cardiac arrhythmia with loratadine as the single suspect drug. See sections 7.2.9 and 8.6 for additional discussion on this topic.

The OTC label for loratadine warns consumers to avoid use if they ever had an allergic reaction to the product (Claritin) or any of its ingredients. Those with liver or kidney disease are advised to ask a doctor before use. Consumers are warned against taking more than directed, which may cause drowsiness.

## 2.5 Presubmission Regulatory Activity

The original NDA19-658 for loratadine (Claritin Tablets) was approved on April 12, 1993. Since then, NDAs have been approved for Claritin-D (loratadine-pseudoephedrine), Claritin syrup, and Claritin RediTabs Orally Disintegrating Tablets. On November 12, 2002 Claritin tablets were approved in a prescription-to-over-the-counter (Rx-OTC) switch. Since then, all Claritin products have been approved for OTC use. Table 1 below shows these products.

**Table 1. Claritin product approvals**

NDA #	Product Name	Year of Approval
19-658	Claritin Tablets	1993
19-670	Claritin-D 12 Hour Tablets	2002 (now discontinued)
20-470	Claritin-D 24 Hour Tablets	2002
20-641	Claritin Syrup	2002
20-704	Claritin RediTabs Orally Disintegrating Tablets	2003

## 2.6 Other Relevant Background Information

The Sponsor did not report any foreign market withdrawal of Claritin products.

### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### 3.1 CMC (and Product Microbiology, if Applicable)

Not applicable.

#### 3.2 Animal Pharmacology/Toxicology

No new animal data or toxicology data were submitted.

### 4.0 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

#### 4.1 Sources of Clinical Data

The Sponsor provided results of one biopharmaceutical equivalence trial, Protocol #CL2003-02, a safety update, and the proposed OTC labeling, all of which are considered in this review. The Sponsor referenced data from the original NDA. These data included the original NDA 20-641 for Claritin syrup, the pediatric labeling supplement, the Rx-to-OTC switch supplement (S-009) to NDA 20-641, and the Claritin Tablets NDA 19-658, S-016. These are shown below:

Reference is made to:

1. The Original New Drug Application, NDA 20-641 in its entirety, for CLARITIN (loratadine) Syrup, dated October 13, 1995, approved October 10, 1996. The Overall Index is provided in attachment 1 to this section.
2. CLARITIN Syrup NDA 20-641, Pediatric Labeling Supplement S-001, submitted on November 24, 1999 in response to the Official Written Request for pediatric studies in children ages 2 up to 6 years.
3. Claritin Syrup NDA 20-641, Rx-to-OTC Switch Supplement S-009, submitted on January 25, 2002, approved on November 27, 2002, and all subsequent Quarterly Reports.
4. Claritin Tablets NDA 19-658, S-016, submitted on March 23, 1999, approved on July 23, 1999, for composition of formula used as the RLD in the enclosed bioequivalence study.

#### 4.2 Tables of Clinical Studies

The Sponsor submitted one biopharmaceutical equivalence trial study to this NDA submission: Protocol #CL2003-02. The Sponsor referenced studies from prior submissions to NDA 20-641, the currently-marketed OTC Children's Claritin Syrup (loratadine 5 mg/ 5ml) for pre-clinical and clinical information, pediatric dosing, and foreign marketing history. The Sponsor also

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referenced NDA 19-658, the currently marketed OTC Claritin Tablet (loratadine 10 mg) that was used as the reference listed drug in study #CL2003-02.

### **4.3 Review Strategy**

This review covers the safety update. The efficacy portion of Protocol #CL2003-02 will be reviewed by the biopharmaceutics reviewer.

### **4.4 Data Quality and Integrity**

Not applicable. There were no DSI audits conducted for the study site or data analyses.

### **4.5 Compliance with Good Clinical Practices**

Not applicable to this review.

### **4.6 Financial Disclosures**

The Sponsor conducted one new study, Protocol #CL2003-02, that involved only one clinical site and only one investigator. The Sponsor submitted Form 3454 certifying no financial interest by the investigator. There were no financial disclosures that would cast doubt on the findings.

## **5 CLINICAL PHARMACOLOGY**

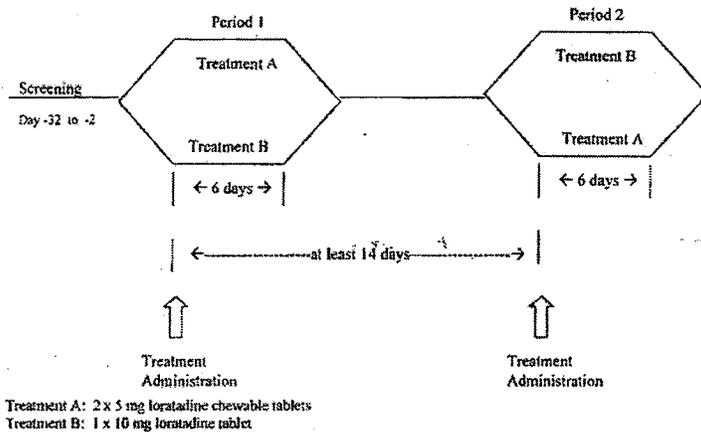
### **5.1 PHARMACOKINETICS**

The proposed indication for Claritin chewable tablets is the temporary relief of symptoms due to hay fever or other respiratory allergies. The biopharmaceutical reviewer is reviewing the only study for this review, study # CL2003-02, which assessed the bioequivalence of orally administered Claritin Chewable Tablets (2 x 5 mg loratadine tablets) and the reference product, Claritin Tablet (loratadine 10 mg). Below is a brief summary of this study.

In study # CL2003-02, 48 healthy adult subjects, ages 18-45 years old, were admitted to the randomized, open-label, single-dose, two-way crossover, bioequivalence study. The study was not blinded to the subjects or the investigator; however, laboratory personnel were blinded to the treatment sequence. Subjects were screened for eligibility within 32 days of receiving the first dose of study medication. Eligible subjects reported to the study clinic at least 12 hours prior to the first dose of study medication. Subjects were randomly assigned to one of two treatment sequences (2 x 5 mg loratadine chewable tablets, then 1 x 10 mg loratadine tablet; or, 1 x 10 mg loratadine tablet then 2 x 5 mg loratadine chewable tablets), with single dose administration in each period. A 14-day washout period separated the two doses of study medication. All subjects fasted for at least 10 hours before dosing and remained fasted for four hours post drug treatment. Subjects were confined to the study site on the day prior to study drug administration and for 120

hours following study drug administration for collection of pharmacokinetic blood samples and safety monitoring. The study design schematic and treatments administered appears in Figure 1 below. Table 2 below shows the study tests (assessments) and procedures from Day -32 to Day 6.

**Figure 1. Study Design Schematic**



**Treatments administered**

Subjects were randomly assigned to one of two treatment sequences as follows:  
 Sequence 1: 2 x 5 mg loratadine chewable tablets → 1 x 10 mg loratadine tablet  
 Sequence 2: 1 x 10 mg loratadine tablet → 2 x 5 mg loratadine chewable tablets.

