CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-470/S005

APPROVAL LETTER

HFD-613/OCD

NDA 20-470/S-005

DEC 4 1998

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President
US Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your supplemental new drug application dated March 4, 1998, received March 5, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Claritin-D 24 Hour (10 mg loratadine/240 mg pseudoephedrine sulfate, USP) Extended Release Tablets.

We acknowledge receipt of your submissions dated May 26, July 2 and 13, August 24 and 26, October 23, November 5 and 23, and December 3,1998.

This supplemental new drug application provides for a reformulated tablet with a new shape and coating.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling. Accordingly, the supplemental applicationis approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted December 3,1998, immediate container and carton labels submitted March 4, 1998).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-470/S-005." Approval of this submission by FDA is not required before the labeling is used. We remind you of your agreement to revise the carton and container labels to read "Take with a full glass of water" in place of the current "Take with a glass of water" within three months of the date of this letter.

We remind you of your Phase 4 commitments specified in your submission dated December 3, 1998. These commitments, along with any completion dates agreed upon, are listed below.

1. You will conduct a single-dose, 5-way cross-over bioavailability study with the reformulated Claritin-D 24 Hour product, Claritin-D 12 Hour,, Claritin Tablets, Claritin RediTabs, and Claritin Syrup in adults. A second single-dose, two-way, within-batch, replicate, cross-over study will be conducted with Claritin Syrup in adults. The protocols for these studies will be sent to the FDA within 30 days of the date of this letter. You will initiate the studies within two months of the date of this letter, and submit the study reports within eight months of the date of this letter.

2. You will initiate a prospective active surveillance program as outlined in your December 3, 1998, letter. The protocol for this surveillance effort should be submitted to the FDA within 30 days of the date of this letter, and the study will be initiated within two months of the date of this letter.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, under 21 CFR 3 14.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition we remind you of the following agreements.

1. You will replace/exchange all existing Claritin-D 24 Hour marketed product to the pharmacy level within 14 days of the date of this letter.

2. You will submit a prior-approval supplement for any extension of the 18-month expiration dating period according to the approved stability protocol.

3. Within six months of the date of this letter you will develop and submit, as a changes-being-effected supplement, a new test method which will meet the appropriate specifications according to ICH guidelines for unspecified and total impurities.

4. You will initiate mailing of the "Important Prescribing Information" correspondence as included in the December 3, 1998, submission no later than December 11, 1998.

5. You will issue the press release included in the December 3, 1998, submission no later than Monday, December 7, 1998.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We request that a copy of your letter communicating important information about this drug product (i.e., the "Dear Health Care Practitioner" letter) be submitted to the NDA, and a copy be submitted to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-470/S005

FINAL PRINTED LABELING

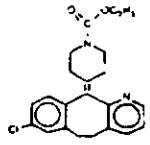
CLARITIN-D® 24 HOUR

brand of loratadine and pseudoephedrine sulfate, USP

Extended Release Tablets

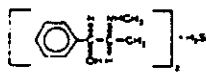
DESCRIPTION: CLARITIN-D® 24 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets contain 10 mg loratadine in the tablet coating for immediate release and 240 mg pseudoephedrine sulfate, USP in the tablet core which is released slowly allowing for once-daily administration.

Loratadine is a long-acting antihistamine having the empirical formula $C_{22}H_{23}ClN_2O_2$; the chemical name ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate; and the following chemical structure:



The molecular weight of loratadine is 382.89. It is a white to off-white powder, not soluble in water but very soluble in acetone, alcohol, and chloroform.

Pseudoephedrine sulfate is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect sympathomimetic amine. The empirical formula for pseudoephedrine sulfate is $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$; the chemical name is α-[1-(methyl-amino) ethyl]-[*S*-(*R**,*R**)]-benzenemethanol sulfate (2:1)(salt); and the chemical structure is:



The molecular weight of pseudoephedrine sulfate is 428.54. It is a white powder, freely soluble in water and methanol and sparingly soluble in chloroform.

The inactive ingredients for oval, biconvex CLARITIN-D 24 HOUR Extended Release Tablets are calcium phosphate, carnauba wax, ethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, povidone, silicon dioxide, sugar, titanium dioxide, and white wax.

CLINICAL PHARMACOLOGY: The following information is based upon studies of loratadine alone or pseudoephedrine alone, except as indicated.

Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity.

Human histamine skin wheal studies following single and repeated oral doses of loratadine have shown that the drug exhibits an antihistaminic effect beginning within 1 to 3 hours, reaching a maximum at 8 to 12 hours, and lasting in excess of 24 hours. There was no evidence of tolerance to this effect developing after 28 days of dosing with loratadine.

Pharmacokinetic studies following single and multiple oral doses of loratadine in 115 volunteers showed that loratadine is rapidly absorbed and extensively metabolized to an active metabolite (descarboethoxyloratadine). Approximately 80% of the total dose administered can be found equally distributed between urine and feces in the form of metabolic products after 10 days. The mean elimination half-lives found in studies in normal adult subjects (n = 54) were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the major active metabolite (descarboethoxyloratadine). In nearly all patients, exposure (AUC) to the metabolite is greater than exposure to parent loratadine. Loratadine and descarboethoxyloratadine reached steady state in most patients by approximately the fifth dosing day. The pharmacokinetics of loratadine and descarboethoxyloratadine are dose independent over the dose range of 10 to 40 mg and are not significantly altered by the duration of treatment.

In vitro studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by P450 CYP3A4 and, to a lesser extent, by P450 CYP2D6. In the presence of a CYP3A4 inhibitor ketoconazole, loratadine is metabolized to descarboethoxyloratadine predominantly by CYP2D6. Concurrent administration of loratadine with either ketoconazole, erythromycin (both CYP3A4 inhibitors), or cimetidine (CYP2D6 and CYP3A4 inhibitor) to healthy volunteers was associated with significantly increased plasma concentrations of loratadine (see **Drug Interactions** section).

In a study involving 12 healthy geriatric subjects (66 to 78 years old), the AUC and peak plasma levels (C_{max}) of both loratadine and descarboethoxyloratadine were significantly higher (approximately 50% increased) than in studies of younger subjects. The mean elimination half-lives for the elderly subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11 to 38 hours) for the active metabolite.

In patients with chronic renal impairment (creatinine clearance ≤30 mL/min) both the AUC and peak plasma levels (C_{max}) increased on average by approximately 73% for loratadine; and approximately by 120% for descarboethoxyloratadine, compared to individuals with normal renal function. The mean elimination half-lives of loratadine (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not significantly different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite (descarboethoxyloratadine) in subjects with chronic renal impairment.

In patients with chronic alcoholic liver disease the AUC and peak plasma levels (C_{max}) of loratadine were double while the pharmacokinetic profile of the active metabolite (descarboethoxyloratadine) was not significantly changed from that in normals. The elimination half-lives for loratadine and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

There was considerable variability in the pharmacokinetic data in all studies of loratadine, probably due to the extensive first-pass metabolism. Individual histograms of area under the curve, clearance, and volume of distribution showed a log normal distribution with a 25-fold range in distribution in healthy subjects.

Loratadine is about 97% bound to plasma proteins at the expected plasma concentrations (2.5 to 100 ng/mL) after a therapeutic dose. Loratadine does not affect the plasma protein binding of warfarin and digoxin. The metabolite descarboethoxyloratadine is 73% to 77% bound to plasma proteins (at 0.5 to 100 ng/mL).

Whole body autoradiographic studies in rats and monkeys, radiolabeled tissue distribution studies in mice and rats, and *in vivo* radioligand studies in mice have shown that neither loratadine nor its metabolites readily cross the blood-brain barrier. Radioligand binding studies with guinea pig pulmonary and brain H_1-receptors indicate that there was preferential binding to peripheral versus central nervous system H_1-receptors.

In a study in which loratadine alone was administered at four times the clinical dose for 90 days, no clinically significant increase in the QT, was seen on ECGs.

In a single-rising dose study of loratadine alone in which doses up to 160 mg (16 times the clinical dose) were administered, no clinically significant changes on the QT, interval in the ECGs were observed.

Pseudoephedrine sulfate (d-isoephedrine sulfate) is an orally active sympathomimetic amine which exerts a decongestant action on the nasal mucosa. It is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

The bioavailability of loratadine and pseudoephedrine sulfate from CLARITIN-D 24 HOUR Extended Release Tablets is similar to that achieved with separate administration of the components. Coadministration of loratadine and pseudoephedrine does not significantly affect the bioavailability of either component.

In a single-dose study, food increased the AUC of loratadine by approximately 125% and C_{max} by approximately 80%. However, food did not significantly affect the pharmacokinetics of pseudoephedrine sulfate or descarboethoxyloratadine.

Clinical Studies: Clinical trials of CLARITIN-D 24 HOUR Extended Release Tablets involved a total of approximately 2000 patients with seasonal allergic rhinitis. One study involved 879 patients, who received either the combination product (loratadine 10 mg and pseudoephedrine sulfate 240 mg), loratadine (10 mg once daily) or pseudoephedrine sulfate (120 mg twice daily) alone, or placebo, in a double-blind randomized design. Improvement in nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion in patients receiving CLARITIN-D 24 HOUR Extended Release Tablets was significantly greater than in placebo recipients, and generally greater than that achieved with loratadine or pseudoephedrine sulfate alone. In this study, CLARITIN-D 24 HOUR Extended Release Tablets were well tolerated, with a frequency of sedation similar to that seen with placebo, and a frequency of nervousness and insomnia similar to that seen with pseudoephedrine sulfate given alone.

In another study of 469 patients, once-daily administration of CLARITIN-D 24 HOUR Extended Release Tablets provided effects similar to those achieved with twice-daily administration of CLARITIN-D 12 HOUR Extended Release Tablets, a combination product containing 5 mg loratadine plus 120 mg pseudoephedrine sulfate, USP, extended release.

The end of dosing interval efficacy of the pseudoephedrine component of CLARITIN-D 24 HOUR Extended Release Tablets on the symptom of nasal stuffiness was evaluated in a study of 695 patients who were randomized to receive CLARITIN-D 24 HOUR Extended Release Tablets, CLARITIN Tablets, or placebo. Patients who received CLARITIN-D 24 HOUR Extended Release Tablets had significantly more improvement in nasal stuffiness scores at the end of the dosing interval than those patients receiving CLARITIN Tablets or placebo throughout the course of the trial.

In a 6-week, placebo-controlled study of 193 patients with seasonal allergic rhinitis and concomitant mild to moderate asthma, CLARITIN-D 12 HOUR Extended Release Tablets twice daily improved seasonal allergic rhinitis signs and symptoms with no decrease in pulmonary function or adverse effect on asthma symptoms. This supports the safety of administering CLARITIN-D 24 HOUR Extended Release Tablets to seasonal allergic rhinitis patients with asthma.

INDICATIONS AND USAGE: CLARITIN-D 24 HOUR Extended Release Tablets are indicated for the relief of symptoms of seasonal allergic rhinitis. CLARITIN-D 24 HOUR Extended Release Tablets should be administered when both the antihistaminic properties of CLARITIN® (loratadine) and the nasal decongestant activity of pseudoephedrine sulfate are desired (see **CLINICAL PHARMACOLOGY** section).

CONTRAINDICATIONS: CLARITIN-D 24 HOUR Extended Release Tablets are contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

This product, due to its pseudoephedrine component, is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment. (See **PRECAUTIONS: Drug Interactions** section.) It is also contraindicated in patients with severe hypertension, severe coronary artery disease, and in those who have shown hypersensitivity or idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include: insomnia, dizziness, weakness, tremor, or arrhythmias.

WARNINGS: CLARITIN-D 24 HOUR Extended Release Tablets should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy. Central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension may be produced by sympathomimetic amines.

Use in Patients Approximately 60 Years of Age and Older: The safety and efficacy of CLARITIN-D 24 HOUR Extended Release Tablets in patients greater than 60 years old have not been investigated in placebo-controlled clinical trials. The elderly are more likely to have adverse reactions to sympathomimetic amines.

PRECAUTIONS: General: Because there have been reports of esophageal obstruction and perforation in patients who have taken a previously marketed formulation of CLARITIN-D 24 HOUR Extended Release Tablets, it is recommended that patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis not use this product. Furthermore, since it is not known whether this formulation of CLARITIN-D 24 HOUR Extended Release Tablets has the potential for this adverse event, it is reasonable to recommend that all patients take this product with a full glass of water (see **PRECAUTIONS: Information for Patients, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION**). Because the doses of this fixed combination product cannot be individually titrated and hepatic insufficiency results in a reduced clearance of loratadine to a much greater extent than pseudoephedrine, CLARITIN-D 24 HOUR Extended Release Tablets should generally be avoided in patients with hepatic insufficiency. Patients with renal insufficiency (GFR <30 mL/min) should be given a lower initial dose (one tablet every other day) because they have reduced clearance of loratadine and pseudoephedrine.

Information for Patients: Patients taking CLARITIN-D 24 HOUR Extended Release Tablets should receive the following information: CLARITIN-D 24 HOUR Extended Release Tablets are prescribed for the relief of symptoms of seasonal allergic rhinitis. Patients should be instructed to take CLARITIN-D 24 HOUR Extended Release Tablets only as prescribed and not to exceed the prescribed dose. Patients should also be advised against the concurrent use of CLARITIN-D 24 HOUR Extended Release Tablets with over-the-counter antihistamines and decongestants. Patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use this product.

This product should not be used by patients who are hypersensitive to it or to any of its ingredients. Due to its pseudoephedrine component, this product should not be used by patients with narrow-angle glaucoma, urinary retention, or by patients receiving a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of an MAO inhibitor. It also should not be used by patients with severe hypertension or severe coronary artery disease.

Patients who are or may become pregnant should be told that this product should be used in pregnancy or during lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant.

Patients should be instructed not to break or chew the tablet and to take it with a full glass of water (see **PRECAUTIONS: General, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION**).

Drug Interactions: No specific interaction studies have been conducted with CLARITIN-D 24 HOUR Extended Release Tablets. However, loratadine (10 mg once daily) has been safely coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies. Although increased plasma concentrations (AUC 0-24 hrs) of loratadine and/or descarboethoxyloratadine were observed following coadministration of loratadine with each of these drugs in normal volunteers (n = 24 in each study), there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and

adverse events. There were no significant effects on QT, intervals and no reports of sedation or syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations (AUC 0-24 hrs) of erythromycin decreased 15% with coadministration of loratadine relative to that observed with erythromycin alone. The clinical relevance of this difference is unknown. These above findings are summarized in the following table:

Effects on Plasma Concentrations (AUC 0-24 hrs) of Loratadine and Descarboethoxyloratadine After 10 Days of Coadministration (Loratadine 10 mg) in Normal Volunteers

	Loratadine	Descarboethoxy-loratadine
Erythromycin (500 mg Q8h)	+ 40%	+46%
Cimetidine (300 mg Q8)	+103%	+ 6%
Ketoconazole (200 mg Q12h)	+307%	+73%

There does not appear to be an increase in adverse events in subjects who received oral contraceptives and loratadine.

CLARITIN-D 24 HOUR Extended Release Tablets (pseudoephedrine component) are contraindicated in patients taking monoamine oxidase inhibitors and for 2 weeks after stopping use of an MAO inhibitor. The antihypertensive effects of beta-adrenergic blocking agents, methyldopa, mecamylamine, reserpine and veratrum alkaloids may be reduced by sympathomimetics. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis.

Drug/Laboratory Test Interactions: The *in vitro* addition of pseudoephedrine to sera containing the cardiac isoenzyme MB of serum creatinine phosphokinase progressively inhibits the activity of the enzyme. The inhibition becomes complete over 6 hours.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There are no animal or laboratory studies on the combination product loratadine and pseudoephedrine sulfate to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

In an 18-month carcinogenicity study in mice and a 2-year study in rats loratadine was administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (active metabolite) times higher than in humans given the maximum recommended daily oral dose. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (active metabolite) times higher than in humans given the maximum recommended daily oral dose. Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg and in males and females given 25 mg/kg. The clinical significance of these findings during long-term use of loratadine is not known.

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Programs (NTP) uncovered no evidence of carcinogenic potential of ephedrine sulfate at doses up to 10 and 27 mg/kg respectively (approximately 16% and 100% of the maximum recommended human daily oral dose of pseudoephedrine sulfate on a mg/m² basis).