**Table 2. Study assessments and procedures**

Evaluation	Screening	Periods* 1 & 2							
	(Day -32 to -2)	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	
Informed Consent <sup>b</sup>	X								
Inclusion/Exclusion Criteria Review	X								
Concomitant Medication Review	X	X							
Medical History	X								
Physical Exam	X							X <sup>b</sup>	
Body Weight (kg)	X								
Height (cm)	X								
Laboratory Tests <sup>c</sup>	X	X						X <sup>h</sup>	
HIV/HbsAg/Hep C Antibody	X								
Urine Cotinine Test	X								
Urine Drug Screen	X	X							
ECG <sup>d</sup>	X							X <sup>b</sup>	
Serum/Urine Pregnancy Test	X	X						X <sup>h</sup>	
Vital Signs <sup>e</sup>	X	X	X	X	X	X	X	X	
Volunteer Confinement <sup>f</sup>		X	X	X	X	X	X	X	
Treatment Administration			X						
Blood Samples <sup>g</sup>			X	X	X	X	X	X	

The test product (2 x 5 mg loratadine chewable tablets) was considered bioequivalent to the reference product (1 x 10 mg loratadine tablet) with 90% confidence intervals around the ratio of the least squares means for the C<sub>max</sub> and AUC for loratadine and desloratadine all falling within

the bioequivalence interval of 0.8 to 1.25. Of note, the Sponsor performed a fasted study, but not a fed study.

*Comment:*

*The study should have included a fed study. The biopharmaceutics reviewer will address how this will impact the approvability of the study.*

## 5.2 Pharmacodynamics

No new pharmacodynamic data were submitted with this application.

## 5.3 Exposure-Response Relationships

No new exposure-response relationship data were submitted with this application.

## 6 INTEGRATED REVIEW OF EFFICACY

Efficacy of the product is extrapolated based on PK data. No new efficacy studies were performed with this formulation.

## 7 INTEGRATED REVIEW OF SAFETY

The Integrated Summary of Safety (ISS) submitted on August 3, 2005 included:

- safety data gathered during the PK study, #CL2003-02.

The four-month safety update submitted on March 3, 2006 included the following data, which is discussed in section 7.2.9 of this review:

- Sponsor-received adverse events for the period November 27, 2004-November 26, 2005
- Update of the FDA Adverse Event Reporting System (AERS) database for the period November 1, 2003-January 31, 2006.
- Literature update for loratadine for the period November 1, 2003-December 31, 2005.

### 7.1 Methods and Findings

The Sponsor defined an adverse event (AE) as any untoward medical occurrence or unfavorable and unintended sign in a subject administered a pharmaceutical product, whether or not considered related to the use of that product. This included the onset of new illness and the exacerbation of pre-existing conditions. A serious adverse event (SAE) was any adverse drug experience occurring at any dose that resulted in any of the following outcomes:

- death
- life-threatening AE (i.e., one that placed the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred)

- persistent or significant disability/incapacity
- required in-patient hospitalization, or prolonged hospitalization
- congenital anomaly or birth defect

Historically, from clinical trials, the most common AEs reported with the use of loratadine are headache, somnolence, fatigue, and dry mouth. All subjects in study #CL2003-02, who received at least one dose of study drug, were included in the safety analyses. The occurrence of these events was recorded in the subject's medical records and on the CRF, regardless of causality. All AEs were followed to satisfactory resolution or stabilization of the event(s).

### **7.1.1 Deaths**

There were no reported deaths in study# CL2003-02. The proposed product is a new formulation and there are no reported deaths with its use. Worldwide, there were two reported deaths in the AERS Database for loratadine during the period November 1, 2003-December 31, 2005. One death occurred overseas in 2004 in an elderly Japanese male on dialysis who had a cerebral hemorrhage. The other death was reported in 2004, but occurred in 2001, in a male of unstated age who had heart disease and coronary artery surgery. Followup disclosed he had not taken Claritin for three years before his death. Thus, both of the deaths were unlikely related to loratadine. Fatalities associated with the intentional overdose or abuses of the active ingredient, loratadine, are discussed in sections 7.1.16 and 7.1.17 of this review.

### **7.1.2 Other Serious Adverse Events**

No serious AEs occurred during study # CL2003-02.

### **7.1.3 Dropouts and Other Significant Adverse Events**

Subject nos. 16 and 43 were dropped from study # CL2003-02 due to a withdrawal of consent and noncompliance (failed drug test), respectively. No subjects dropped out due to an adverse event.

#### **7.1.3.1 Overall profile of dropouts**

Subject #16, a 22 year old female, withdrew consent but did not state a reason on Day 18 of sequence two (see Figure 1 for sequence). Subject # 43, a 37 year old female, was removed from study #CL2003-02 on Day 15 of sequence one due to a positive drug screen.

#### **7.1.3.2 Adverse events associated with dropouts**

The two dropouts in study # CL2003-02 were not associated with adverse events.

### 7.1.3.3 Other significant adverse events

Not applicable.

### 7.1.4 Other Search Strategies

Not applicable.

### 7.1.5 Common Adverse Events

The number of subjects reporting treatment-emergent AEs was low for both treatment groups (1/48, 2.1% for the 2 x 5 mg group and 3/47, 6.4% for the 1 x 10 mg group; see Table 3 below). Three (3/47, 6.4%) subjects in the 1 x 10 mg group reported headache, eye redness, and allergy to arthropod bite, respectively, and one (1/48, 2.1%) subject in the 2 x 5 mg group reported dermatitis NOS.

**Table 3. Overall summary of adverse events**

Category	2 x 5 mg	1 x 10 mg	Overall
	N=48	N=47	N=48
	Number (%) of Subjects		
Any AE	1 (2.1%)	3 (6.4%)	4 (8.3%)
Treatment-emergent AE	1 (2.1%)	3 (6.4%)	4 (8.3%)
Treatment-related AE	0	1 (2.1%)	1 (2.1%)
SAEs, including death	0	0	0
AE causing discontinuation of study medication	0	0	0
AE causing interruption of study medication or dosing change	0	0	0
Severe AE	0	0	0

AE=Adverse event; SAE=Serious adverse event

Note: 2 x 5 mg=test product; 1 x 10 mg=reference product

Treatment-emergent AEs in MedDRA terminology are shown in Table 4 below.

**Table 4. Incidence of treatment-emergent AEs**

MedDRA System Organ Class MedDRA Preferred Term	2 x 5 mg	1 x 10 mg	Overall
	N=48	N=47	N=48
	Number (%) of Subjects		
Number of Subjects with an AE	1 (2.1%)	3 (6.4%)	4 (8.3%)
Eye Disorders	0	1 (2.1%)	1 (2.1%)
Eye redness	0	1 (2.1%)	1 (2.1%)
Immune System Disorders	0	1 (2.1%)	1 (2.1%)
Allergy to arthropod bite	0	1 (2.1%)	1 (2.1%)
Nervous System Disorders	0	1 (2.1%)	1 (2.1%)
Headache*	0	1 (2.1%)	1 (2.1%)
Skin and Subcutaneous Tissue Disorders	1 (2.1%)	0	1 (2.1%)
Dermatitis NOS	1 (2.1%)	0	1 (2.1%)

\*Headache (mild) was the only AE reported that was considered treatment-related

NOS=Not otherwise specified

Note: 2 x 5 mg=test product; 1 x 10 mg=reference product

#### 7.1.5.1 Eliciting adverse events data in the development program

Safety was assessed through the monitoring of adverse events (AEs), vital signs, clinical laboratory evaluations, physical examinations, and 12-lead electrocardiograms (see Table 2). Subjects were questioned or examined by the investigator for evidence of AEs. A diary was not kept by the subjects.