In mutagenicity studies with loratadine alone, there was no evidence of mutagenic potential in reverse (Ames) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (Rat Primary Hepatocyte Unscheduled DNA Assay) or in two assays for chromosomal aberrations (Human Peripheral Blood Lymphocyte Clastogenesis Assay and the Mouse Bone Marrow Erythrocyte Micronucleus Assay). In the Mouse Lymphoma Assay, a positive finding occurred in the nonactivated but not the activated phase of the study.

Decreased fertility in male rats, shown by lower female conception rates, occurred at 64 mg/kg of loratadine (approximately 50 times the maximum recommended human daily oral dose based on mg/m²) and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at 24 mg/kg (approximately 20 times the maximum recommended human daily oral dose on a mg/m² basis).

Pregnancy Category B: The combination product loratadine and pseudoephedrine sulfate was evaluated for teratogenicity in rats and rabbits. There was no evidence of teratogenicity in reproduction studies with this combination of the same clinical ratio (1:24) at oral doses up to 150 mg/kg (approximately 5 times the maximum recommended human daily oral dose on a mg/m² basis) in rats, and 120 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m² basis) in rabbits. Similarly, no evidence of animal teratogenicity in rats and rabbits was reported at oral doses up to 96 mg/kg of loratadine alone (approximately 75 and 150 times, respectively, the maximum human daily oral dose on a mg/m² basis). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CLARITIN-D 24 HOUR Extended Release Tablets should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known if this combination product is excreted in human milk. However, loratadine when administered alone and its metabolite descarboethoxyloratadine pass easily into breast milk and achieve concentrations that are equivalent to plasma levels, with an AUC_{∞}/AUC_{∞} ratio of 1.17 and 0.85 for the parent and active metabolite, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and metabolite was excreted into the breast milk (approximately 0.03% of 40 mg over 48 hours). Pseudoephedrine administered alone also distributes into breast milk of the lactating human female. Pseudoephedrine concentrations in milk are consistently higher than those in plasma. The total amount of drug in milk as judged by the area under the curve (AUC) is 2 to 3 times greater than in plasma. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4% to 0.7%. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when CLARITIN-D 24 HOUR Extended Release Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.

ADVERSE REACTIONS: Information on adverse reactions is provided from placebo-controlled studies involving over 2000 patients, 605 of whom received CLARITIN-D 24 HOUR Extended Release Tablets once daily for up to 2 weeks. In these studies, the incidence of adverse events reported with CLARITIN-D 24 HOUR Extended Release Tablets was similar to those reported with twice-daily (q12h) 120 mg sustained-release pseudoephedrine alone.

REPORTED ADVERSE EVENTS WITH AN INCIDENCE OF ≥2% IN CLARITIN-D 24 HOUR EXTENDED RELEASE TABLETS TREATMENT GROUP IN DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIALS

	PERCENT OF PATIENTS REPORTING			
	CLARITIN-D® 24 HOUR (n = 605)	Loratadine 10 mg (n = 449)	Pseudo-ephedrine 120 mg q12h (n = 220)	Placebo (n = 605)
Dry Mouth	8	2	7	2
Somnolence	6	4	5	4
Insomnia	5	1	9	1
Pharyngitis	5	5	5	5
Dizziness	4	2	3	2
Coughing	3	2	3	1
Fatigue	3	4	1	2
Nausea	3	2	4	2
Nervousness	3	1	4	1
Anorexia	2	<1	2	0
Dysmenorrhea	2	2	2	1

Adverse events occurring in greater than or equal to 2% of CLARITIN-D 24 HOUR Extended Release Tablets-treated patients, but that were more common in the placebo-treated group, include headache.

Adverse events did not appear to significantly differ based on age, sex, or race, although the number of non-whites was relatively small.

In addition to those adverse events reported above, the following adverse events have been reported in fewer than 2% of patients who received CLARITIN-D 24 HOUR Extended Release Tablets:

Autonomic Nervous System: Altered lacrimation, flushing, increased sweating, mydriasis, thirst.

Body As A Whole: Abnormal vision, asthenia, back pain, chest pain, conjunctivitis, earache, eye pain, facial edema, fever, flu-like symptoms, leg cramps, lymphadenopathy, malaise, rigors, tinnitus.

Cardiovascular System: Hypertension, palpitation, tachycardia.

Central and Peripheral Nervous System: Convulsions, dysphonia, hyperkinesis, hypertonia, migraine, paresthesia, tremor.

Gastrointestinal System: Abdominal distension, altered taste, constipation, diarrhea, dyspepsia, flatulence, gastritis, stomatitis, tongue ulceration, toothache, vomiting.

Liver and Biliary System: Cholelithiasis.

Musculoskeletal System: Arthralgia, musculoskeletal pain, myalgia, tendinitis.

Psychiatric: Agitation, depression, emotional lability, irritability.

Reproductive System: Vaginitis.

Resistance Mechanism: Abscess, viral infection.

Respiratory System: Bronchospasm, dyspnea, epistaxis, hemoptysis, nasal congestion, nasal irritation, pleurisy, pneumonia, sinusitis, sputum increased, wheezing.

Skin and Appendages: Acne, pruritus.

Urinary System: Oliguria, micturition frequency, urinary retention, urinary tract infection.

Additional adverse events reported with the combination of loratadine and pseudoephedrine include abnormal hepatic function, aggressive reaction, anxiety, apathy, confusion, euphoria, paronirla, postural hypotension, syncope, urticaria, vertigo, weight gain.

The following additional adverse events have been reported with CLARITIN Tablets: abdominal distress, alopecia, altered micturition, altered salivation, amnesia, anaphylaxis, angioneurotic edema, blepharospasm, breast enlargement, breast pain, bronchitis, decreased libido, dermatitis, dry hair, dry skin, erythema multiforme, hypoesthesia, impaired concentration, impotence, increased appetite laryngitis, menorrhagia, nasal dryness, peripheral edema, photosensitivity reaction, purpura, rash, seizures, sneezing, supraventricular tachyarrhythmias, upper respiratory infection, urinary discoloration.

Pseudoephedrine may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, drowsiness, tachycardia, palpitation, pressor activity, and cardiac arrhythmias have been reported. Sympathomimetic drugs have also been associated with other untoward effects such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

There have been postmarketing reports of mechanical upper gastrointestinal tract obstruction and esophageal perforation in patients taking a previously marketed formulation of CLARITIN-D 24 HOUR Extended Release Tablets. In some, but not all, of these cases, patients have had known upper gastrointestinal narrowing or abnormal esophageal peristalsis. It is not known whether this reformulation of CLARITIN-D 24 HOUR Extended Release Tablets has the potential for this adverse event (see **PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

DRUG ABUSE AND DEPENDENCE: There is no information to indicate that abuse or dependency occurs with loratadine. Pseudoephedrine, like other central nervous system stimulants, has been abused. At high doses, subjects commonly experience an elevation of mood, a sense of increased energy and alertness, and decreased appetite. Some individuals become anxious, irritable, and loquacious. In addition to the marked euphoria, the user experiences a sense of markedly enhanced physical strength and mental capacity. With continued use, tolerance develops, the user increases the dose, and toxic signs and symptoms appear. Depression may follow rapid withdrawal.

OVERDOSAGE: In the event of overdosage, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary. Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents. Loratadine is not eliminated by hemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

Somnolence, tachycardia, and headache have been reported with doses of 40 to 180 mg of loratadine. In large doses, sympathomimetics may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusions and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsions, coma, and respiratory failure.

The oral median lethal dose for the mixture of the two drugs was greater than 525 and 1839 mg/kg in mice and rats, respectively (approximately 10 and 58 times the maximum recommended human daily oral dose on a mg/m² basis). The oral median lethal dose for loratadine was greater than 5000 mg/kg in rats and mice (greater than 2000 times the maximum recommended human daily oral dose on a mg/m² basis). Single oral doses of loratadine showed no effects in rats, mice, and monkeys at doses as high as 10 times the maximum recommended human daily oral dose on a mg/m² basis.

DOSAGE AND ADMINISTRATION: Adults and children 12 years of age and over: one tablet daily taken with a full glass of water (see **PRECAUTIONS; ADVERSE REACTIONS**). Because the doses of this fixed combination product cannot be individually titrated and hepatic insufficiency results in a reduced clearance of loratadine to a much greater extent than pseudoephedrine, CLARITIN-D 24 HOUR Extended Release Tablets should generally be avoided in patients with hepatic insufficiency. Patients with renal insufficiency (GFR <30 mL/min) should be given a lower initial dose (one tablet every other day) because they have reduced clearance of loratadine and pseudoephedrine. Patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use this product (see **PRECAUTIONS: Information for Patients, and ADVERSE REACTIONS**).

HOW SUPPLIED: CLARITIN-D 24 HOUR Extended Release Tablets contain 10 mg loratadine in the tablet coating for immediate release and 240 mg pseudoephedrine sulfate, USP in an extended-release core. CLARITIN-D 24 HOUR Extended Release Tablets are white to off-white oval, biconvex, coated tablets branded in black with "CLARITIN-D 24 HOUR": high-density polyethylene bottles of 100 (NDC 0085-1233-01) and blister packages of 10 x 10 tablet Unit Dose-Hospital Pack (NDC 0085-1233-02).

Protect Unit Dose-Hospital Pack from light and store in a dry place. Store between 15° and 25°C (59° and 77°F).

U.S. Patent Nos. 5,314,697; 4,731,447; and 4,282,233.

CLARITIN-D® 24 HOUR

brand of loratadine and pseudoephedrine sulfate, USP

Extended Release Tablets

Rev. 7/98

8-21880108
21861804T

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-470/S005

MEDICAL REVIEW(S)

DIV FILE

DEC - 4 1998

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA 20-470	APPLICATION TYPE:	CMC Supplement
SPONSOR:	Schering	PRODUCT/PROPRIETARY NAME:	Claritin-D 24 Hour
		USAN / Established Name:	Loratadine/PSE
CATEGORY OF DRUG:	Antihistamine/ decongestant	ROUTE OF ADMINISTRATION:	oral
REVIEWER:	Honig	REVIEW DATE:	December 4, 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
December 3, 1998	December 4, 1998	Response to FDA comments	see below under overview

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review: After extensive negotiation, the sponsor has agreed to the FDA proposed labeling of the reformulated product as well as to conduct a 5-way, crossover bioavailability study with the approved Claritin products. A two-way, within-batch, replicate study with Claritin Syrup in adults will also be conducted. Furthermore, the sponsor has agreed to conduct an active surveillance program using available claims databases to assess whether the problem of esophageal obstruction has been eliminated. The protocols for all these efforts will be submitted to FDA within 30 days of approval of this supplement. The proposed timelines for initiation and completion of these studies outlined in the letter are acceptable.

Additionally, the sponsor agrees to replace/exchange all existing Claritin-D 24 Hour (round) at the pharmacy level within 14 days of approval of this supplement.

The revised labeling is acceptable and exactly as proposed by FDA. Similarly, the 'Dear Dr' correspondence and proposed distribution list is acceptable. Initial mailing of the correspondence will commence December 11, 1998.

The Schering press release is also acceptable. The PM should call the sponsor and determine when it will be issued. A copy of this press release as well as the 'Dear Dr' letter should be forwarded to the FDA press office. Copies of these and the approved product label should be forwarded to MedWatch.

The CMC issues will be addressed in the chemistry review.

Recommendation: An approval letter should be drafted for signature today. The approval letter should acknowledge the Phase 4 commitments.

Recommended Regulatory Action: Approval letter

N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: x Approvable _____ Not Approvable

Signed: Medical Reviewer: /S/ Date: 12/4/98

Medical Team Leader: /S/ Date: 12/4/98

DUPE

DEC - 2 1998

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA 20-470	APPLICATION TYPE:	CMC Supplement
SPONSOR:	Schering	PRODUCT/PROPRIETARY NAME:	Claritin-D 24 Hour
		USAN / Established Name:	Loratadine/PSE
CATEGORY OF DRUG:	Antihistamine/ decongestant	ROUTE OF ADMINISTRATION:	oral
REVIEWER:	Honig	REVIEW DATE:	December 1, 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
November 23, 1998	November 23, 1998	Additional Response to FDA request	see below under overview

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review: Reports of serious adverse events involving esophageal and upper gastrointestinal obstruction associated with use of Claritin-D 24 Hour tablets has resulted in labeling changes for the approved product. In addition, the sponsor has attempted to address the issue by reformulating the product to change its physiochemical properties (i.e. shape and stickiness). The reformulated product (Oval tablet) was not approved because bioequivalence to the approved Claritin-D 24 Hour has not been demonstrated. Specifically, the reformulated product is not bioequivalent to the reference product for parent loratadine. As serious adverse events involving esophageal obstruction continued to be received (>55 to date), the sponsor was asked to relabel the currently marketed product and follow-up with a 'Dear Dr.' correspondence while a clinical trial was being designed and conducted. Subsequent discussions with the sponsor addressed the possibility of approving the previously NA's supplement on the basis of PK/PD analyses from the existing Claritin and Claritin-D 24 Hour database. Specifically, the sponsor was asked to demonstrate that the bioinequivalence of parent loratadine (10% decrease) was clinically irrelevant on the basis of cross-study comparisons of relevant pharmacokinetic and efficacy data. These data are reviewed below.

Outstanding Issues: Phase 4 commitments

Recommended Regulatory Action: Approval letter

N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: ____x____ Approvable _____ Not Approvable

Signed: Medical Reviewer: /S/ Date: 12/1/98

Medical Team Leader: /S/ Date: 12/4/98

cc DIV DMC mem.
Initial 12/3/98

Background:

The reformulated product (Oval) was bioequivalent for the metabolite (DCL) and pseudoephedrine components. The table below summarizes the findings for parent loratadine.

Summary of BE data for the loratadine component:

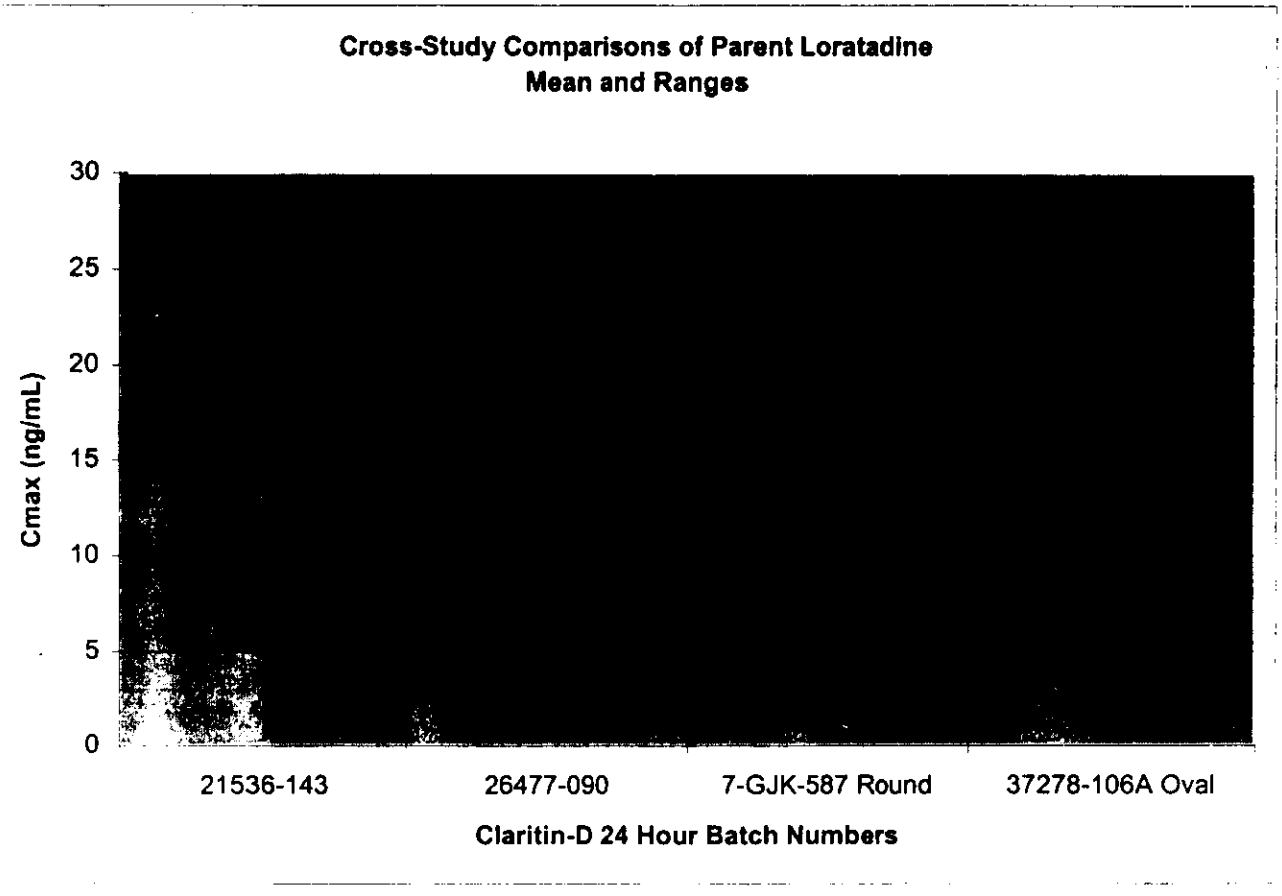
Parameter	Unit	n	Approved Claritin-D 24 Hour (mean)	Reformulated Claritin-D 24 Hour (mean)	Point Estimate	90% CI
Cmax	ng/mL	24	11.2	9.75	0.91	0.77-1.08
AUC0-∞	ng-hr/mL	24	63.1	57.5	0.89	0.71-1.12

The sponsor has submitted summary PK data from the Claritin-D 24 Hour and Claritin RediTabs programs. These are summarized in the figures below. In each of the figures, the mean and ranges for Cmax and AUC of parent loratadine are shown.

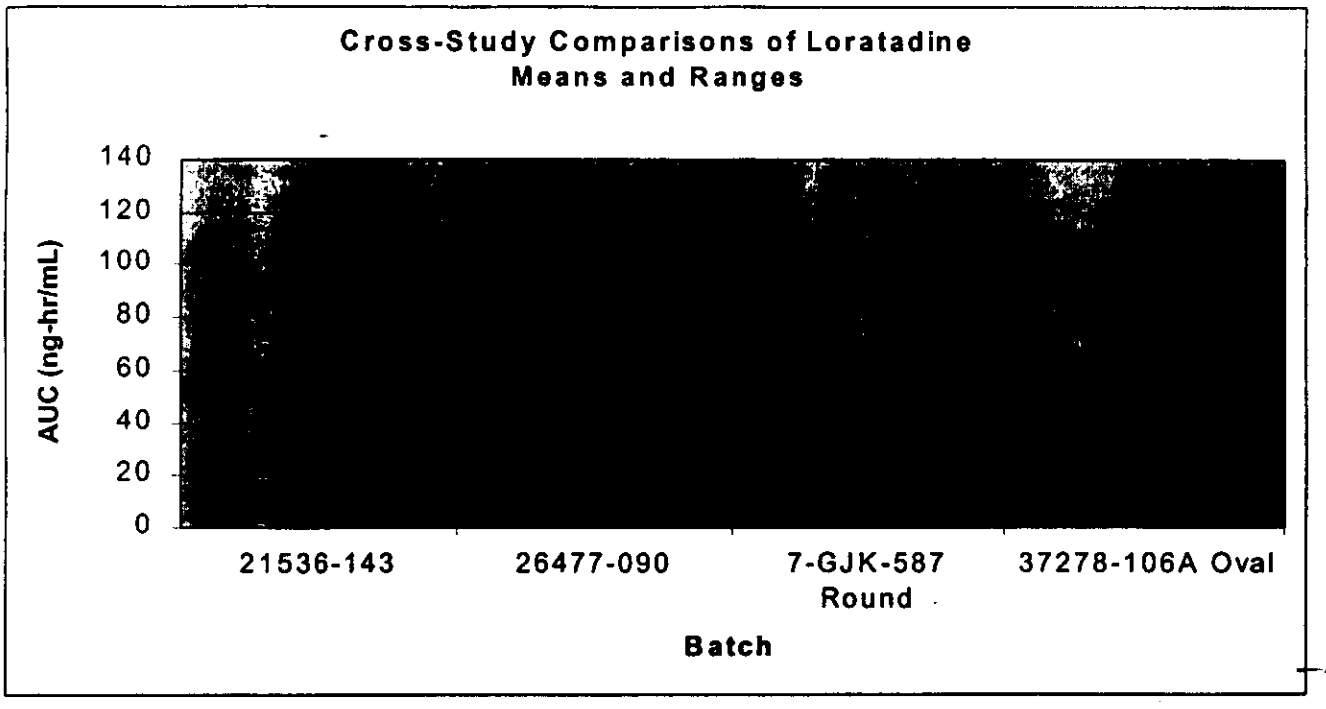
1. Claritin-D 24 Hour program:

These are data obtained from studies with TBM batches of Claritin-D 24 Hour. The proposed reformulation is designated by Batch #37278-106A (Oval).

Cmax:



AUC:



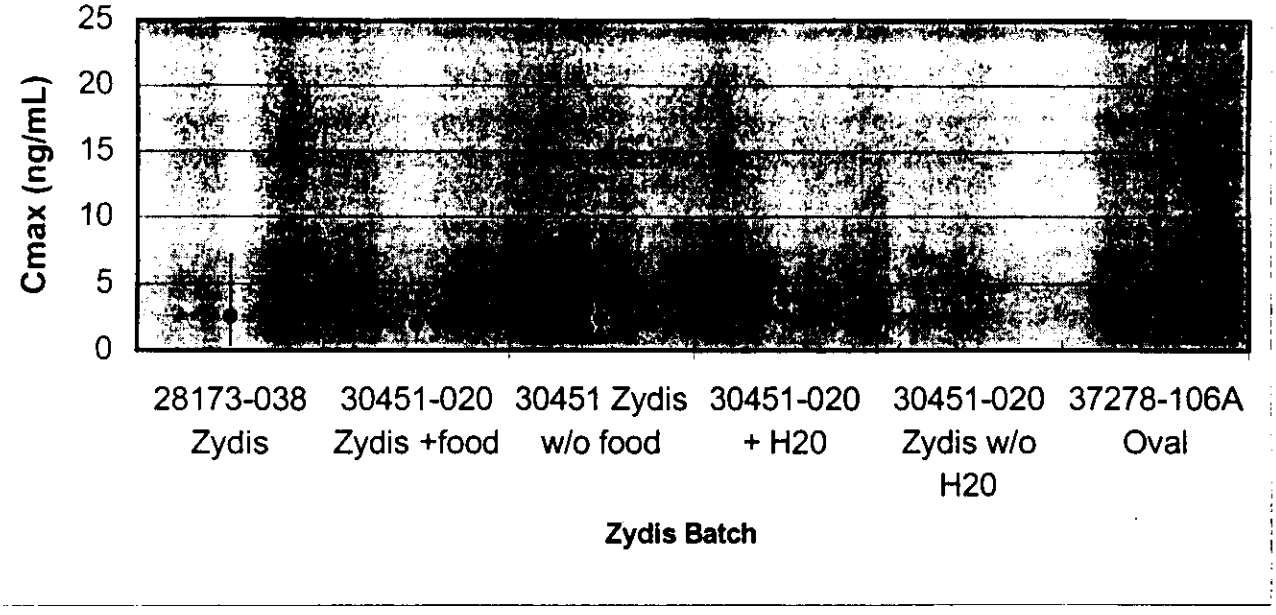
Reviewer comment: These cross-study comparisons of PK parameters provides an interesting perspective on the variability of the loratadine moiety after administration of the same nominal dose to various subjects. What is particularly fascinating is the consistently higher point estimates for parent loratadine in the bioavailability study conducted with the reformulated product. The point estimates for Cmax and AUC are approximately 3 and 5 times higher, respectively, for both formulations tested in that study than seen in the other studies shown above. All studies were relatively small (18-24 patients) and employed single-dose administration of the loratadine product. The sponsor was asked for potential explanations for this phenomenon and none were offered. The sponsor has provided assurance that the assay has remained consistent and unchanged throughout these studies. It is also very interesting that, in the face of these large cross-study differences in loratadine concentrations, the metabolite (DCL) concentrations were relatively consistent across all studies (AUCs = 27.7 to 43.8 ng-hr/mL). There were no pharmacokinetic data obtained during the course of efficacy studies that would allow a direct comparison of PK-clinical effect relationships.

2. Claritin RediTabs Program:

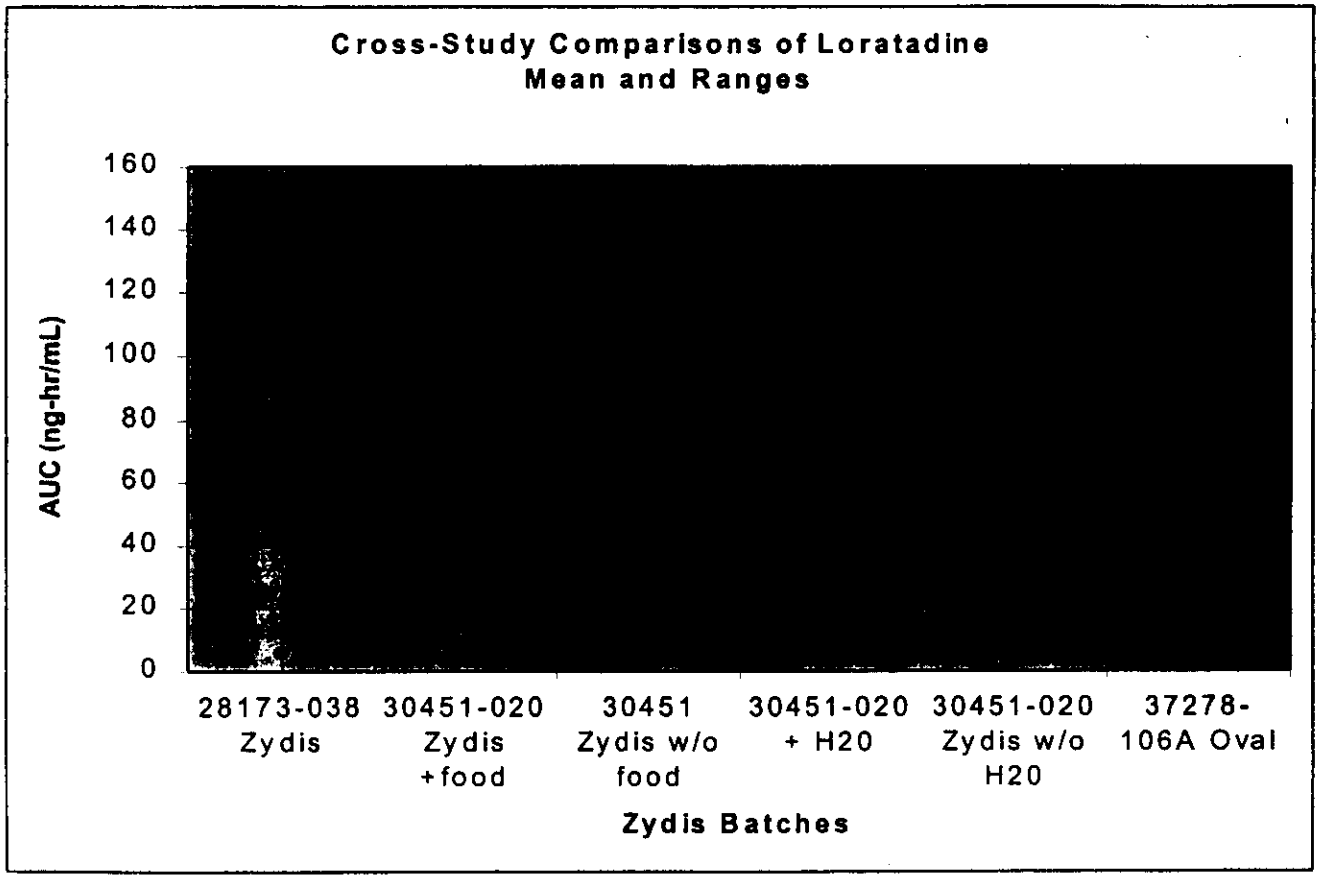
These are data obtained from studies with TBM batches of Claritin RediTabs (Zydis). There are also data from the approved Claritin Tablet formulation. For ease of comparison, the summary data from the proposed reformulation is included and designated by Batch #37278-106A (Oval).

Cmax:

Mean and Ranges



AUC:



Reviewer comment: Again, the concentrations observed in the Claritin-D 24 Hour reformulation are higher than those observed for Claritin RediTabs. The lower ranges for both parameters are lower for RediTabs than the Oval reformulation are therefore 'bracketed' by the available data. Again, there are no clinical efficacy data directly linked to the pharmacokinetic data provided.

Data from Claritin Tablets:

The sponsor has also included data from Claritin Tablets. In each case, these are the only head-to-head comparisons to Claritin-D 24 Hour or Claritin RediTabs that are available. These data for the loratadine component are summarized in the tables below.

Claritin Tablet:

	Loratadine		DCL	
Formulation	Cmax (ng/mL) Range	AUC (ng-hr/mL) (Range)	Cmax (ng/mL) Range	AUC (ng-hr/mL) (Range)
Claritin-D 24 Hour	2.79	6.36	2.28	29.1
Claritin	2.55	5.87	2.14	27.7

Reviewer comment: These data indicate that the loratadine component of the approved Claritin Tablets is 8.6% less for Cmax and 7.7% less for AUC than the TBM Claritin-D 24 Hour tablet. The clinical development program for Claritin-D 24 Hour consisted of studies of the product versus its components versus placebo (Studies S89-136/206). These data are extensively reviewed in the MOR for NDA 20-470 dated 3/15/95.. For the antihistamine responsive complex of Total Symptom Score less congestion, both Claritin-D 24 Hour and Claritin Tablets were statistically superior to placebo. These data provide a link from the pharmacokinetic differences seen above and clinical efficacy data and allow a conclusion that up to an 8.6% reduction in Cmax or a 7.7% reduction in AUC result in a clinically effective product. The reformulated Claritin-D 24 Hour product has approximately a 10% reduction in Cmax and AUC from the marketed product.

Data provided by the sponsor also allows direct head-to-head comparison of Claritin Reditabs to Claritin Tablets. These data from Study C91-339 are reviewed in detail in the MOR for NDA 20-704 (Zydis) dated 9/5/96 are summarized below

	Loratadine		DCL	
Formulation	Cmax (ng/mL) Range	AUC (ng-hr/mL) (Range)	Cmax (ng/mL) Range	AUC (ng-hr/mL) (Range)
RediTabs	2.56	6.14	3.72	49.1
Claritin	2.11	4.64	3.66	48.4

Reviewer comment: Approved Claritin Tablets are bioequivalent to RediTabs for the DCL moiety but have a 17.5% relative reduction in Cmax and a 24.4% relative reduction in AUC from RediTabs for parent loratadine. The sponsor conducted a clinical program for RediTabs which included one study which evaluated RediTabs and the approved Claritin Tablets versus placebo. This was a large study in which approximately 175 patients were randomized to each of the treatment arms. This study (C94-038) is reviewed in detail in the MOR for NDA 20-704. In brief, for all composite endpoints (TSS, TNS, TNNS), Claritin RediTabs was numerically superior to Claritin Tablets. Furthermore, for the patient-diary reflectively and point-in-time scored endpoints of TSS, RediTabs and not Claritin Tablets were statistically superior to placebo at all timepoints. Claritin Tablets were only statistically superior to placebo at the Week 1 analysis of reflective TSS. Therefore, the relative reduction of 24.4% in AUC and 17.5% in Cmax was clinically meaningful in that Claritin Tablets were not able to demonstrate superiority to placebo in a study in which RediTabs had no difficulty demonstrating statistically significant differences from placebo.