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms were appropriate. MedDRA terminology was used.

#### 7.1.5.3 Incidence of common adverse events

The only adverse event associated with loratadine use in study #CL2003-02 was one incidence of headache.

#### 7.1.5.4 Common adverse event tables

The number of subjects exposed and the number of adverse events was too few to assess the incidence of the more common or less common adverse events.

#### 7.1.5.5 Identifying common and drug-related adverse events

Only one event (headache) was considered treatment-related, and all AEs were mild.

#### 7.1.5.6 Additional analyses and explorations

Not applicable.

#### 7.1.6 Less Common Adverse Events

The number of subjects exposed and the number of adverse events was too few to assess the incidence of the more common or less common adverse events.

#### 7.1.7 Laboratory Findings

Mean values for serum chemistry parameters remained within normal range at every time point during the study. Mean values for urinalysis parameters of pH and specific gravity remained within normal range at every time point during the study.

Mean values for hematology parameters remained within normal range at every time point during the study. The mean (SD) value for hemoglobin was 13.25 g/ dL (1.267) at the End of Study (normal range: 14.0-18.0 g/ dL for males and 12.0- 16.0 g/ dL for females); the mean (SD) values for hematocrit were 38.92% (3.623) at Day - 1, Period 2 and 38.28% ( 3.165) at the

End of Study (normal range: 39.0- 54.0% for males and 34.0- 47.0% for females). The Sponsor notes that serial blood samples were drawn for pharmacokinetics and that approximately half of all subjects in this study were females, so an average value just below lower limit of normal range for males for these parameters is not surprising.

The number of subjects with abnormal serum chemistry values was generally low throughout the study. Abnormal potassium, glucose, phosphorus, SGOT, and triglycerides were observed in a few subjects as noted in Table 5 below.

**Table 5. Summary of Abnormalities of Serum Chemistry Parameters**

Parameter	Screening N=48	Period 1, Day -1 N=48	Period 2, Day -2 N=48	End of Study N=48
	Number (%) of Subjects			
Potassium	0	1 (2.1%)	1 (2.1%)	0
Glucose	1 (2.1%)	3 (6.3%)	0	1 (2.1%)
Phosphorus	1 (2.1%)	7 (14.6%)	2 (4.2%)	0
SGOT	1 (2.1%)	0	2 (4.2%)	0
Triglycerides	2 (4.2%)	4 (8.3%)	1 (2.1%)	6 (12.5%)

*Comment:*

*The 14.6% abnormalities in phosphorus in Period 1, Day-1, Table 5 above are noted but are without explanation. The abnormalities are not related to loratadine since it is a Day -1 finding.*

The number of subjects with abnormal hematology values was generally low except for hemoglobin, hematocrit, and RBCs. The number of subjects with abnormal hematology values increased from screening to any post-baseline assessment for the following parameters: hemoglobin, hematocrit, RBC, MCHC, % monocytes, % eosinophils, and % large unstained cells (Table 6 below). Again, the increase in abnormalities for these parameters is not surprising considering that serial blood samples were drawn for pharmacokinetics.

**Table 6. Summary of Abnormalities of Hematology Parameters**

Parameter	Screening N=48	Period 1, Day -1 N=48	Period 2, Day -2 N=48	End of Study N=48
	Number (%) of Subjects			
Hemoglobin	12 (25%)	12 (25%)	18 (37.5%)	15 (31.3%)
Hematocrit	3 (6.3%)	3 (6.3%)	7 (14.6%)	9 (18.8%)
RBC	10 (20.8%)	9 (18.8%)	20 (41.7%)	15 (31.3%)
MCHC	3 (6.3%)	3 (6.3%)	1 (2.1%)	4 (8.3%)
Monocytes (%)	0	0	1 (2.1%)	0
Eosinophils (%)	0	0	0	1 (2.1%)
Large unstained cells (%)	2 (4.2%)	1 (2.1%)	4 (8.3%)	4 (8.3%)

*Comment:*

*The Sponsor considered none of the abnormal laboratory values reported during study CL2003-02 to be clinically significant, and the Sponsor noted no clinical laboratory-related adverse events during the study.*

7.1.7.1 Overview of laboratory testing in the development program

The safety and pharmacokinetic measures used in this study are standard for Phase I bioequivalence studies. The criteria for bioequivalence (90% confidence intervals within 80 to 125% of the ratio of the LS Means for C<sub>max</sub> and AUC) are consistent with the FDA guidance for the establishment of bioequivalence of orally administered drug products.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

There was no control group in study #CL2003-02; therefore, drug-control comparisons were not performed.

7.1.7.3 Standard analyses and explorations of laboratory data

Mean values for serum chemistry parameters remained within normal range at every time point during the study. Mean values for hematology parameters remained within normal range at every time point during the study. The mean value for hemoglobin was 13.25 g/dL (s.d.1.267) at the End of Study (normal range: 14.0-18.0 g/dL for males and 12.0-16.0 g/dL for females).

7.1.7.3.1 Analyses focused on measures of central tendency

Not applicable.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

None.

7.1.7.4 Additional analyses and explorations

12-Lead ECGs were recorded at 25 mm/s and included results for ventricular rate, PR, QRS, QT, and QTc intervals.

7.1.7.5 Special assessments

Not applicable.

### 7.1.8 Vital Signs

Vital signs were obtained after the subject had been in a seated position for 3 minutes. Most mean values for vital sign measurements were within normal range. The only clinically significant change in vital sign measurements was an increase in pulse rate for one subject in the 2 x 5 mg group. Her pulse rate was 130 on Day 6 compared to 99 at screening. No AE related to this change was reported, and the subject's pulse returned to within baseline limits by the end of the study.

#### 7.1.8.1 Overview of vital signs testing in the development program

Vital signs were tested daily on Day-1 through Day 6.

#### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

#### 7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable.

##### 7.1.8.3.1 Analyses focused on measures of central tendencies

Not applicable.

##### 7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

##### 7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no marked outliers or dropouts for vital sign abnormalities in study # CL2003-02.

#### 7.1.8.4 Additional analyses and explorations

Not applicable.

### 7.1.9 Electrocardiograms (ECGs)

No clinically significant electrocardiogram findings were reported for any subjects at the follow-up assessment in study # CL2003-02.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing looks for abnormalities in cardiac rhythm, such as Torsade de Pointes, or in cardiac intervals, such as the QT interval. No clinically significant electrocardiogram findings were reported in study # CL2003-02.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable.

7.1.9.3.1 Analyses focused on measures of central tendency

Not applicable.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Not applicable.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

No immunogenicity studies were performed for this submission. There are no known immunogenicity issues related to loratadine.