***Reviewer conclusions**: There are no quantitatively defined PK/PD relationship for loratadine that would allow an easy interpretation of the clinical significance of whether a 10% reduction in Cmax and AUC for a reformulated product would be clinically significant. Head-to-head PK comparisons of bioinequivalent formulations of loratadine in conjunction with the few clinical trials in which these same formulations were studied allow some clinical foundation for a determination that an 8.6% reduction in Cmax and 7.7% reduction in AUC do not result in a clinically ineffective product. Furthermore, data from the Claritin Zydis program indicate that a 17.5% reduction in Cmax and 24.4%*

reduction in AUC result in a failure to demonstrate efficacy versus placebo in an otherwise successful study. This does not answer the question of whether the demonstrate 10% reduction in Cmax and AUC for the reformulated Claritin-D 24 Hour product leaves us with a clinically effective product. Cross-study PK comparisons indicate that Claritin-D 24 Hour is 'bracketed' on the low side by the point estimates and the lower ranges in these studies. These comparisons are, however, not scientifically rigorous.

Reviewer recommendation: *Based on cross-study analyses, dosing with the reformulated Claritin-D 24 Hour product results in plasma parent loratadine concentrations above those seen with other approved Claritin products. It can also be concluded that a reduction of up to 8.6% in Cmax and 7.7% in AUC results in a product that remains clinically effective. · Some comfort is derived from the fact that the reformulated product is bioequivalent to the marketed product for the major metabolite which is more potent as an antihistamine and may confer the bulk of the therapeutic benefit of the drug product. This conclusion is supported by preclinical data which indicate that the H1-receptor potency of the metabolite ranges from 2 to 10 times that of the parent loratadine. Furthermore, it is likely that DCL confers the bulk of the therapeutic benefit of the drug product because loratadine has a very short half-life, is nearly completely cleared from the plasma within 12 hours of dosing, and does not accumulate. Because the overriding public health benefit for getting the existing product off the market outweighs the benefit of relabeling the exisiting product for an AE that is not predictable, I recommend that this reformulated product be approved with the following stipulations as Phase 4 commitments.*

1. *The sponsor agrees to conduct single-dose, 5-way [redacted] crossover, bioavailability study with the reformulated Claritin-D 24 Hour product, Claritin-D 12 Hour, Claritin Tablets, Claritin RediTabs, and Claritin Syrup in adults. The protocol for this study should be received within 90 days of approval of this supplement and the trial should be initiated within 2 months.*

2. *The sponsor agrees to develop a prospective active surveillance program for assessing whether the issue of esophageal obstruction is eliminated by the availability of the reformulated product.* [redacted]

In addition to the above **Phase 4 commitments, the sponsor should agree to the following.**

1. Replacement/exchange of all existing Claritin-D 24 Hour marketed product at the pharmacy level within 14 days of approval.

2. The new product should be labeled as follows:

   Precautions, General: Because there have been reports of esophageal obstruction and perforation in patients who have taken a previously marketed formulation of Claritin-D 24 Hour Extended Release Tablets, it is recommended that patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis not use this product. Furthermore, since it is not known whether this formulation of Claritin-D 24 Hour Extended Release Tablets has the potential for this adverse event, it is reasonable to recommend that all patients take this product with a full glass of water (see Precautions, Information for patients; Adverse Reactions, Dosage and Administration).
   Because the doses…..

   Precautions, Information for Patients; same language as existing product (see Precautions, General; Adverse Reactions; Dosage and Administration)

   Adverse Reactions:

   …and cardiovascular collapse.
   There have been postmarketing reports of mechanical upper gastrointestinal tract obstruction and esophageal perforation in patients taking a previously marketed formulation of Claritin-D 24 Hour Extended Release Tablets. In some, but not all, of these cases, patients have had known upper gastrointestinal narrowing or abnormal

esophageal peristalsis. It is not known whether this reformulation of Claritin-D 24 Hour Extended Release Tablets has the potential for this adverse event (see Precautions, Dosage and Administration).

Dosage and Administration: same language as existing product except that 'glass of water' should be modified to 'full glass of water'. (see Precautions, Adverse Reactions).

3. Schering should prepare a straightforward 'Important Prescribing Information' correspondence detailing the problem with the old formulation, the reformulation to address this problem, and the revised product labeling. This should be prepared for DPDP review within 2 working days and be devoid of promotional language. A proposed distribution list should accompany the submission. Schering should consider offering to voluntarily exchange individual patient's supplies of the currently marketed Claritin-D 24 Hour Extended Release Tablets.

4. Schering should defer preparation of a PPI at this time.

4. FDA will prepare a talk paper to be released coincident with the approval of the new formulation.

cc:

NDA 20-470/Division file
HFD-570/MO/Honig
HFD-570/Biopharm/Uppoor
HFD-570/PM/Trout

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-4770/S005

CHEMISTRY REVIEW(S)

DEC - 4 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-570 DPDP	2. NDA NUMBER 20-470
3. NAME AND ADDRESS OF APPLICANT (City and State) Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S) SCS-005[BZ](11/5/98)* SCS-005[BZ](12/3/98)* *Subjects of current review
6. NAME OF DRUG Claritin-D 24 Hour Extended Release Tablets	7. NONPROPRIETARY NAME loratadine 10 mg/pseudoephedrine sulfate 240 mg	
8. SUPPLEMENT PROVIDES FOR: A different-shaped tablet (from round to oval) and the use of a [redacted] finishing coat with a [redacted] to minimize the potential for tablets to get lodged or adhere to the oropharyngeal cavity or gastrointestinal tract. Applicant is also including an additional blister packaging presentation,		
9. PHARMACOLOGICAL CATEGORY Antihistamine and decongestant	10. HOW DISPENSED RX x OTC ___	11. RELATED IND/NDA/DMF [redacted]
12. DOSAGE FORM(S) Tablet	13. POTENCY loratadine 10 mg and pseudoephedrine sulfate 240 mg	
14. CHEMICAL NAME AND STRUCTURE See USAN Dictionary.		15. RECORDS AND REPORTS CURRENT YES_NO_ REVIEWED YES_NO_

16. COMMENTS:
cc:
Orig. NDA #20-470
HFD-570/Div. File
HFD-570/CKim/
HFD-570/GPoochikian
HFD-570/GTrout
HFD-570/PHonig
R/D Init. By: 12/4/98
F/T by: CKim/12-04-98
*doc #:*N20470r2.s05.doc

17. CONCLUSIONS AND RECOMMENDATIONS
The supplement is approvable from CMC standpoints. However, project manager should remind applicant of their Phase IV commitments in the approval letter.

18. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Chong-Ho Kim, Ph.D.	CMC /S/	12-04-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-470/S005

STATISTICAL REVIEW(S)

DEC - 3 1998

STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

NDA Number:	20-470
Applicant:	Schering
Name of Drug:	Claritin-D (Loratadine/ pseudoephedrine hydrochloride combination tablet)
Statistical Reviewer:	Barbara Elashoff, M.S. (HFD-715)
Chemistry Reviewer:	Chong-Ho Kim, Ph.D. (HFD-570)
Document Reviewed:	November 5, 1998 Supplement
Date of Consult:	November 23, 1998

Summary of Review

- The sponsor proposed a 36-month expiration date based on 15-months of data for 30-, 100-, and 500-count bottles and a 21-month expiration date based on 15-months of data for [redacted] blister packages.

- The data support a 36-month expiration date for the 30- and 500-count bottles and a 21-month expiration date for the blister packages. However, these results are based on data extrapolation 21 and 6 months, respectively, beyond the range of storage time actually observed.

- The data for loratadine assay for the 100-count bottles fell out of specifications at 17 months for one batch (Batch #37278-97-AB). The batch had a negative, or downward, trend which was not seen in either of the other 2 batches for the 100-count bottles, nor any of the other batches for the other bottles or the blister packages. If this particular batch were ignored, the data for loratadine assay for the 100-count bottles support a 36 month expiration date. (These results are based on data extrapolation 21 months beyond the range of storage time actually observed.) However, if this batch is excluded, the requirement of testing at least 3 batches for this package type is no longer met.

I. Introduction

Schering has submitted 15-month stability data on 30-, 100- and 500-count HDPE bottles and [redacted] blister packages for Claritin-D. The sponsor has proposed a 36 month expiration period for all bottles and a 21 month expiration period for the blister packages. The reviewing chemist has requested Division of Biometrics to perform a statistical review and evaluation of the sponsor's stability data for the 30-, 100- and 500-count bottles and blister packages for each of the following parameters using the specifications listed below.

Table 1: Factors Used to Estimate Expiration Dates

Test Parameter	Minimum Specification	Maximum Specification
Moisture		
Loratadine Assay		
Pseudoephedrine Assay		
Dissolution Loratadine .5 hours		
Dissolution Pseudoephedrine 1 hour		
Dissolution Pseudoephedrine 2 hours		
Dissolution Pseudoephedrine 4 hours		

II. Reviewer's Analyses

The statistical procedures described in the FDA Guidelines (February 1987) were applied to the stability data provided by the sponsor. For all the parameters with both upper and lower specifications, the estimated expiration dates were calculated from the specifications limits and the two-sided 95% confidence intervals of the regression lines. For Dissolution of Loratadine [redacted] the estimated expiration dates were calculated from the lower specification limit and the lower one-sided 95% confidence intervals of the regression lines. The estimated expiration dating periods for the four package types are listed in Table 2.

The usual practice in stability analyses is to use 95% confidence intervals. The sponsor performed analyses using 90% confidence intervals. For this reason, expiration dates based on both 90% and 95% confidence intervals are presented in Table 2 below.

Table 2: Summary Table of Expiration Dates

(The estimated expiration date reflects the shortest time that a batch went out of specifications. For the estimated expiration dates of all the individual batches, see Appendix A Table A1.)

Package	Parameter	Intercepts	Slopes	Est. Exp. Date (95%)	Est. Exp. Date (90%)
30 count Bottles	Moisture	Separate	Pooled	≥ 48	≥ 48
	Loratadine Assay	Separate	Pooled	≥ 48	≥ 48
	Pseudoephedrine Assay	Pooled	Pooled	≥ 48	≥ 48
	Dissolution Loratadine .5 hours	Separate	Pooled	≥ 48	≥ 48
	Dissolution Pseudoephedrine 1 hour	Separate	Pooled	≥ 48	≥ 48
	Dissolution Pseudoephedrine 2 hours	Separate	Pooled	≥ 48	≥ 48
	Dissolution Pseudoephedrine 4 hours	Separate	Pooled	≥ 48	≥ 48
100 count Bottles	Moisture	Separate	Pooled	≥ 48	≥ 48
	[redacted]	[redacted]	[redacted]	17	19
	Pseudoephedrine Assay	Pooled	Pooled	≥ 48	≥ 48
	Dissolution Loratadine .5 hours	Separate	Pooled	≥ 48	≥ 48
	Dissolution Pseudoephedrine 1 hour	Separate	Pooled	≥ 48	≥ 48
	Dissolution Pseudoephedrine 2 hours	Separate	Pooled	≥ 48	≥ 48
	Dissolution Pseudoephedrine 4 hours	Separate	Pooled	≥ 48	≥ 48
500 count Bottles	Moisture	Separate	Separate	40	47
	Loratadine Assay	Separate	Pooled	≥ 48	≥ 48
	Pseudoephedrine Assay	Pooled	Pooled	≥ 48	≥ 48
	Dissolution Loratadine .5 hours	Separate	Pooled	≥ 48	≥ 48
	Dissolution Pseudoephedrine 1 hour	Separate	Pooled	≥ 48	≥ 48
	Dissolution Pseudoephedrine 2 hours	Separate	Separate	≥ 48	≥ 48
	Dissolution Pseudoephedrine 4 hours	Pooled	Pooled	≥ 48	≥ 48
Blisters	Moisture	Separate	Pooled	30	32
	Loratadine Assay	Separate	Pooled	≥ 48	≥ 48
	Pseudoephedrine Assay	Separate	Pooled	≥ 48	≥ 48
	Dissolution Loratadine .5 hours	Separate	Pooled	≥ 48	≥ 48
	Dissolution Pseudoephedrine 1 hour	Separate	Separate	34	38
	Dissolution Pseudoephedrine 2 hours	Separate	Separate	37	41
	Dissolution Pseudoephedrine 4 hours	Separate	Separate	34	39

The sponsor proposes a 36 month expiration date for all bottles and a 21 month expiration date for the blister packages. The data support a 36 month expiration date for 30- and 500-count bottles and a 21 month expiration date for the blister packages. The data do not support a 36 month expiration date for the 100-count bottles because the lower confidence limits of two batches exceeded the loratadine assay lower specification limit in less than 30 months (using all data for all batches). The remainder of this review focuses on the loratadine assay data.

III. Loratadine Assay Data

Graphs of the loratadine assay data for all batches for all bottles and the blister packages are in the Appendix. Table 3 below presents the expiration dates for all the batches for loratadine assay for the 100-count bottles.

Table 3: Loratadine Assay for 100-count Bottles

	Estimated Expiration Date (months)	
Batch	95% CI	90% CI
96-AB	39	44
97-AB	17	19
106-AB	29	46

The sponsor concluded that the data support a 36 month expiration date for the 100-count bottles. The discrepancy with the reviewer's results was due to

a) the sponsor deleting an outlier, the 12 month time point in Batch #97-AB; and
b) the sponsor using 90% confidence intervals.

In order to examine the reasoning behind the sponsor's deletion of an outlier, the following table presents the results of the 100 Count Bottles for Loratadine Assay for the 25/60% RH data in Batch #97-AB:

Table 4: 100 Count Bottles Loratadine Assay at 25/60% RH
Batch 37278-097-AB

Time	Loratadine Assay	
	(mg/tab)	(% LS)
Initial	9.56	95.6
3	9.56	95.6
6	9.50	95.0
9	9.45	94.5
12	9.19	91.9
15	9.39	93.9
Mean*		94.92
Std Dev*		0.73
Mean ± 2 Std Dev		(93.5, 96.4)

* Excludes month 12.

The expiration dates calculated using the 90 and 95% confidence intervals with and without the 12 month data for Batch #97 are presented below.

Table 5: Expiration Dates Using 90 and 95% CI with and without aberrant data point

	90% CI		95% CI	
Batch	Including Month 12	Excluding Month 12	Including Month 12	Excluding Month 12
097-AB	19	37	17	35

The sponsor deleted the 12-month time point because "the 91.9% value lies beyond two sigma levels from the mean assay value for this batch which suggest that, although the value is valid and within specification, it may not be representative of the loratadine stability trend," (page 5 of sponsor's report). Actually, the 91.9% value is the third of four decreasing values, therefore, it *is* representative of the loratadine stability trend in this batch.

The sponsor also argues that the aberrant data point in Batch #97 should be deleted because it "did not represent the loratadine stability trend observed in the three other package types for this batch". The graphs show the trends for all the package types for loratadine assay (see Appendix A). The trends in all the batches, except for Batch #97, are increasing. Batch #97 decreases. This may support ignoring the entire batch (discussed further below on page 6), however, it does not support deleting one specific data point. The data point in question, as stated above, is the third of four decreasing values. Therefore, it is not the only data point contributing to the downward trend.

The sponsor's analysis of this "outlier" value is flawed for three additional reasons:

- When defining an "outlier", the mean and standard deviation should be calculated *including* the aberrant data point, not excluding it. When including month 12 in Batch #97-AB, the mean ± SD are: 94.4 and 1.40. The month 12 time point (91.9%) is within 2 standard deviations of the mean (91.6, 97.2).

- The sponsor does not apply the "more than 2 standard deviations away from the mean" consistently. When the sponsor's rule for excluding outliers is applied to the data from the other batches, Batch #106 100-count Bottles has an expiration date of 14 months (see Appendix B).

- When the results are dependent on time, an "outlier" data point should be compared with other data points that are likely to have similar values (e.g., other month 12 values in other batches) not other data points which are likely to be different (e.g., data points during months before and after month 12). When the month 12 data point in Batch 97-AB (91.9%) is compared against other data points at month 12 in the other batches, it is within 2 standard deviations from the mean (89.9, 100.0). See Appendix C for more details.

Therefore, the data point should not be excluded from the analysis.

In general, it is not a good practice to delete specific observations from analyses, unless they have known assay or other errors. However, it is noteworthy that there were 11 batches (using the 30-, 100-, and 500-count bottles and the blister packages) that had small increasing trends for loratadine assay (slopes ranged

from [redacted] and only 1 batch with a decreasing trend. This may indicate that the batch with the decreasing trend is not a reliable source of information. When the entire batch is excluded from the analysis the slopes can be pooled which results in smaller standard errors and narrower confidence intervals. The data, excluding Batch #97 from the analysis, support a 36 month expiration date. However, if Batch #97 is excluded, the requirement of testing at least three batches for this package type is no longer met.

Table 6: Loratadine Assay for 100-count Bottles

	Estimated Expiration Date (months)	
Batch	95% CI	90% CI
96-AB	≥ 48	≥ 48
106-AB	≥ 48	≥ 48

IV. Conclusions

The estimated expiry dating periods presented in this review are based on data extrapolation beyond the range of storage time actually observed, which is valid under the assumption that the pattern of deterioration does not change significantly over the extrapolation period.

The proposed 36 month expiration date for 30- and 500-count bottles and the proposed 21 month expiration date for the blister packages are supported by the 15 month data the sponsor submitted. This is based on the specification limits of moisture, assay, and dissolution.

The proposed 36 month expiration date for the 100-count bottles is not supported by the loratadine assay data if the data at 12 months from Batch #97 is included in the analysis. Batch #97 is the only batch (out of 11) with a negative slope for loratadine assay. It is possible that it is not representative of the true loratadine assay trend. If all the data from Batch #97 are excluded from the analysis, the data from Batches #96 and #106 do support a 36 month expiration date. However, if Batch #97 is excluded, the requirement of testing at least 3 batches for this package type is no longer met.

/S/
Barbara Elashoff

Concur: Dr. Lin /S/ 12/3/98

cc:
Orig. NDA 20-470
HFD-570 / Division File
HFD-570 / GTrout, CHKim, GPoochikian, Y-YChiu, PHonig
HFD-715 / Division File
HFD-715 / ENevius, SWilson, KLin, BElashoff

Appendix A

Table A1: Summary Table of All Intercepts and Slopes (using all observed data)

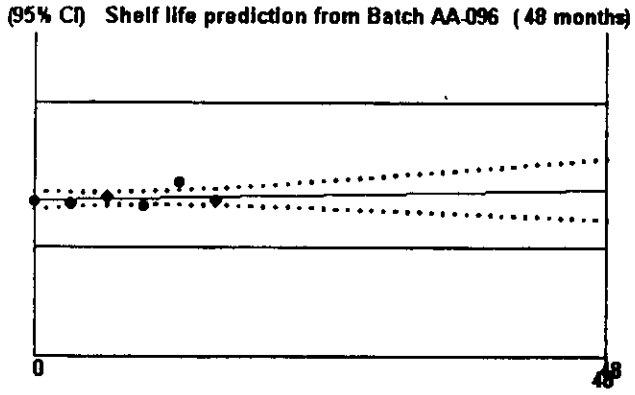
Package	Parameter	Batch	N	# of Months with observed data	Intercept	Slope	Estimated Expiration Date
30 Count Bottles	Moisture	AA-096	6	15	3.7	.027	48
		AA-097	6	15	3.8	.027	48
		AA-106	6	15	2.6	.027	48
	Assay: Lorat	AA-096	6	15	96.5	.033	48
		AA-097	6	15	94.6	.033	48
		AA-106	6	15	93.2	.033	48
	Assay: Pseudo	All Batches	18	15	98.2	.031	48
	Diss Lorat .5 hr	AA-096	6	15	93.6	.076	48
		AA-097	6	15	88.8	.076	48
		AA-106	6	15	90.9	.076	48
	Diss Pseud 1 hr	AA-096	6	15	24.	.025	48
		AA-097	6	15	22.6	.025	48
		AA-106	6	15	24.1	.025	48
	Diss Pseud 2 hr	AA-096	6	15	34.9	.013	48
		AA-097	6	15	33.7	.013	48
		AA-106	6	15	35.4	.013	48
	Diss Pseud 4 hr	AA-096	6	15	50.4	.019	48
		AA-097	6	15	49.2	.019	48
		AA-106	6	15	50.7	.019	48
100 Count Bottles	Moisture	AB-096	6	15	3.6	.018	48
		AB-097	6	15	3.7	.018	48
		AB-106	6	15	2.5	.018	48
	Assay: Lorat	AB-096	6	15	96.2	.161	39
		AB-097	6	15	95.9	-.191	17
		AB-106	6	15	92.4	.116	29
	Assay: Pseudo	All Batches	18	15	98.3	.021	48
	Diss: Lorat .5 hr	AB-096	6	15	93.3	.14	48
		AB-097	6	15	89.3	.14	48
		AB-106	6	15	89.	.14	48
	Diss: Pseud 1 hr	AB-096	6	15	24.2	.041	48
		AB-097	6	15	22.7	.041	48
		AB-106	6	15	24.	.041	48
	Diss: Pseud 2 hr	AB-096	6	15	35.4	-.032	48
		AB-097	6	15	34.4	-.032	48
		AB-106	6	15	35.6	-.032	48
	Diss: Pseud 4 hr	AB-096	6	15	51.1	-.01	48
		AB-097	6	15	49.4	-.01	48
		AB-106	6	15	50.9	-.01	48

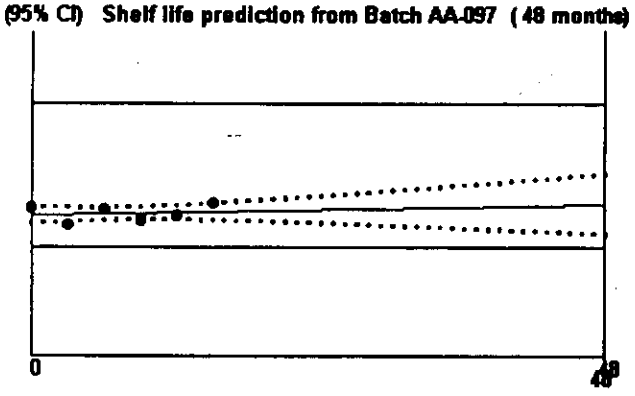
Package	Test	Batch	N	# of Months with observed data	Intercept	Slope	Estimated Expiration Date
500 Count Bottles	Moisture	AC-96	6	15	3.6	.008	48
		AC-97	6	15	3.5	.027	45
		AC-106	6	15	2.6	-.005	40
	Assay: Lorat	AC-96	6	15	95.6	.13	48
		AC-97	6	15	93.2	.13	48
		AC-106	6	15	92.5	.13	48
	Assay: Pseudo	All Batches	18	15	98.	.049	48
	Diss: Lorat .5 hr	AC-096	6	15	92.1	.146	48
		AC-097	6	15	90.7	.146	48
		AC-106	6	15	89.2	.146	48
	Diss: Pseud 1 hr	AC-096	6	15	24.3	<0.001	48
		AC-097	6	15	23.7	<0.001	48
		AC-106	6	15	23.7	<0.001	48
	Diss: Pseud 2 hr	AC-096	6	15	35.	.029	48
		AC-097	6	15	34.8	.01	48
		AC-106	6	15	35.7	-.133	48
	Diss: Pseud 4 hr	All Batches	18	15	50.7	-.054	48
Blister Packages	Moisture	AE-96	6	15	3.6	.059	31
		AE-97	6	15	3.6	.059	30
		AE-106	6	15	2.6	.059	44
	Assay: Lorat	AE-96	6	15	96.4	.02	48
		AE-97	6	15	94.6	.02	48
		AE-106	6	15	94.	.02	48
	Assay: Pseudo	AE-96	6	15	98.6	.005	48
		AE-97	6	15	97.7	.005	48
		AE-106	6	15	99.1	.005	48
	Diss: Lorat .5 hr	AE-096	6	15	91.8	-.06	48
		AE-097	6	15	90.	-.06	48
		AE-106	6	15	90.1	-.06	48
	Diss: Pseud 1 hr	AE-096	6	15	23.	.133	34
		AE-097	6	15	23.2	.019	48
		AE-106	6	15	24.1	-.019	48
	Diss: Pseud 2 hr	AE-096	6	15	33.4	.21	37
		AE-097	6	15	35.1	-.086	48
		AE-106	6	15	36.	-.095	48
	Diss: Pseud 4 hr	AE-096	6	15	49.2	.152	34
		AE-097	6	15	50.2	-.076	48
		AE-106	6	15	52.	-.133	48

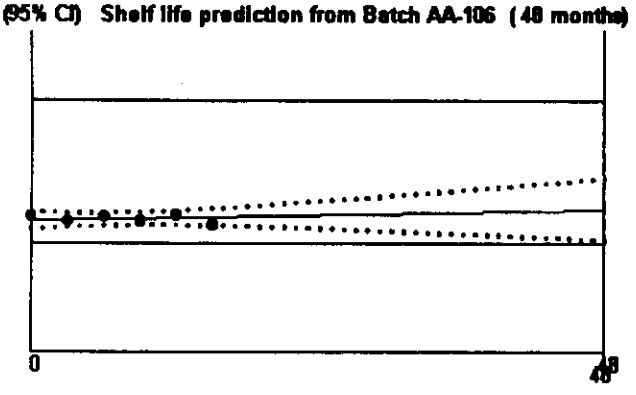
30 Count Bottles: Loratadine Assay Expiry

AA-096	48	Max Spec:
AA-097	48	Min Spec:
AA-106	48	

Separate intercepts and common slope





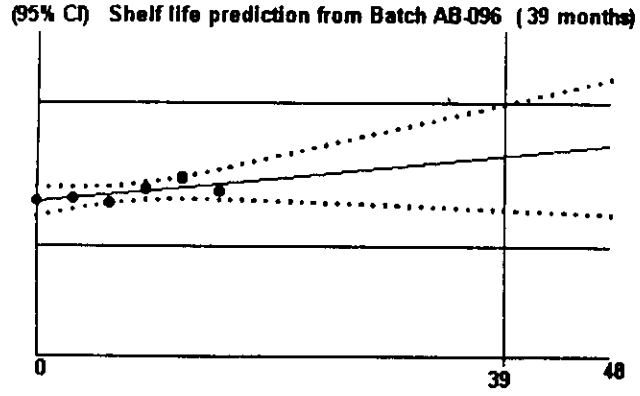


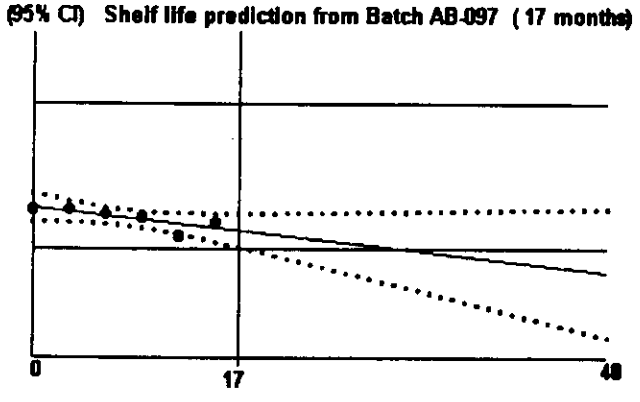
APPEARS THIS WAY
ON ORIGINAL

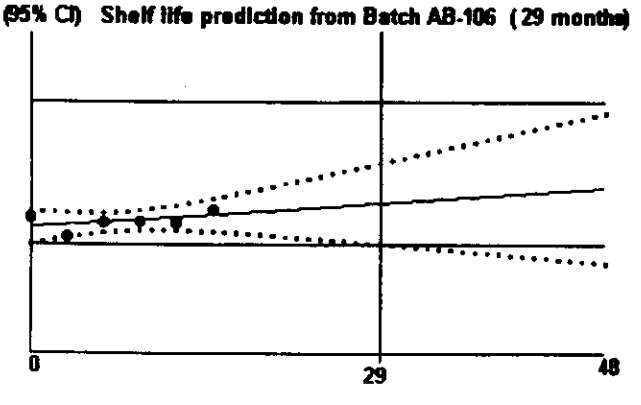
100 Count Bottles: Loratadine Assay Expiry

AB-096	39	Max Spec:
AB-097	17	Min Spec:
AB-106	29	

Separate intercepts and separate slopes







APPEARS THIS WAY
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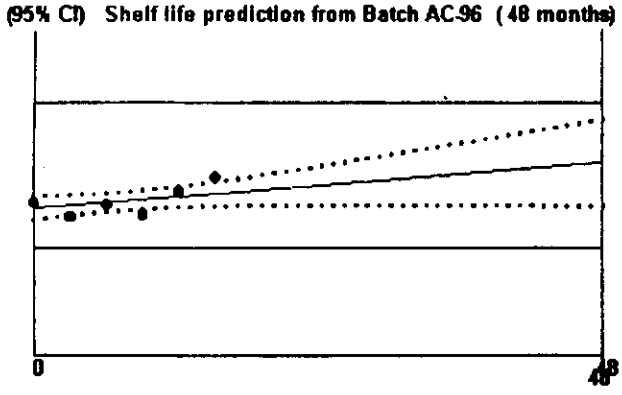
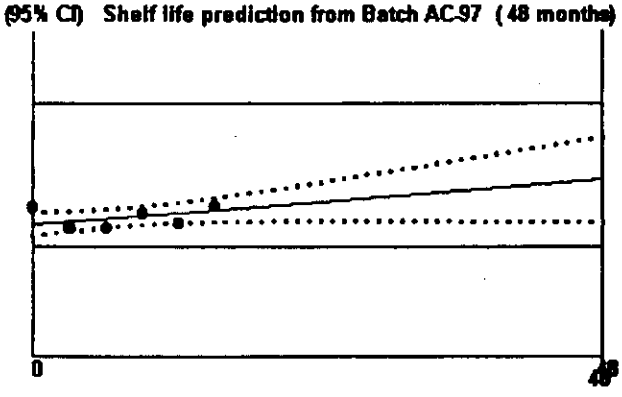
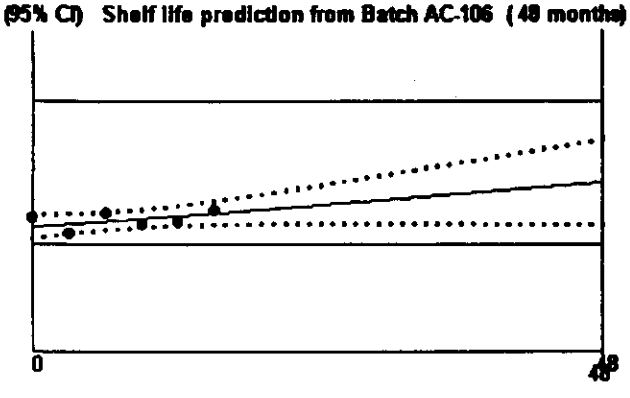
500 Count Bottles: Loratadine Assay Expiry

AC-96	48	Max Spec:
AC-97	48	Min Spec:
AC-106	48	

Separate intercepts and common slope





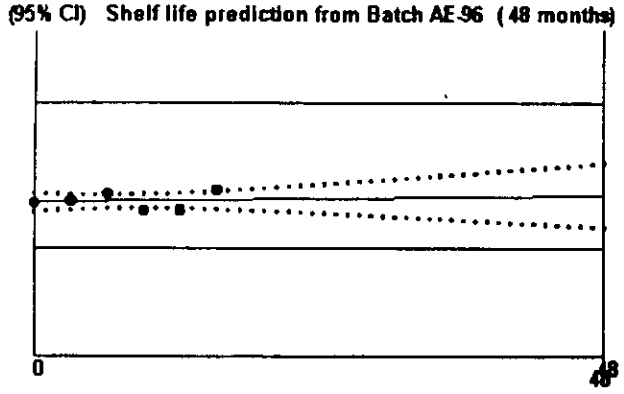


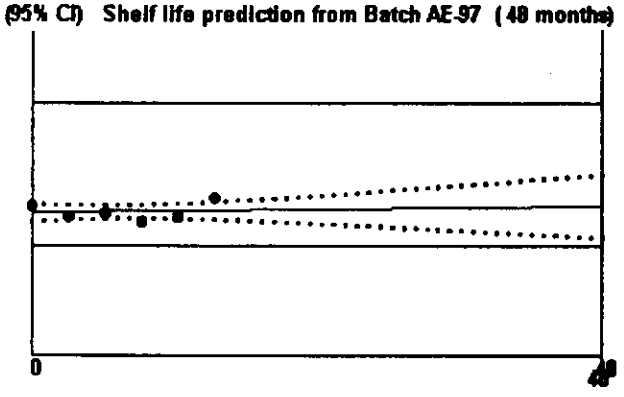
APPEARS THIS WAY
ON ORIGINAL

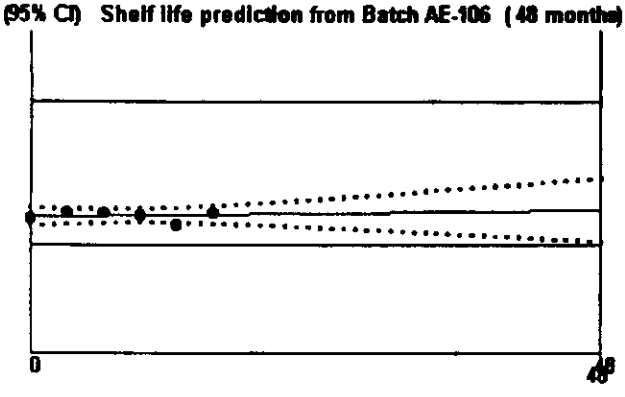
Blister Packages: Loratadine Assay Expiry

AE-96	48	Max Spec:
AE-97	48	Min Spec:
AE-106	48	

Separate intercepts and common slope







APPEARS THIS WAY
ON ORIGINAL

Appendix B

The sponsor includes values that are more than 2 standard deviations away from the mean in other batches for this test parameter (loratadine assay) and other test parameters in the analyses. For example, the 15 month time point in 100-count bottles, Batch #106 for loratadine assay as shown in the following table, is more than 2 standard deviations away from the mean and is included in the sponsor's analysis.