7.1.11 Human Carcinogenicity

There are no known carcinogenicity issues related to loratadine.

7.1.12 Special Safety Studies

There were no special safety studies requested or performed for this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no history of a withdrawal syndrome for loratadine. The FDA Adverse Event Reporting System (AERS) database for the period November 1, 2003-January 31, 2006 found one subject, an 18 year old female, who abused Claritin in a suicide attempt.

#### 7.1.14 Human Reproduction and Pregnancy Data

No human reproduction or pregnancy studies were performed for this submission.

#### 7.1.15 Assessment of Effect on Growth

There were no data submitted on effects on growth.

#### 7.1.16 Overdose Experience

The Sponsor submitted data regarding an overdose experience on March 3, 2006. This data is reviewed in section 7.2.9.

As noted in section 7.1.13 there was one subject, an 18-year-old female, in the FDA Adverse Event Reporting System (AERS) database for the period November 1, 2003-January 31, 2006 who overdosed on Claritin in a multi-drug overdose suicide attempt.

#### 7.1.17 Postmarketing Experience

Postmarketing experience data submitted to this NDA comes from two different sources: the Sponsor's database and FDA's AERS database. With this submission the Sponsor submitted adverse event data for the bioequivalence study #CL2003-02. Subsequently, the Sponsor submitted an annual report for NDAs 19-658, 20-641, and 20-704 that covered the period November 27, 2004-November 26, 2005 and included postmarketing adverse event data and literature references. The Sponsor reported no new significant safety data during this one year period for any of the three NDAs. The Sponsor submitted abstracts or summaries of 4 non-clinical laboratory studies and 23 clinical laboratory studies conducted during this period in which loratadine was mentioned. See the section 8.6 (Literature Review) for comments on these 27 references.

#### AERS Database

This reviewer queried the AERS Database for FDA individual safety reports (ISRs, MedWatch forms) describing all serious adverse events worldwide, expected and unexpected, reported for Claritin as a primary drug suspect since approval of the most recent Claritin NDA in November 2003. These loratadine products were manufactured by Schering Corporation or its subsidiaries (Schering Plough, Schering Pharmaceutical Corporation, Schering Plough Healthcare Products, Inc, Schering Plough Research Institute). This query excluded Claritin combination products (i.e. loratadine-pseudoephedrine) or generic loratadine manufactured by other Sponsors. See Appendix 1 at the end of this review for the complete search criteria. The query yielded a total of

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105 reports for Claritin products from November 1, 2003-January 31, 2006 listing Schering Corporation's Claritin-loratadine as the suspect drug. There were 2 deaths and 24 life-threatening reactions. Twenty two of the reports were domestic (USA) and 83 were foreign (non-USA). These results are shown for the referenced Claritin products in Table 8 below:

**Table 8. Serious AEs with Schering Corporation\*-manufactured loratadine as primary drug suspect. Cases by ISR type; domestic and foreign.**

FDA AERS Database Cases By ISR Type November 2003 to January 2006									
ISR Type	Total	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention	
Expected (Y-Dist)	163	2	84	71	7	5	23	0	
Domestic	21	1	14	9	2	1	3	0	
Foreign	82	1	80	62	5	4	20	0	
Unexpected (Y-Dist)	1	0	1	1	0	0	1	0	
Domestic	1	0	1	1	0	0	0	0	
Foreign	0	0	0	0	0	0	1	0	
	165	2	86	73	7	5	24	0	

Table 9 below shows the breakdown of the AEs for each Claritin-referenced product.

**Table 9. Serious AEs with Schering Corporation (or subsidiaries)-manufactured loratadine as primary drug suspect. Cases by formulation.**

Formulation	Total	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Claritin Tablets 10mg	93	2	59	6	5	21	0	
Claritin syrup	10	0	8	1	0	3	0	
Claritin Redi-tabs 10mg	7	0	6	0	0	0	0	

Tables 10, and 11 below show the same data by year and quarter and by gender and age group, respectively.

**Table 10. Serious AEs with Schering Corporation\*-manufactured loratadine as primary drug suspect. Cases by year and quarter.**

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**FDA AERS Database**  
**Cases By Year and Quarter**  
**November 2003 to January 2006**

Year	Quarter	Total	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
2003	4	16	1	15	10	1	2	3	0
	<b>Yearly Totals:</b>	16	1	15	10	1	2	3	0
2004	1	9	0	8	6	1	1	1	0
	2	13	0	12	9	0	1	3	0
	3	17	1	16	10	2	0	6	0
	4	5	0	5	3	1	0	2	0
	<b>Yearly Totals:</b>	44	1	41	28	4	3	12	0
2005	1	6	0	6	4	1	1	1	0
	2	14	0	11	10	3	0	2	0
	3	15	0	14	12	0	0	5	0
	4	8	0	7	7	0	0	1	0
	<b>Yearly Totals:</b>	43	0	38	33	2	1	9	0
2006	1	2	0	2	2	0	0	0	0
	<b>Yearly Totals:</b>	2	0	2	2	0	0	0	0
<b>Grand Totals:</b>		105	2	96	73	7	5	24	0

**Table 11. Serious AEs with Schering Corporation\*-manufactured loratadine as primary drug suspect. Cases by gender and age group.**

**FDA AERS Database**  
**Cases By Gender and Age Group**  
**November 2003 to January 2006**

Gender	Age Group	Total	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Female	Null	1	0	1	0	0	1	0	0
	Newborn	0	0	0	0	0	0	0	0
	Infant	3	0	2	2	0	0	1	0
	Child	4	0	3	2	1	0	0	0
	Adolescent	2	0	1	1	0	0	0	0
	Adult	30	0	28	22	2	1	8	0
	Elderly	17	0	16	14	0	0	4	0
	<b>Gender Total:</b>	58	0	51	41	3	2	13	0
Male	Null	3	0	3	2	1	0	1	0
	Newborn	1	0	1	0	0	1	0	0
	Infant	2	0	2	2	0	0	2	0
	Child	6	0	5	5	0	0	2	0
	Adolescent	3	0	2	1	0	0	1	0
	Adult	21	0	21	15	3	0	3	0
	Elderly	9	1	7	6	0	0	0	0
	<b>Gender Total:</b>	44	1	41	31	4	1	11	0
Not Specified	Null	5	1	4	1	0	2	0	0
	Newborn	0	0	0	0	0	0	0	0
	Infant	0	0	0	0	0	0	0	0
	Child	0	0	0	0	0	0	0	0
	Adolescent	0	0	0	0	0	0	0	0
	Adult	0	0	0	0	0	0	0	0
	Elderly	0	0	0	0	0	0	0	0
	<b>Gender Total:</b>	5	1	4	1	0	2	0	0

**Comment:**

*The two deaths were in elderly people with concomitant illnesses and who were taking other medications. There were no deaths in the younger age groups targeted for Claritin 5 mg Chewable Tablets.*

Table 12 below shows the top ten categories of serious AEs by body system or organ class with particular types of AEs of interest noted, such as Torsade de Pointes.