Table B1: 100 Count Bottles Loratadine Assay
Batch 37278-106-AB

Time	Loratadine Assay	
	(mg/tab)	(% LS)
Initial	9.38	93.8
3	9.12	91.2
6	9.31	93.1
9	9.33	93.3
12	9.32	93.2
15	9.50	95.0
Mean*		92.92
Std Dev*		1.00
Mean ± 2 Std Dev		(90.9, 94.9)

* Excludes month 15.

The expiration dates calculated using the 90% and 95% confidence intervals with and without the 15 month data for Batch #106 are presented below.

Table B2: Expiration Dates Using 90% and 95% CI with and without aberrant datapoint

	90% CI		95% CI	
Batch	Including Month 15	Excluding Month 15	Including Month 15	Excluding Month 15
106-AB	46	[redacted]	29	[redacted]

Including the aberrant data point here *extends* the expiration date (rather than shortening it as it does in Batch #97). Therefore, if one were to apply a consistent exclusion rule to all the batches (i.e., exclude all data points more than 2 standard deviations from the mean), the data would support a 14-month expiration dating period.

Table B3: Loratadine Assay for 100-count Bottles

Estimated Expiration Date (months) Using 95% CI		
Batch	Exclude Data > 2 SD from mean	Include Data > 2 SD from mean
96-AB	39	39
97-AB	35	17
106-AB	14	29

Therefore, either with or without data points that are more than 2 standard deviations from the mean (using the sponsor's method of calculating the mean and standard deviation without the aberrant data point), the 100-count bottles have an expiration dating period less than 20 months.

Appendix C

The "outlier" data point should be compared with other data points that are likely to have similar values (such as other month 12 values in other batches) not other data points which are likely to be different (time dependent data). The month 12 data point from Batch #97 is within 2 standard deviations of the mean using the month 12 time points from the other batches.

Table ?: Month 12 from all the Batches

Package	Batch #	Loratadine Assay	
		(mg/tab)	(% LS)
30 ct Bottles	96-AA	9.91	99.1
	97-AA	9.45	94.5
	106-AA	9.41	94.1
100 ct Bottles	96-AB	9.96	99.6
	97-AB	9.19	91.9
	106-AB	9.32	93.2
500 ct Bottles	96-AC	9.78	97.8
	97-AC	9.34	93.4
	106-AC	9.33	93.3
Blisters	96-AE	9.54	95.4
	97-AE	9.41	94.1
	106-AE	9.30	93.0
	Mean*		94.95
	Std Dev*		2.52
	Mean ± 2 Std Dev		(89.90, 100.00)

*** Includes month 12 from batch 97-AB. The conclusions are similar when excluding Batch 97-AB from the calculation of the mean and standard deviation (Mean ± 2 SD: (90.33, 100.12). The conclusions are also similar when excluding the blisters.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-470/S005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DJ 1-12

DEC 3 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,470 SCS-005

SUBMISSION DATE: August 24, 1998
November 2, 1998
November 5, 1998
November 23, 1998

DRUG NAME AND FORMULATION: Claritin-D 24 tablets
(loratadine/pseudoephedrine sulfate extended release tablets)

SPONSOR: Schering Corporation, Kenilworth, NJ 07033

REVIEWER: Venkata Ramana S. Uppoor, Ph.D.

TYPE OF SUBMISSION: Tablet reformulation issue

BACKGROUND: Claritin-D 24 tablets contain 10 mg immediate release loratadine and 240 mg extended release pseudoephedrine. Claritin-D 24 hour tablet was approved on August 23, 1996 and is currently marketed as a round tablet. Several adverse events related to esophageal obstructions (and some cases of esophageal perforations) have been reported with this Claritin-D 24 tablet formulation, possibly due to sticking characteristics of this product. The sponsor has therefore reformulated the round Claritin-D tablet to an oval shaped tablet with an added [redacted] coating and an [redacted] In support of this reformulation, a 2-way crossover bioequivalence study was conducted. This study failed to meet the bioequivalence criteria on the parent loratadine (with a point estimate of 0.91 on Cmax and 0.89 on AUC and a confidence interval of 0.77 – 1.08 and 0.71 – 1.12 on Cmax and AUC). The sponsor was sent a non-approval letter since bioequivalence was not demonstrated between the currently approved and the reformulated Claritin-D 24 hour tablet. In addition, during the review cycle, the sponsor was requested to submit dissolution data on the loratadine entity (data on pseudoephedrine previously submitted and reviewed, see review dated 11/23/98 by Dr. Brad Gillespie).

OBJECTIVE: This review will cover four submissions that were sent by the sponsor in response to the non-approval letter. These submissions cover the sponsor's responses to provide

1) Rationale for decision making based solely on pharmacokinetics of DCL metabolite
2) A pharmacokinetic justification to widen the confidence intervals, based on high intrasubject variability
3) Dissolution profiles of loratadine comparing the reformulated Claritin-D 24 hour tablet to the round, original Claritin-D 24 hour tablet and
4) Justification to demonstrate that the lower point estimate on parent loratadine

Cmax and AUC is not clinically relevant.

Points 1, 2 and 3 above will be covered in this review. Point 4 will be reviewed separately by the Medical Officer assigned to this drug product.

CURRENT SUBMISSION:

1. Rationale for decision making based solely on DCL metabolite: The sponsor states that the DCL metabolite is the major active moiety with up to ten times more potency than parent loratadine and has less variability. Therefore, the decision for approval of the oval Claritin-D 24 hour tablet should be based on DCL alone.

COMMENT: The use of parent drug is more appropriate than the metabolite for bioequivalence comparison in that parent is more sensitive to the formulation differences, if any. Further, both parent loratadine and the DCL metabolite are active. Therefore, it is important to evaluate both loratadine and the DCL metabolite.

2. Rationale of high intrasubject variability to approve the reformulated oval shaped Claritin-D 24 hour tablet even though it failed to demonstrate bioequivalence: The sponsor submitted a study report of study C97-006 titled "SCH29851: Study evaluating the bioequivalence of two standard commercial batches of Claritin 10 mg tablets: A 2-sequence, 4-period crossover study". This study evaluates the intrasubject variability (by administering Claritin tablets from the same batch twice in the same subjects) as well as inter-batch variability (by looking at 2 different batches of Claritin tablets).

According to the sponsor, results of this study indicate that the within subject variability on AUC of parent loratadine is in the range of 52 to 68% (for 2 batches) and on Cmax is 45 to 58%. The within-subject variability on the DCL metabolite (SCH 34117) was 17 to 35% on AUC and 16 to 31% on Cmax. Therefore, the sponsor claims that due to high intrasubject variability on parent loratadine, the decision of bioequivalence and the approval of the reformulated, oval Claritin-D 24 hour tablet should be based on the DCL metabolite. However, this data has not been critically evaluated by this reviewer.

COMMENTS: This study report and the data provided do not support widening the equivalence intervals to approve the new Claritin-D 24 hour product due to the following reasons:

1) The bioequivalence study C97-197-01 submitted previously to support the reformulation shows that it is not just variability that led to the results of lack of bioequivalence. The mean differences between the test and reference averages were different, by approximately 10%.
2) While the present submission indicates high intrasubject variability, this study was

conducted using Claritin tablets, not Claritin-D 24 tablets. Hence, one is not sure whether this intrasubject variability obtained from Claritin tablets apply to the current product under consideration. Further, we do not know if the intrasubject variability data obtained is truly due to variability in loratadine pharmacokinetics itself or indicative of poor product quality of the Claritin tablets.

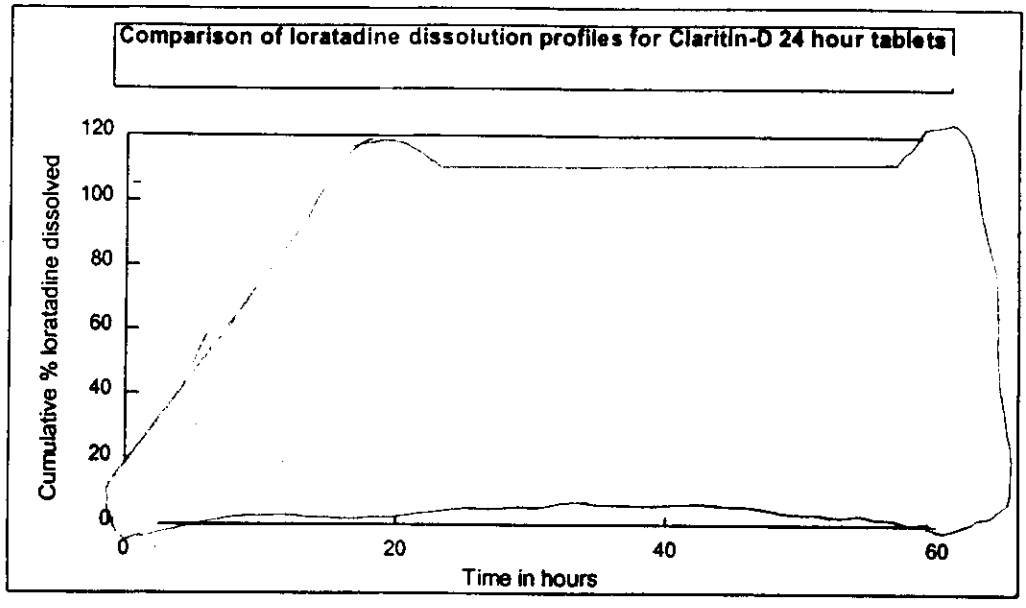
3) Further, this study C97-006 actually shows some unexpected results. Experience with bioequivalence data so far on loratadine indicates that the DCL metabolite did not fail the bioequivalence criteria. However, interestingly in this study, the 90% confidence intervals on Cmax for one batch ranged from 106 – 141 which is clearly not bioequivalent.

CONCLUSIONS: The information provided by the sponsor in items 1 and 2 above do not support the contention of using metabolite alone or widening the confidence intervals of parent for comparison. Therefore, the bioequivalence study and corresponding justification is not acceptable.

3. *Loratadine dissolution profiles as per [redacted] requested by the previous reviewer Dr. Gillespie*: In the original supplement, the sponsor provided comparative dissolution profiles in the approved dissolution media for pseudoephedrine moiety only. No such data was provided for loratadine. Should this reformulated product be approved, before its approval, the dissolution profiles for the new formulation should be compared to the currently approved product. The sponsor has submitted comparative dissolution profiles of loratadine using [redacted] The dissolution data is shown in the figure below.

COMMENT: These results suggest that dissolution profiles are comparable for the reformulated oval tablet compared to the currently marketed round tablets. Since within [redacted] valid f_2 comparisons could not be made between the two formulations. Note that slightly lower dissolution was found for the oval reformulated tablets, however these were 12 month stability samples which are being compared to the release ('0' time) samples of the round tablets.

CONCLUSION: The dissolution method, specifications and time points for the oval Claritin-D 24 hour tablets should be identical to those of the round currently marketed Claritin-D 24 hour tablets.



RECOMMENDATION:

These submissions have been reviewed by the Division of Pharmaceutical Evaluation-II in the Office of Clinical Pharmacology and Biopharmaceutics. Intrasubject variability data provided is not adequate to justify the approval of this product. The clinical justification provided is currently being reviewed by the Medical Officer. The dissolution method, time points and specifications for the reformulated oval shaped Claritin-D 24 hour tablet formulation should remain the same as the currently marketed round Claritin-D 24 hour formulation.

No comments need to be forwarded to the sponsor at this time.

/S/ 12/3/98

Venkata Ramana S. Uppoor, Ph.D.
Division of Pharmaceutical Evaluation - II

FT Initialed by Mei-Ling Chen, Ph.D /S/ 12/3/98

CC list: HFD-570: NDA 20,470; Division file; Gretchen Trout; Honig; HFD-870: Venkata Ramana S. Uppoor; Mei-Ling Chen, John Hunt, HFD-850: Lesko; CDR: Attn: Barbara Murphy.

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-470/S005

ADMINISTRATIVE DOCUMENTS

IMPORTANT PRESCRIBING INFORMATION

December 3, 1998

Dear Doctor:

Schering announces the introduction of new oval-shaped CLARITIN-D® 24 HOUR (10 mg loratadine/240 mg pseudoephedrine sulfate, USP) Extended Release Tablets to replace the existing round-shaped CLARITIN-D® 24 HOUR Extended Release Tablets. This conversion will occur immediately and will coincide with the discontinuation of the current tablet.

Associated with the current round CLARITIN-D® 24 HOUR, there have been post-marketing reports of mechanical upper gastrointestinal tract and esophageal/pharyngeal obstruction. In many of these cases, patients have required endoscopy to remove the tablet, and two of these patients have experienced esophageal perforation. Although some of these patients have had prior swallowing difficulties, most events have occurred in patients with no prior history. Therefore, swallowing difficulties cannot always be predicted.

As a result, a new oval-shaped CLARITIN-D® 24 HOUR tablet will be made available immediately to replace this round-shaped tablet. The new oval-shaped tablet is similar to that of a variety of other medications which have been safely marketed worldwide.

The new product will include the following labeling:

> **PRECAUTIONS: General:** Because there have been reports of esophageal obstruction and perforation in patients who have taken a previously marketed formulation of CLARITIN-D 24 HOUR Extended Release Tablets, it is recommended that patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis not use this product. Furthermore, since it is not known whether this formulation of CLARITIN-D 24 HOUR Extended Release Tablets has the potential for this adverse event, it is reasonable to recommend that all patients take this product with a full glass of water.
>
> **ADVERSE REACTIONS:** There have been postmarketing reports of mechanical upper gastrointestinal tract obstruction and esophageal perforation in patients taking a previously marketed formulation of CLARITIN-D 24 HOUR Extended Release Tablets. In some, but not all, of these cases, patients have had known upper gastrointestinal narrowing or abnormal esophageal peristalsis. It is not known whether this reformulation of CLARITIN-D 24 HOUR Extended Release Tablets has the potential for this adverse event.
>
> **DOSAGE AND ADMINISTRATION**: Adults and children 12 years of age and over: one tablet daily taken with a full glass of water.

Your Schering sales representative will make available to you sample packages of the new oval-shaped CLARITIN-D 24 HOUR tablet that you can provide to patients that you believe should not continue to use their current supply of the round-shaped CLARITIN-D 24 HOUR tablet.

You can further our understanding of adverse events by reporting all cases to Schering at 1-800-526-4099 or to the FDA MEDWATCH program by phone 1-800-FDA-1088, by FAX at 1-800-FDA-0178, by modem 1-800-FDA-7737, or by mail:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Additional questions concerning either the new or current CLARITIN-D® 24 HOUR (10 mg loratadine/240 mg pseudoephedrine sulfate, USP) Extended Release Tablets should be directed to Schering's Drug Information Services at 1-800-526-4099.