**Table 12. Serious adverse events from AERS database with loratadine as suspect medication\***

<i>Body System/Organ Class</i>	<i>Number of Serious Cases</i>	<i>Particular Type of AE</i>
cardiac disorders	16	3 Torsade de Pointes
gastrointestinal disorders	15	
general disorders	39	
hepatobiliary disorders	18	
infections and infestations	15	
investigations (laboratory)	35	
nervous system disorders	35	24 somnolence or stupor
psychiatric disorders	16	
respiratory, thoracic, and mediastinal disorders	15	14 dyspnea
skin and subcutaneous tissue disorders	40	4 Stevens-Johnson syndrome

\*Top ten categories; each case may have multiple preferred terms

**Comments:**

*1. The 3 AEs of Torsade de Pointes are actually only two cases, since one case of a 73 year old female with recurrent ventricular tachycardia taking loratadine and amiodarone was doubly reported. In that case the amiodarone was a co-suspect. The other case was a 65 year old female*

*2. The 24 cases of somnolence or stupor shows that some patients experience drowsiness, occasionally severe despite the "non-sedating" characteristic of loratadine. The label appropriately states that "taking more than directed may cause drowsiness", though there is no mention of taking more than directed for these cases.*

On November 30, 2005, FDA requested additional safety data to include postmarketing safety data and worldwide safety data for loratadine, a summary of adverse event data from the AERS database and a summary of safety and adverse event data from the literature on loratadine, all for the time period November 19, 2003-present (the date of the last Claritin approval, for hives relief, was November 19, 2003). See section 7.2.9 for the Sponsor's submission of additional safety data.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The updated safety database comprised 48 subjects in study # CL2003-02. Four subjects had nonserious adverse events.

#### Protocol Deviations

Seven subjects did not have a BMI between 19 and 27 kg/m<sup>2</sup> at the screening visit. Exemptions were granted for all 7 subjects. Subject 043 had a positive urine drug screen at check-in to Period 2 and was discontinued from the study. Although the protocol specified that end of study ECGs would be performed after collection of the 120-hour PK sample, ECGs were performed prior to blood sampling to accommodate the clinic schedule.

#### 7.2.1.1 Study type and design/patient enumeration

The Sponsor submitted one study, Protocol # CL2003-02, to support the application. This study was randomized, open, and single-dose. Laboratory personnel were blinded.

#### 7.2.1.2 Demographics

Forty-eight subjects (23 males, 25 females; 40 Hispanics, 6 African Americans, 1 Caucasian, and 1 other) were enrolled in this study. The subjects were between the ages of 19 and 45 inclusive (mean = 33.2 years). The subjects' mean height was 165.0 centimeters (range 140-188 centimeters) and the subjects' mean weight was 66.3 kilograms (range 48-92 kilograms). This data is shown in Table 13 below.

**Table 13. Demographics of Protocol # CL2003-02 by sequence and overall totals.**

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Characteristic	Sequence 1 (n=24)	Sequence 2 (n=24)	Overall (n=48)
Age (years)			
Mean (SD)	33.3 (9.75)	33.2 (6.88)	33.2 (8.34)
Median	37.5	35.5	37.0
(Min, Max)	(19, 45)	(22, 44)	(19, 45)
BMI (kg/m <sup>2</sup> )			
Mean (SD)	24.1 (2.40)	24.4 (2.33)	24.2 (2.35)
Median	24.0	24.3	24.2
(Min, Max)	(20, 28)	(20, 28)	(20, 28)
Gender		n (%)	
Female	15 (62.5%)	10 (41.7%)	25 (52.1%)
Male	9 (37.5%)	14 (58.3%)	23 (47.9%)
Ethnic Group		n (%)	
Hispanic	19 (79.2%)	21 (87.5%)	40 (83.3%)
African American	4 (16.7%)	2 (8.3%)	6 (12.5%)
Caucasian	1 (4.2%)	0	1 (2.1%)
Other	0	1 (4.2%)	1 (2.1%)
Asian	0	0	0

BMI=Body mass index; Max=Maximum; Min=Minimum; SD=Standard deviation

### 7.2.1.3 Extent of exposure (dose/duration)

Forty-seven of the 48 subjects received both single doses of study medication. Subject 043 (Sequence 1) was discontinued from the study for a positive urine drug screen at check-in to Period 2, prior to receiving the 1<sup>st</sup> x 10 mg dose.

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Data from the Sponsor's safety update is discussed in section 7.1.17 and data from the AERS Database is discussed in section 7.2.9. Safety data from the literature is discussed in section 8.6 of this review.

### 7.2.3 Adequacy of Overall Clinical Experience

This is a supplemental application. The original submission of this NDA contained full safety data for the ingredient, loratadine. No safety issues were identified at the time of the original application.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal or in vitro data were not provided in this application.

### 7.2.5 Adequacy of Routine Clinical Testing

Not applicable for this supplemental safety data submission.

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The Sponsor provided sufficient data to characterize the pharmacological profile of loratadine during the original submission of the NDA.

#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

From a clinical safety perspective there are no recommendations for further studies.

#### 7.2.8 Assessment of Quality and Completeness of Data

From a clinical safety perspective, this application is adequate and complete.

#### 7.2.9 Additional Submissions, Including Safety Update

On March 3, 2006 the Sponsor submitted the following additional data:

- Schering-Plough internal summary of adverse events for the period December 1, 2002-September 30, 2005
- World Health Organization (WHO) adverse events for the period November 27, 2002-September 30, 2005
- FDA AERS data for the period November 27, 2002-May 31, 2005
- the Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers from January 1, 2002-December 31, 2005
- Worldwide human and pre-clinical peer-reviewed literature for the period December 1, 2002-December 31, 2005

The Schering-Plough internal summary of adverse events for the period December 1, 2002-September 30, 2005 yielded 15,604 non-serious AEs and 169 serious AEs. The 169 cases were similar to the serious AEs discussed in section 7.1.17; however, there were 3 deaths, 13 cardiac disorders including isolated palpitations, wandering pacemaker, bradycardia, and 1 case of Torsade de Pointes. Eight cases of convulsions were noted in people with known seizure disorders, except for one case in a child with fever. The three deaths were in early 2003, prior to the period of interest for this review. The Sponsor did not list the exact dates for the seizure cases or the case of Torsade de Pointes.

#### *Comment:*

*The Sponsor's internal summary of adverse events for the period December 1, 2002-September 30, 2005 is not stratified to show only cases since the November 19, 2003 approval for Claritin for hives relief. However, the data is similar to that discussed in section 7.1.17.*

The Sponsor's AERS Database submission, covering the period November 27, 2002-May 31, 2005 yielded 226 serious adverse events, including 4 deaths and 26 convulsions. All 4 deaths and half of these serious AEs occurred in 2003. Fourteen of the convulsions were in 2005. The Sponsor's search terms were the same as this reviewer's, except that the Sponsor included all

loratadine products (instead of Claritin-brand or Schering Corporations loratadine). The Sponsor's search yielded more cases than this reviewer's search, possibly due to the wider scope and additional time frame of November 27, 2002--November 18, 2003. Analysis of the four deaths showed three were in subjects older than 65 years and one had an unspecified age. Three were taking loratadine for less than one week, while the length of use was unspecified in one case. The Sponsor did not provide the case forms or specific dates of the deaths.