Please see enclosed full Prescribing Information.

Sincerely,

Richard Lorber, MD
Senior Director, Clinical Research, Allergy

CH0496/22388509 12/98

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-470/S005

CORRESPONDENCE

Dw File

INDUSTRY TELECONFERENCE MINUTES

Schering
NDA 20-470/S-005
Claritin-D 24 Hour
December 1, 1998

FDA REPRESENTATIVES

Laura Bradbard, Public Affairs Specialist, HFD-210
Peter Honig, Medical Officer, HFD-570
John Jenkins, Division Director, HFD-570
Gretchen Trout, Project Manager, HFD-570

SPONSOR REPRESENTATIVES

Alex Giaquinto, Regulatory Affairs

BACKGROUND: The Division requested this teleconference with Schering to discuss options with regard to this product.

The Division informed Schering that our primary public health goal is the approval of this supplement allowing for the marketing of the reformulated tablet. Therefore the Division has diverted resources and determined that we can most likely approve the new formulation fairly expediently; however, this is dependent on Schering's agreement to certain issues. These issues were discussed internally with Dr. Bilstad and Dr. Houn who agreed with the Division's position.

Before getting to the issues, the Division would like to make two points. First, the data and argument submitted by Schering referring to the bio-inequivalence issue was weak. However the Division conducted some cross-study comparisons and extrapolations to existing efficacy data and determined that the reformulated tablet is safe and effective. Due to the overriding public health benefit of removing the old formulation from the market, we will accept Schering's position. Second, the Division has diverted reviewers from other projects and we cannot continue to do this. The Division wants to approve the supplement by the end of the week; therefore Schering needs to respond to the issues within 24-48 hours.

Issue 1: Schering will exchange the new formulation for the old formulation down to the pharmacy level, and will commit to completing the exchange within 1-2 weeks of approval of the supplement. In addition, while this is not a requirement, Schering should consider offering an exchange program for patients with an existing supply of the current formulation.

Issue 2: Labeling for the reformulated tablet. Schering should submit draft labeling with the following language (this was read to Dr. Giaquinto and then sent via facsimile on December 1, 1998).

Precautions, General: *Because there have been reports of esophageal obstruction and perforation in patients who have taken a previously marketed formulation of Claritin-D 24 Hour Extended Release Tablets, it is recommended that patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis not use this product. Furthermore, since it is not known whether this formulation of Claritin-D 24 Hour Extended Release Tablets has the potential for this adverse event, it is reasonable to recommend that all patients take this product with a full glass of water (see Precautions, Information for patients; Adverse Reactions, Dosage and Administration).*

Because the doses.....

Precautions, Information for Patients; *same language as existing product (see Precautions, General; Adverse Reactions; Dosage and Administration)*

Adverse Reactions:

...and cardiovascular collapse.

There have been postmarketing reports of mechanical upper gastrointestinal tract obstruction and esophageal perforation in patients taking a previously marketed formulation of Claritin-D 24 Hour Extended Release Tablets. In some, but not all, of these cases, patients have had known upper gastrointestinal narrowing or abnormal esophageal peristalsis. It is not known whether this reformulation of Claritin-D 24 Hour Extended Release Tablets has the potential for this adverse event (see Precautions, Dosage and Administration).

Dosage and Administration: *same language as existing product except that 'glass of water' should be modified to 'full glass of water'. (see Precautions, Adverse Reactions).*

The **How Supplied** section will have to change to accommodate the new formulation (e.g., shape of the tablet etc.).

With regard to the Patient's Package Insert (PPI), this referred to the problem with the current formulation; not the reformulated tablet so the Division will not require a PPI at this time.

Issue 3: Upon approval of the supplement, Schering will issue a "Dear Doctor" letter that will be an "Important Prescribing Information" letter. This letter should communicate that the formulation has been changed and that the change is intended to address the esophageal obstruction issue, however it is unknown if the reformulation has alleviated the problem. This letter cannot be promotional. Schering should submit a draft letter within two days. A similar distribution list as was agreed to previously should be employed.

Issue 4: Phase 4 Commitments.

1. The Division wants a commitment from Schering to conduct a comparative bioavailability study of all the approved Claritin formulations, including the reformulated Claritin-D 24 Hour, with a [redacted]

The protocol will be submitted within 30 days of approval of the new formulations, and the study will initiate within two months of approval.

2. In order to determine whether the reformulation has solved the problem of esophageal obstruction, The Division wants a commitment from Schering to conduct an active surveillance study. The protocol should be submitted within 30 days. The Division will comment on the protocol and help Schering with the design if necessary.

Issue 5: CMC issues.

1. There are outstanding uncertainties with regard to the stability of this product, and based on the data submitted by Schering they can only get an 18 month expiration dating period for all packaging (bottles and blister packs). Any extension of this shelf life requires a prior approval supplement.

2. The stability protocol needs to be revised. We will fax specific comments to Schering by the end of the day.

3. The impurity specifications for the drug product need to be consistent with ICH guidelines.

CONCLUSION: Dr. Giaquinto agreed to discuss these issues with his management and submit a correspondence outlining the above commitments and agreements.

FOLLOW-UP TELECONFERENCE
December 2, 1998

FDA: Peter Honig, Medical Team Leader
John Jenkins, Division Director
Gretchen Trout, Project Manager
Ramana Uppoor, Clinical Pharmacology and Biopharmaceutics Team Leader

SCHERING: Mel Affrime, Clinical Pharmacology
Christopher Banfield, Clinical Pharmacology
Gerry Hajian, Biostatistics
Maggie Salfi, Biostatistics

Schering telephoned to ask for more information about the five-way replicate study that the Division requested. Schering questioned what the objective of the study was. The Division replied that there were two objectives: to characterize the relative bioavailability of the approved loratadine formulations

Schering replied that they now understand what the Division is looking for but stated that they do not know how to evaluate a five-way replicate study statistically. The published literature only includes methods for analysis for a two by four study.

The Division and Schering agreed that Schering will conduct a five-way, crossover study using all of the approved Claritin formulations (using the reformulated Claritin-D 24 Hour, not the old formulation), and then will do a second replicate study with just the syrup (within the same batch of syrup). Schering stated that they wil[redacted] The Division replied that this was reasonable.

The Division questioned if Schering had any explanation as to why the bioequivalence study of the oval vs. round Claritin-D 24 hour gave such different levels of DCL and loratadine compared to all prior PK studies. Schering had several speculations, but their bottom line was that they did not know.

CONCLUSION: Schering will conduct a five-way crossover study using all of the approved Claritin formulations, then will do a replicate study with the syrup. Schering will include language with regard to the design of the study in their commitment letter.

/S/

Gretchen Trout
Project Manager

cc: NDA 20-470
Div. File
HFD-570/Honig
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Uppoor
HFD-570/Jenkins
HFD-570/Trout

APPEARS THIS WAY
ON ORIGINAL

Concurrence on final draft:
Honig/12-8-98
Jenkins/12-9-98

MINUTES

DIN File

INDUSTRY TELECONFERENCE MINUTES

Schering
NDA 20-470/S-005
Claritin-D 24 Hour
December 11, 1998

FDA REPRESENTATIVES

Gretchen Trout, Project Manager, HFD-570

SPONSOR REPRESENTATIVES

Mary Jane Nehring, Director Marketing Products Support

BACKGROUND: Reference is made to the submission dated December 7, 1998, which contains a copy of the "Dear Healthcare Practitioner" letter which was issued with regard to the reformulated Claritin-D 24 Hour Tablet.

I telephoned Ms. Nehring to confirm that the letter which issued was in fact enclosed in a plain envelope, as was submitted to the NDA. Ms. Nehring confirmed that the letter was sent out in a plain envelope (i.e., "Important Prescribing Information" was not printed on the envelope). Ms. Nehring explained that Schering decided to use a plain envelope because this letter was a step down from the previous letter that the Division had requested (about the safety concerns with the round tablet), and the round tablet is already being taken off of the market. Ms. Nehring informed me that 550,000 of the 800,000 letters have already issued.

/S/

Gretchen Trout
Project Manager

cc: NDA 20-470
Div. File
HFD-570/Honig
HFD-570/Jenkins
HFD-570/Trout

APPEARS THIS WAY
ON ORIGINAL

MINUTES

Div File

DEC 2 4 1998

NDA 20-470

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Alexander R. Giaquinto, Ph.D.
Senior Vice President
Worldwide Regulatory Affairs

Dear Dr. Giaquinto:

Reference is made to your new drug application (NDA) 20-470 for Claritin-D 24 Hour (loratadine/pseudoephedrine sulfate) Extended Release Tablets, and to your submission dated December 7, 1998, which contained a copy of the "Important Prescribing Information" letter which Schering mailed to healthcare practitioners on December 7, 1998.

The issuance of the "Important Prescribing Information" letter was one of the agreements Schering made with this Division prior to the approval of supplement S-005 which provided for a reformulated tablet. The agreements and Phase 4 commitments related to the approval of supplement S-005 were discussed during a telephone conference between myself, Dr. Peter Honig, Ms. Laura Bradbard, and Ms. Gretchen Trout of the Agency, and you on December 1, 1998. During that teleconference I informed you that the "Dear Healthcare Practitioner" letter requested by the Division to be issued upon the approval of supplement S-005 should be an "Important Prescribing Information" letter. FDA regulations (21 CFR 200.5) state that for "Important Prescribing Information" letters the statement "Important Prescribing Information" shall appear on the far left third of the front of the envelope in 36 point type.

After approval of supplement S-005, we became aware that Schering had mailed the "Important Prescribing Information" letter in a plain envelope that did not comply with 21 CFR 200.5(c)(2). Schering did not discuss this deviation from the applicable regulations with the Division prior to mailing the letter. Ms. Mary Jane Nehring of Schering explained to Ms. Gretchen Trout during a teleconference on December 11, 1998, that Schering decided to utilize a plain envelope because this letter was a "step down" from the safety concerns for the original formulation, which were to be conveyed in an "Important Drug Warning" letter. While we agree that the letter regarding the reformulated Claritin-D 24 Hour Extended Release Tablet was a "step down" from the "Important Drug Warning" letter that had been planned in relation to the old Claritin-D 24 Hour Extended Release Tablet, the "Important Prescribing Information" letter for the reformulated tablet still conveyed important information that the Division believed needed to be communicated to physicians and other healthcare providers in a timely manner. The use of a plain envelope makes it more likely

that this letter was ignored by its recipients and, therefore, did not achieve its full intended educational effect. The clear intent of the distinctive envelope called for under 21 CFR 200.5 is to alert physicians and other healthcare providers of the important contents of the envelope in order to differentiate it from more routine mailings.

I am very disappointed by Schering's actions in this regard as they are out of step with the cooperative spirit the Division worked under in expediting the approval of supplement S-005 to address an important public health safety issue. I expect that Schering will fully comply with all of the other agreements and Phase 4 commitments detailed in our letter dated December 4, 1998, approving supplement S-005.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Div File

DEC - 4 1998

PROJECT MANAGER LABELING REVIEW

NDA: 20-470

PRODUCT: Claritin-D 24 Hour

SPONSOR: Schering

SUBMISSION: SCS-005 BZ

SUBMISSION DATE: December 3, 1998

REVIEW

This draft package insert was submitted as part of a chemistry supplement. The changes made to the package insert were either included in the original supplement submission (dated March 4, 1998) or were additional changes requested by the Division during the review process. These changes were reviewed by the Medical Officer or the Chemist and were found to be acceptable. I compared this draft package insert (dated December 3, 1998) with the last approved package insert for this product (SLR 002 dated August 19, 1997, approved on October 6, 1997) and found no additional changes, therefore this package insert is acceptable.

/S/

Gretchen Trout
Project Manager

CONCUR:

/S/ 12/4/98

Cathie Schumaker
Chief Project Manager

Cc: Orig. NDA 20-470
Div. File
HFD-570/Trout

APPEARS THIS WAY ON ORIGINAL

PROJECT MANAGER LABELING REVIEW

NDA:	20-470/S-005
REVIEW DATE:	March 16, 1999
DRUG:	Claritin-D 24 Hour (loratadine/pseudoephedrine) Extended-Release Tablets
SPONSOR:	Schering Corporation
PROJECT MANAGER:	Gretchen Trout
SUBMISSION:	December 18, 1998 (FA)

Background

The Division approved a chemistry supplement on December 4, 1998, including a draft package insert, submitted on December 3, 1998, and draft immediate container and carton labels submitted on March 4, 1998.

Review

The submitted FA is identical to the approved draft labeling, with the following exception. On the immediate carton and container labels, the statement [redacted] has been deleted and replaced with "RX only". This change is acceptable as per 63 FR 39100, July 21, 1998.

In the December 4, 1998, approval letter, the Division included an agreement by Schering to revise the carton and container labels within 3 months of the approval letter to read "Take with a full glass of water" in place of [redacted] I verified with Ms. Mary Jane Boyle, of Schering, on March 17, 1999, that Schering had revised the carton and container labels accordingly.

NOTE: The March 4, 1998, sample carton and container labels did not include a 30 count bottle label. However, the final printed 30 count bottle label has identical language to the 100 count bottle label, it is just a smaller label.

Recommendation

This labeling should be acknowledged and retained.

[redacted]

Gretchen Trout
Project Manager

3/18/99
Date

APPEARS THIS WAY
ON ORIGINAL

DIV File

MEMORANDUM

DATE: December 3, 1998

TO: NDA 20-470, SC8-005

FROM: John K. Jenkins, M.D
Director, Division of Pulmonary Drug Products HFD-570

12/3/98

SUBJECT: Overview of NDA Supplement Review Issues

This memorandum is written as an addendum to the Medical Officer Review prepared by Dr. Peter Honig dated December 2, 1998, regarding the above referenced supplemental application.

As noted in Dr. Honig's review, this supplemental application provides for a change in the formulation of Claritin-D 24 Hour Extended Release Tablets to address problems of esophageal obstruction that have been reported in association with the currently marketed formulation of Claritin-D 24 Hour. The new tablet includes a change in shape from round to oval and the addition of a new final coating. Schering believes that these changes will alleviate the esophageal obstruction problem seen with the currently marketed round, un-coated tablet. This belief is based on the fact that the shape, size, and coating of the new oval tablet are very similar to that of a Drixoral product that Schering has marketed for many years with no reports of esophageal obstruction.

In support of the reformulation, the sponsor conducted a comparative bioavailability study of the currently marketed Claritin-D 24 Hour tablet and the reformulated oval tablet. That study demonstrated that the two products were bioequivalent with regard to the pseudoephedrine component and the major active metabolite of loratadine (DCL) using the usual 80-125 bioequivalence interval standard. The two products were not bioequivalent for parent loratadine; i.e., the point estimates for the ratio of reformulated product to currently marketed product were 0.91 (90% CI 0.77-1.08) for Cmax and 0.89 (90% CI 0.71-1.12) for AUC. Thus the lower bound of the confidence interval was slightly below the usual boundary.

While there is no requirement for a showing of bioequivalence for approval of a new drug under an NDA (as opposed to the approval of a switchable drug under an ANDA), the failure to demonstrate bioequivalence for parent loratadine raised concerns regarding the efficacy of the new oval tablet. In other words, would the new oval tablet still be effective for relief of the antihistamine responsive symptoms of seasonal allergic rhinitis (SAR)? In the original supplemental application, the sponsor did not provide any clinical data to support a conclusion that the 10% mean decrease in parent loratadine seen with the reformulated product would have no impact on the efficacy of the product. Consequently, the supplemental application was not approved (there were also several CMC deficiencies noted in the action letter) and the

was advised that they would need to conduct a clinical trial with the reformulated to demonstrate efficacy for the antihistamine responsive symptoms of seasonal allergic rhinitis. This approach was similar to the approval standard for other new formulations of loratadine products, including the original approval of the currently marketed Claritin-D 24 Hour product (i.e., the approvals have been based on clinical efficacy and safety data, not a showing of bioequivalence).