*Comment:*

*Part of this time period for the Sponsor's AERS Database submission includes prescription use, since the first OTC approval for Claritin was in November 2002. The Sponsor did not stratify the data to show only those cases reported since the November 19, 2003 approval for Claritin for hives relief. In the Sponsor's internal database review the cases of convulsions were in patients with known seizure disorders, plus there is no control group for comparison, which precludes making any conclusion about seizure causality from loratadine. However, it is possible that loratadine could lower the seizure threshold, so these data bear further monitoring.*

To evaluate overdose experience, the Sponsor analyzed data gathered from the Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers for the period January 1, 2002- December 31, 2005. During this period, US Poison Control Centers received 22,000 reports in which loratadine was ingested in an overdose event. A total of 393 reports were from December 2002 (none earlier in 2002), 5,770 from 2003, 7,427 from 2004, and 8,455 from 2005. About 19,000 cases were unintentional and 3,000 intentional. Eighty percent involved exposure to loratadine alone, and of these 2,000 cases had a known or estimated amount of loratadine ingested. There were 360 patients admitted to a critical care setting and 351 admitted to a non-critical care bed or a psychiatric inpatient facility. The average number of estimated or confirmed tablets ingested was 18-25, and the range was 1-89 tablets. The mean patient age was 11 years, with a range of 1 month to 95 years old. The most common gastric decontamination performed was oral activated charcoal followed by gastric lavage or a cathartic. There were four deaths, all in females and all involving multiple drug ingestion. Three of the four deaths were suicide attempts and the reason for exposure in one patient was unknown. No deaths occurred with loratadine-only exposure.

*Comments:*

*1. Part of this time period includes prescription use since the first OTC approval for Claritin was in November 2002. The Sponsor did not stratify the data to show only those cases reported since the November 2003 approval for Claritin for hives relief.*

*2. The TESS data show that the number of overdose reports in which loratadine was ingested increased each year from 2003-2005; however, only about 9% (2,000 of 22,000) of the reports involved loratadine as the sole overdose drug. The Sponsor concluded that the overdose data do not show a safety signal or trend that indicates that loratadine is unsafe, even in an overdose. This conclusion appears to be correct.*

The Sponsor's additional literature review is discussed in section 8.6.

### 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

### 7.4 General Methodology

#### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The Sponsor submitted one study with adverse event data. The Sponsor referenced five other NDAs for Claritin products: Claritin Tablets, Claritin-D 12 Hour tablets, Claritin-D 24 Hour tablets, Claritin Syrup, and Claritin Reditabs. Safety data were evaluated in the medical reviews for the approval of these referenced NDAs. The Sponsor did not combine new safety data with the previously-conducted studies. Therefore, no pooled data analyses were done.

##### 7.4.1.1 Pooled data vs. individual study data

Not applicable.

##### 7.4.1.2 Combining data

Not applicable.

#### 7.4.2 Explorations for Predictive Factors

The submitted study, Protocol # CL2003-02, was a single-dose trial. There was no analysis based upon dose, duration of use, or concomitant medication.

##### 7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable, as Protocol # CL2003-02, was a single-dose trial.

##### 7.4.2.2 Explorations for time dependency for adverse findings

Not applicable, as the product is single-dose.

##### 7.4.2.3 Explorations for drug-demographic interactions

The Sponsor has not conducted any study exploring drug-demographic interactions for this product. There were only 4 AEs in the submitted study. In the Sponsor's pediatric trials with loratadine syrup, dysphonia, nervousness, hyperkinesia, abdominal pain and conjunctivitis were noted at a slightly higher incidence in the 10-mg loratadine group vs. placebo. In adult loratadine trials fatigue, headache, dry mouth, dry nose, pruritus, and somnolence occurred at a greater

incidence in the loratadine-treated groups. This data suggests that younger subjects might be more likely to experience nervousness or hyperkinesia while older subjects might be more likely to experience sedation with loratadine compared to placebo.

#### 7.4.2.4 Explorations for drug-disease interactions

The Sponsor has not conducted any study exploring drug-disease interactions for this product. The current product label does not indicate any known drug-disease interactions; however, those with liver or kidney disease are advised to ask a doctor before use.

#### 7.4.2.5 Explorations for drug-drug interactions

No drug-drug interactions were evaluated in this safety update or in the current trial, Protocol # CL2003-02. However, in a FDA safety assessment for the OTC switch (May 12, 2000, reference 7, the potential interaction between loratadine with erythromycin, cimetidine, and ketoconazole was reviewed and found not to be associated with adverse events, though an increase was noted in the AUC (area under the curve) values for loratadine and its active metabolite (descarboethoxyloratadine or desloratadine).

#### 7.4.3 Causality Determination

The Sponsor did not perform special causality assessments.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

For children age 2 to under 6, one 5-mg tablet daily; for adults and children 6 years of age and older, two 5-mg tablets daily

### 8.2 Drug-Drug Interactions

See section 7.4.2.5.

### 8.3 Special Populations

The current label advises those who have ever had an allergic reaction to the product or any of its ingredients to not use the product.

### 8.4 Pediatrics

In the current submission the Sponsor studied subjects 18-45 years old. The Sponsor previously studied pediatric subjects, and FDA previously reviewed the data, for the approval of NDA 20-641, Claritin Syrup. Since the last Claritin product approval in November 2003, a total 105 AEs

have been reported to the FDA AERS database, of which 8 cases were in children younger than 36 months. Two of the eight cases were exposures via the mother's use of Claritin. No deaths have been reported in children.

This reviewer's literature search (see section 8.6) noted 3 articles (references 4, 5, and 8) discussing safety of loratadine in children. Based on the AE reports and literature review noted above, no new safety-related concerns were noted in children for the proposed use of loratadine for the indication of relief of hay fever and upper respiratory allergy symptoms in adults and children 2 years of age and older.

### 8.5 Advisory Committee Meeting

No advisory committee meetings addressed this application.

### 8.6 Literature Review

In the 2005 annual report for NDA 19-658 (Claritin Allergy 24 Hour Tablets), NDA 20-641 (Claritin Syrup), and NDA 20-704 (Claritin RediTabs Orally Disintegrating Tablets) the Sponsor provided 33 articles regarding loratadine products. The report covered the period November 27, 2004-November 26, 2005. Of these, 3 references dealt with pertinent safety topics.

In reference 1 (MMWR 2004), the CDC analyzed data from the National Birth Defects Prevention Study (NBDPS), an ongoing, multistate, case-control study of environmental and genetic risk factors for major birth defects. This study reviewed data on the risk of congenital hypospadias in children born to women exposed to loratadine during pregnancy. The study populations consisted of 563 male infants with hypospadias and 1,444 male infant controls; all were born during October 1, 1997-June 30, 2001. Exposure was defined as any maternal use of loratadine from 1 month before pregnancy through the first trimester. The report summarized the result of that analysis, which determined that no increased risk for second- or third-degree hypospadias existed among infants of women who used loratadine in early pregnancy.

*Comment:*

*1. A previous study from Sweden had suggested a possible correlation between male congenital hypospadias and pre-natal use of loratadine, but that study included first-degree hypospadias which the CDC felt was less likely drug-related than second or third degree hypospadias.*

In reference 2 (Bender et al. 2003), the authors performed a meta-analysis looking at sedation and performance impairment of diphenhydramine compared with second-generation antihistamines, including loratadine. The authors concluded that there is no consistent distinction between sedating and non-sedating anti-histamines.

In reference 3 (Lange B and Bachert C 2004), the authors reviewed the literature and queried pharmaceutical manufacturers as well as the German regulatory authority for information on the adverse reaction profiles of antihistamines. They concluded that the antihistamine influences on cardiac repolarization differs among antihistamines with cetirizine, desloratadine and

levocetirizine bearing the lowest risk. They note that antihistamines in single cases cause liver disorders and hepatitis; however, the risk is not different from the background of idiopathic hepatitis. Experience with exposure to antihistamines during the first trimester is limited but, in general, there is no increased risk of teratogenicity. Data on a potentially increased risk of hypospadias after exposure to loratadine cannot be definitely judged yet. In Germany, they note that cetirizine and desloratadine are approved for children aged 2 years and older.

In addition, this reviewer performed a PubMed literature search utilizing the terms "loratadine safety", "Claritin Averse Events", "Claritin Torsade de Pointes", and "Claritin Hypospadias" for the period November 2003 to December 31, 2005 to capture any safety references not previously submitted. The search yielded 39 papers. Of these, 4 papers provided pertinent safety information (reference 1, discussed above and references 4-6 discussed below).

In reference 4 (Gilbert C, et al. 2005), the authors review the fetal safety of drugs used in the treatment of allergic rhinitis. They note that loratadine is the most studied second-generation antihistamine, with a total patient cohort of 2147 exposed women, and does not appear to increase the risk of major congenital malformations, but it has not been as well studied as the earlier antihistamines. Also, since desloratadine is the principal metabolite of loratadine, they state it can be assumed to have a similar safety profile as loratadine although no direct human studies have been done. They state that overall benefit-risk considerations favor the safety of intranasal corticosteroids over antihistamines during pregnancy.

In reference 5 (Bloom M, Staudinger H, Herron J. 2004), the authors studied the safety and tolerability of desloratadine syrup in children (note that desloratadine is the principal metabolite of loratadine). They conducted a double-blind, placebo-controlled, study in 231 children aged 2 years-11 years with allergic rhinitis. Over 14 days, subjects aged 2 years-5 years were randomly assigned to receive once a day either 1.25 mg of desloratadine syrup (0.5 mg/mL) or matching placebo, and subjects aged 6 years-11 years were randomly assigned to receive once a day either 2.5 mg of desloratadine syrup or matching placebo. The incidence of adverse events for subjects aged 2 years-5 years (n = 111), was 7/55 for the group treated with desloratadine and 6/56 for placebo. The incidence of adverse events in subjects aged 6 years-11 years (n = 120), was 1/60 for the group treated with desloratadine and 6/60 for placebo. No severe or serious adverse events occurred, and no clinically relevant changes were noted in median clinical laboratory test values or mean vital signs in either group. There were no significant ECG results in any group.

In reference 6 (Atar S et al. 2003), the authors highlight a case of Torsades de pointes (TdP) in a 73-year old woman on chronic treatment with amiodarone for atrial fibrillation. The patient received loratadine and presented with syncope and multiple episodes of TdP. The authors suggested that the QT interval should be monitored when loratadine is co-administered with drugs that may potentially prolong QT.

*Comment:*

*The case that Atar et al. refer to in reference 6 is also noted in the FDA AERS database (see section 7.2.9 and Table 12).*

In the addendum of March 3, 2006 the Sponsor submitted and reviewed 44 articles covering the period December 1, 2002-December 31, 2005. This addendum included the 27 articles from the annual report noted above for NDAs 19-658, 20-641 and 20-704 (November 27, 2004-November 26, 2005). From the additional articles, two in particular (references 7 and 8) addressed pertinent safety topics.

In reference 8 (Grimfeld et al. 2004) the authors performed a randomized, double-blind, placebo-controlled study of the safety and efficacy of loratadine in reducing the number of respiratory infections in children. In this study in 412 patients, the investigators gave Claritin syrup 5 mg/day for children >24 months (or 2.5 mg/day for children ≤ 24 months) or placebo for 12 months. The most frequent adverse events of loratadine were pharyngitis (18.8%) and bronchitis (15.8%). Loratadine was not more sedative than placebo and no cardiovascular events were seen. The authors found that loratadine is safe for long-term (one year) use in children at the doses studied.

*Comment:*

*The proposed label of the Claritin chewable tablets allows adults and children 6 years and older to chew two 5-mg tablets—a dose that is at least double that used in reference 7. The safety data from reference 7 may not necessarily translate to safety at the proposed dose for Claritin Chewable Tablets.*

In reference 9 (Chaikin et al. 2005) the authors assessed the electrocardiographic (ECG) effects of loratadine 10 mg per day and ebastine 20 mg per day when administered alone for five days and when co-administered with ketoconazole for eight days. The study was blinded and placebo-controlled. Alone, loratadine showed no significant ECG effects. When co-administered with ketoconazole the corrected QT interval was insignificantly increased by 10.68 milliseconds. The loratadine concentration (area under the curve, AUC) was increased by 4.5 fold with the desloratadine AUC increased by 1.9 fold. No subjects were withdrawn for ECG changes or drug effects.

## **8.7 Postmarketing Risk Management Plan**

There is no postmarketing risk management plan.

## **8.8 Other Relevant Materials**

There are no other relevant materials submitted for the review.

# **9 OVERALL ASSESSMENT**

## **9.1 Conclusions**

The test product (2 x 5 mg loratadine chewable tablets) was considered bioequivalent to the reference product (1 x 10 mg loratadine tablet)

The 2 x 5 mg treatment had a favorable safety profile when compared to the 1 x 10 mg treatment. Both treatments were well tolerated. Few AEs were reported during the study by a small number of subjects, and only one, a mild headache, was considered related to treatment. No deaths, serious AEs, discontinuations due to AEs, or other significant AEs were reported for subjects in this study. No clinically meaningful trends were observed in clinical laboratory results, vital sign measurements, physical examination findings, or ECG results.

This reviewer's FDA AERS Database search showed 105 serious AEs from November 1, 2003-January 31, 2006, but did not reveal any new or worrisome information about loratadine. The Sponsor's internal AE reports, the Sponsor's AERS Database search and literature search, and this reviewer's literature search also did not reveal any new or worrisome information about loratadine. In particular, there were no unconfounded cases of Torsade de Pointes. Also, a previous potential concern for congenital hypospadias, in male children of mothers with prenatal use of loratadine, was addressed by a CDC study that did not show a link between using loratadine and second or third degree hypospadias. Eight cases of convulsions were noted in the Sponsor's internal database from November 27, 2002-May 31, 2005. These were in patients with known seizure disorders. Fourteen cases were noted in the Sponsor's AERS Database review in 2005. However, there is no control group for comparison, which precludes making any conclusion about seizure causality from loratadine. However, it is possible that loratadine could lower the seizure threshold, so these data bear further watching.

## 9.2 Recommendation on Regulatory Action

The proposed 5-mg loratadine chewable tablet for the indication of the relief of upper respiratory allergy symptoms in adults and children 2 years of age and older has an acceptable safety profile for OTC marketing. Therefore, this application is approvable from the safety standpoint. Final approvability depends on the outcome of the biopharmaceutical equivalence study #CL2003-02, which the biopharmaceutics reviewer is reviewing.

## 9.3 Recommendation on Postmarketing Actions

### 9.3.1 Risk Management Activity

No special postmarketing risk management activities are recommended.

### 9.3.2 Required Phase 4 Commitments

No special Phase 4 commitments are recommended.

### 9.3.3 Other Phase 4 Requests

None.

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## Labeling Review

The proposed label is presented below. An interdisciplinary scientist in the Office of Nonprescription Products is reviewing the proposed label. The Sponsor incorporated all the important warnings for loratadine. The label is acceptable from a clinical point of view.

**Inactive ingredients<sup>4</sup>**  
aspartame, citric acid anhydrous, colloidal silicon dioxide, D&C red No. 27 aluminum lake, FD&C blue No. 2 aluminum lake, flavor, magnesium stearate, mannitol, microcrystalline cellulose, sodium starch glycolate, stearic acid

**Questions or comments?**  
1-800-CLARITIN (1-800-252-7484) or [www.claritin.com](http://www.claritin.com)

### Side Panel

Children's  
Claritin®  
Allergy

5 or 10 CHEWABLE TABLETS

### Side Panel

[Code Area for Lot & Exp] Children's  
Claritin®  
Allergy

### Bottom Panel

Children's  
Claritin®  
Allergy

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Claritin Chewable Tablets, loratadine tablet, 5 mg

**Back Label**

Claritin®

5 or 10 CHEWABLE TABLETS

<b>Drug Facts</b>	
<b>Active ingredient (in each tablet)</b> Loratadine 5 mg.....	<b>Purpose</b> Antihistamine
<b>Uses</b> temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: <ul style="list-style-type: none"><li>• runny nose</li><li>• itchy, watery eyes</li><li>• sneezing</li><li>• itching of the nose or throat</li></ul>	
<b>Warnings</b> <b>Do not use</b> if you have ever had an allergic reaction to this product or any of its ingredients. <b>Ask a doctor before use</b> if you have liver or kidney disease. Your doctor should determine if you need a different dose. <b>When using this product</b> do not take more than directed. Taking more than directed may cause drowsiness. <b>Stop use and ask a doctor</b> if an allergic reaction to this product occurs. Seek medical help right away. <b>If pregnant or breast-feeding</b> , ask a health professional before use. <b>Keep out of reach of children.</b> In case of overdose, get medical help or contact a Poison Control Center right away.	
<b>Drug Facts (continued)</b>	
<b>Directions</b> [in table format] adults and children 6 years and over      chew 2 tablets daily; not more than 2 tablets in 24 hours children 2 to under 6 years of age      chew 1 tablet daily; not more than 1 tablet in 24 hours consumers with liver or kidney disease      ask a doctor	
<b>Other information</b> <ul style="list-style-type: none"><li>• phenylketonurics: contains phenylalanine 1.4 mg per tablet<sup>2</sup></li><li>• safety sealed: do not use if the individual blister unit imprinted with Children's Claritin® is open or torn<sup>3</sup></li><li>• store between 20° to 25°C (68° to 77°F)</li></ul>	

9.5 Comments to Applicant

No comments.

10 Appendices

Appendix 1 shows the search criteria for the AERS Database search.

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**Appendix 1**

Search Criteria for 105 cases in the FDA Reviewer's query of the FDA Adverse Event Reporting System (AERS) database:

Criteria: PRIMARY DRUG, PRIMARY INGRÉDIENT, MANU, FDA Received Date,  
OUTCOME, REPORT TYPE, DRUG ROLE, BEST REPRESENTATIVE

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**PRIMARY DRUG**

N019658 / CLARITIN,  
N019658 / CLARITIN HIVES RELIEF,  
N020641 / CLARITIN,  
N020641 / CLARITIN HIVES RELIEF,  
N020704 / CLARITIN HIVES RELIEF REDITAB,  
N020704 / CLARITIN REDITABS

**PRIMARY INGREDIENT**

LORATADINE

**MANU**

SCHERING CORP SUB SCHERING PLOUGH CORP,  
SCHERING CORPORATION,  
SCHERING PHARMACEUTICAL CORP,  
SCHERING PLOUGH CORP,  
SCHERING PLOUGH HEALTHCARE PRODUCTS INC,  
SCHERING PLOUGH RESEARCH INSTITUTE,  
SCHERING

**FDA Received Date**

2003NOV-2006JAN

**OUTCOME**

Death, Life-Threatening, Hospitalization - Initial or Prolonged, Disability, Congenital Anomaly, Required Intervention to Prevent Permanent Impairment/Damage

**REPORT TYPE**

Domestic 5 Day, Foreign 5 Day, Unknown 5 Day, Domestic 10 Day, Foreign 10 Day, Unknown 10 Day, Domestic Expedited (15-Day), Foreign Expedited (15-Day), Unknown Expedited (15-Day), Domestic Periodic, Foreign Periodic, Unknown Periodic

**DRUG ROLE**

PRIMARY

**BEST REPRESENTATIVE**

TRUE

## References

1. Centers for Disease Control and Prevention (CDC). Evaluation of an association between loratadine and hypospadias--United States, 1997-2001. *MMWR Morb Mortal Wkly Rep* 2004 Mar 19;53(10):219-21.
2. Bender AG et al. Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. *J. Allergy Clin Immunol* 2003; 111: 770-6.
3. Lange B, Bachert C. Adverse reaction profiles of antihistamines and their clinical relevance 2004.
4. Gilbert C, et al. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. *Drug Saf* 2005; 28:707-19. Review.
5. Bloom M, Staudinger H, Herron J. Safety of desloratadine syrup in children. *Curr Med Res Opin* 2004;20:1959-65.
6. Atar S et al. Torsades de pointes and QT prolongation due to a combination of loratadine and amiodarone. *Pacing Clin Electrophysiol* 2003;26: 785-6.
7. Memorandum from the FDA OTC Switch Review Team (HFD-570, HFD-430) to Robert Meyer, M.D. (FDA Director, Division of Pulmonary and Allergy Drug Products), dated May 12, 2000, titled: Safety assessment of the antihistamines loratadine and fexofenadine.
8. Grimfeld A et al. Prophylactic management of children at risk for recurrent upper respiratory infections: The Preventia I Study. *Clin Exp Allergy* 2004; 34: 1665-72.
9. Chaikin P et al. Co-administration of ketoconazole with H1-antagonists ebastine and loratadine in healthy subjects: pharmacokinetic and pharmacodynamic effects. *Br J Clin Pharmacol* 2005; 59: 346-54.

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MEDICAL OFFICER