Shortly after the not approvable letter was issued, the Division requested a meeting with Schering to discuss the growing number of postmarketing reports of esophageal obstruction, including two cases of esophageal perforation, related to use of Claritin-D 24 Hour tablets. At that meeting, the Division expressed concerns that cases of esophageal obstruction were being reported in patients with no prior history of swallowing difficulties or upper gastrointestinal tract pathology. This observation was of significant concern since it meant that individuals at risk could not be reliably predicted in advance and due to the fact that the reported events were generally of a serious nature; i.e., the vast majority of patients required endoscopy to remove the tablet. At that meeting, Schering declined the Division's suggestion that the round tablet be voluntarily removed from the market pending approval of the reformulated oval tablet. Schering argued that the problem would be best addressed by approval of the reformulated oval tablet as soon as possible and pointed out that the need to conduct a clinical trial would delay resubmission of the supplement until the Fall of 1999. Schering also argued that the slight decrease in parent loratadine levels observed for the oval tablet were not clinically significant and were well within the intrabatch and intrasubject variability seen with loratadine products. Schering was unable, however, to present any data at the meeting to support these claims. At that meeting, Schering agreed to modify the package insert for Claritin-D 24 Hour tablets to add contraindications, warnings, additional precautions, additional instructions for dosing and administration, and to develop a patient package insert to accompany the product. Schering also agreed to communicate these labeling changes to healthcare professionals through a "Dear Doctor" correspondence.

In parallel to the above noted labeling changes and "Dear Doctor" letter, Schering and the Division continued to explore possible ways to address the Division's concerns regarding the clinical impact of the mean 10% relative decrease in loratadine concentrations seen with the new oval tablet. The intent of these efforts was to explore all existing data that might adequately support the safety and effectiveness of the reformulated tablet without the delay that would result from the need to conduct a clinical trial. This parallel approach was considered prudent since it allowed the Division to address the immediate public health concern (i.e., relabeling the currently marketed product) while further exploring ways to expeditiously address the larger public health concern (i.e., cessation of marketing of the round Claritin-D 24 Hour tablet).

In this regard, Schering submitted for the Division's review available pharmacokinetic data from currently approved and marketed loratadine formulations as well as available comparative clinical efficacy data for currently marketed Claritin-D formulations.

One study submitted for review was a crossover PK study in which 30 subjects received tablets

from two separate marketed batches of Claritin tablets in a replicate manner (i.e., each subject received tablets from each batch on two separate study days). The data from this study showed that neither parent loratadine nor DCL were bioequivalent within the same batch. However, when the data from the two batches were combined, both parent loratadine and DCL were bioequivalent. These data confirmed the high degree of PK variability of the Claritin tablet, however, the conclusions that could be reached from these data in support of approval of the oval Claritin-D 24 Hour tablet were limited for several reasons. First, it is unclear whether the high degree of variability seen for loratadine and DCL were caused by an inherently high variability of the pharmacokinetics of orally administered loratadine, factors associated with the conduct of the study, variability of the manufacturing/formulation of Claritin tablets, or some combination of the three. Second, the data were obtained from the Claritin tablet formulation, not the Claritin-D 24 Hour tablets. Third, any attempt to utilize the non-bioequivalence for parent loratadine from this study to "scale" the BE interval for parent loratadine in the comparative study of the round versus oval Claritin-D 24 Hour tablets is confounded by the fact that DCL was also not equivalent in the replicate Claritin study. Thus, the information obtained from the replicate Claritin study was considered supportive, but not definitive, for approval of the oval Claritin-D 24 Hour tablet.

The other cross-study comparative PK and efficacy data submitted by the sponsor in support of approval of the oval Claritin-D 24 Hour tablet are the subject of Dr. Honig's review. A rigorous scientific interpretation of the available data is difficult for the following reasons:

1. As noted in Dr. Honig's review, the absolute plasma concentrations of parent loratadine observed in the round versus oval Claritin-D 24 Hour tablets PK study was much higher than that seen in other PK studies of approved and marketed Claritin formulations. The sponsor has not been able to provide any explanation for these higher parent loratadine levels. This unexplained finding complicates cross-study PK comparisons for the various marketed loratadine formulations.
2. No PK data are available from pivotal clinical efficacy trials for the various approved loratadine formulations. Thus, no direct link between clinical efficacy and observed levels of parent loratadine and DCL can be made. Only cross-study PK/PD analyses can be performed as noted in Dr. Honig's review (i.e., comparative PK data obtained from a pharmacokinetic study versus comparative efficacy data obtained from a separate study).

Despite these limitations, I concur with Dr. Honig's assessment that the available data are adequate to conclude that the reformulated Claritin-D 24 Hour tablet would be safe and effective and, therefore, is clinically approvable. The basis for this conclusion includes the following:

1. Unlike the approval of a generic version of an innovator product, the current supplemental approval of a reformulation of Claritin-D 24 Hour tablets is not an issue of switchability, and therefore, neither bioequivalence nor comparable clinical efficacy to the currently marketed Claritin-D 24 Hour tablet is required. All that is necessary to support approval is a finding that the new tablet is safe and effective.

2. Despite the limitations of the available comparative PK and efficacy data, I believe that it is reasonable to conclude that the slightly lower levels of parent loratadine observed with the oval tablet would not render the oval tablet ineffective for relief of antihistamine responsive symptoms of SAR. This conclusion is supported by the fact that the parent loratadine levels in PK studies of all currently approved loratadine formulations are highly variable. In fact, parent loratadine levels from individual patients for the currently marketed round Claritin-D 24 Hour tablet spanned a 100-fold range in the comparative BE study of the round versus oval tablets. This far exceeds the 10% difference in mean plasma concentrations observed between the two tablets in that same study. Despite this high degree of parent loratadine PK variability, each of the approved loratadine formulations has been demonstrated to be effective in the relief antihistamine responsive symptoms of SAR in clinical trials.
3. Given the facts that the half-life of parent loratadine is very short, that levels of parent loratadine are nearly undetectable 12 hours after dosing, and that parent loratadine does not accumulate with repeated dosing, it is reasonable to conclude that DCL, the major active metabolite of loratadine, is largely responsible for the effectiveness of orally administered loratadine. This conclusion is further supported by the fact that Schering has submitted data from a clinical trial that show that orally administered DCL at doses that achieve comparable systemic exposure of DCL as 10 mg of orally administered loratadine is an effective antihistamine. The oval Claritin-D 24 Hour tablet has been shown to be bioequivalent to the currently marketed, round tablet for DCL. It is reasonable to conclude that the oval tablet, therefore, is effective for relief of the antihistamine responsive symptoms of SAR.
4. The overriding public health benefit of approving the reformulated tablet and hopefully eliminating the problem of esophageal obstruction seen with the current round tablet far outweighs any potential minor negative clinical consequences of approving a potentially slightly less effective formulation of Claritin-D 24 Hour tablets. This conclusion is supported by the fact that the proposed labeling changes for the currently marketed Claritin-D 24 Hour tablets cannot reliably be expected to prevent further cases of esophageal obstruction since they do not allow at risk patients to be accurately identified in advance. The best way to eliminate the risk of esophageal obstruction is to approve the reformulated tablet, which mimics the size, shape, and coating of Drixoral, which has been marketed for many years without any reports of esophageal obstruction.

The available clinical data, the cross-study comparisons, the Division's conclusions, and the proposed action plan for this supplement were discussed with Drs. Bilstad and Houn on December 2, 1998. Both Drs. Bilstad and Houn concurred with the Division's conclusions and proposed plan of action. In addition, Schering has adequately addressed the outstanding CMC issues and therefore, this supplement is approvable with several Phase 4 commitments (see Dr. Honig's review for an outline of the clinical Phase 4 commitments).

Given that the new formulation of Claritin-D 24 Hour tablets is likely to be approved within the next 1-2 days and given that Schering has agreed to replace existing stocks of Claritin-D 24 Hour tablets at the pharmacy level within 2 weeks of approval of the supplement and to offer replacement of patient supplies of the round tablet on a individual patient basis if requested, the

Division will not proceed with approval of the labeling changes and "Dear Doctor" letter for the currently marketed formulation. Note, however, that if any issues arise that preclude a rapid approval of the new formulation, Schering will be required to proceed with the labeling changes and issuance of the "Dear Doctor" letter for the round tablet.

cc:
NDA 20-470
HFD-570/Division Files
Trout
Honig
Schumaker
Jenkins

Div File

INDUSTRY TELECONFERENCE MINUTES

Schering
NDA 20-470/S-005
Claritin-D 24 Hour
Safety/labeling
November 12, 1998

FDA REPRESENTATIVES

Jim Bilstad, Office Director, ODE II
Peter Honig, Medical Officer, HFD-570
John Jenkins, Division Director, HFD-570
Gretchen Trout, Project Manager, HFD-570

SPONSOR REPRESENTATIVES

Mary Jane Boyle, Regulatory Affairs
Alex Giaquinto, Regulatory Affairs

BACKGROUND: Following the issuance of a not-approvable (NA) letter for this supplement on September 4, 1998, a meeting was held between representatives of Schering and the Division on October 27, 1998, to discuss the ongoing safety problem with Claritin-D 24 Hour. At this meeting agreement was reached on additional wording to be added to the label to improve the safety of the currently marketed product until the reformulation can be approved. Following the meeting Schering did not submit new language for the labeling as agreed to and submitted a correspondence on November 2, 1998, stating their position on the issue of [redacted] (which was one of the deficiencies contributing to the NA letter). Following an internal meeting this teleconference was held to revisit the issue of relabeling or withdrawal of the product from the market.

DISCUSSION: Schering was informed that following additional internal discussion the Division concluded that Schering should proceed with the labeling changes and Dear Doctor letter as agreed to at the October 27, 1998, meeting, and the Division will continue to review data submitted to the supplement to determine if the new formulation can be approved.

The Division also requested that Schering submit the pharmacokinetic data (i.e., the full study report) from intra-batch comparisons and pharmacokinetic data for the parent and the metabolite from clinical efficacy studies. Schering should submit summary data on the pharmacokinetics for all of the formulations from the Claritin line with comparisons to the currently marketed Claritin-D 24 Hour product and state how it relates to efficacy. Schering can submit tabular summaries of the data. These data are necessary in order for the Division to consider Schering's response to the NA letter as complete. The Division reminded Schering there are also CMC data which need to be reviewed.

Dr. Giaquinto stated that Schering wants to send their detail people to physician's offices to educate them instead of making the labeling changes. The Division replied that detailing is part of the labeling change and Dear Doctor letters, but used alone it does not cover as broad of a group. Dr. Giaquinto expressed concern that if they change the labeling it will leave them vulnerable to counter detailing by competing companies. The Division reminded Dr. Giaquinto that Schering's other option (in place of the labeling changes) is to voluntarily stop marketing the product until the reformulation is approved. The Division emphasized that the esophageal obstruction is a significant public health problem and the Division and Schering need to do whatever we can to address it. Dr. Giaquinto questioned what would happen to the label when the reformulation is approved. The Division replied that we would entertain Schering's arguments that the label for the old product would not necessarily have to carry over completely to the reformulated product. Dr. Giaquinto proposed that the current wording in the labeling be used for the reformulation. The Division replied that this might be acceptable and Schering should summarize their data from Drixoral (i.e., that the tablets are the same size, shape, and coating as the reformulated Claritin-D 24 Hour, and does not have the problem with esophageal obstruction) and include these data in the submission.

The Division requested that the revised labeling be submitted by Monday, November 16, 1998. Dr. Giaquinto replied that he needs to discuss this with his management so he could not commit to providing the revised labeling by Monday, but would let the Division know their decision by Monday. The Division emphasized that the labeling should be submitted very quickly, it is already two weeks later than what Schering had agreed to previously. The Division also stated that because this issue is a health risk the Agency may consider other options including sending our own Dear Doctor letter or issuing an NOOH proposing to withdraw the product.

CONCLUSION: Schering will contact the Division on Monday, November 16, 1998, to notify the Division of their plans with regard to relabeling of the product or withdrawing the product from the market.

FOLLOW-UP TELECONFERENCE
November 16, 1998

FDA: Peter Honig, John Jenkins, Gretchen Trout
SCHERING: Mel Affrim, Alex Giaquinto, John Spicehandler

Schering telephoned to inform the Division that they will submit the revised labeling as discussed at the October 27, 1998, meeting, on November 17, 1998. The submission will include a patient's package insert and a Dear Doctor letter.

With regard to the pharmacokinetic data the Division requested, the Division clarified that Schering should provide cross-study comparisons containing an analysis of the known pharmacokinetic parameters of the various loratadine formulations versus their

clinical efficacy in the clinical trials. The objective of such an analysis would be the determination of whether the lower concentrations of parent loratadine in the reformulated Claritin-D 24 Hour product are clinically relevant. Schering stated they would not have this data ready to submit by November 17, 1998. The Division replied that was acceptable, however we will not consider their response to the September 4, 1998, NA letter complete until these additional data are submitted (i.e., the PDUFA clock will not restart until the additional data are submitted).

The Division encouraged Schering to have their drug safety staff consider an active surveillance program designed to collect information to determine if the reformulated product, when approved, does not have a similar problem as the currently marketed Claritin-D 24 Hour.

CONCLUSION: Schering will submit revised labeling by November 17, 1998. Additional pharmacokinetic data will be submitted to the Division when ready which will reactive the PDUFA clock for supplement 005.

/S/

Gretchen Trout
Project Manager

cc: NDA 20-470
Div. File
HFD-570/Honig
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Uppoor
HFD-570/Jenkins
HFD-570/Trout
HFD-102/Bilstad
HFD-002/Lumpkin

Concurrence on final draft:
Honig/11-23-98
Jenkins/11-23-98

MINUTES

SCHERING CORPORATION

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December 3, 1998

John Jenkins, M.D., Director
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research
HFD-570, Room 10B03
5600 Fishers Lane
Rockville, MD 20857

NDA 20-470/S-005
CLARITIN-D 24 HOUR (loratadine pseudoephedrine sulfate) Extended Release Tablets

SUBJECT: RESPONSE TO FDA 12/1/98 FAX

Dear Dr. Jenkins:

Based upon discussions between Dr. Alexander R. Giaquinto and yourself (12/2/98), Schering Plough agrees to the following Phase IV commitments following the approval of the CLARITIN-D 24 HOUR formulations supplement:

1. To conduct a single dose, 5 way cross-over bioavailability study with the reformulated CLARITIN-D 24 HOUR product, CLARITIN D 12 HOUR, CLARITIN Tablets, CLARITIN RediTabs, and CLARITIN Syrup in adults. A second single dose study will be conducted. This second study will be a single dose, two way, within batch replicate cross-over study with CLARITIN Syrup in adults. The protocols for these studies will be sent to FDA within 30 days of the approval of this supplement. The studies will initiate within two months of this approval, and the study reports will be submitted within eight months of supplement approval.

2. To develop a prospective active surveillance program for assessing whether the issue of esophageal obstruction is eliminated by the availability of the reformulated product.

In addition to these Phase IV commitments, Schering also agrees to replace/exchange all existing CLARITIN-D 24 HOUR marketed product at the pharmacy level within 14 days of approval.

As requested, attached is the revised package insert, which is accepted verbatim as proposed by FDA, for the new product. Also attached is the proposed "important Prescribing Information" correspondence and distribution list. This mailing is to be initiated no later than 12/11/98.

We also acknowledge our agreement that "full" glass of water is not on the current cartons and labels and will be added at the next printing; however, the initial shipment of product will not have "full" included.

With regard to the list of Chemistry deficiencies and comments, Schering agrees to the following:

1. Acceptance of 18-month expiration dating period for all packages. We will also submit as a prior approval supplement any extension of shelf life according to the approved stability protocol.

2a. [redacted]

2b. Revision of the initial stability protocol to include the specific drug product, CLARITIN-D 24 HOUR and the specific package components as requested in your fax of 12/1/98 (enclosed).

2c. Revision of the stability protocol to include [redacted]

2d. The stability condition of [redacted] is not included in our formal marketed product stability protocol. Furthermore additional data will not be reported at the [redacted] for the ongoing stability batches reported in our NDA dated 3/4/98. The stability protocol for these batches has been revised to drop testing at [redacted] after the 12 month time point.

2e. The stability protocol will incorporate a [redacted] which is identical to the 1987 FDA stability guideline currently in force.

3. Within six months of approval, we will develop and submit as a [redacted] a new test method which will meet the appropriate specifications according to ICH guidelines for unspecified and total impurities as requested in your fax of 12/1/98.

APPEARS THIS WAY
ON ORIGINAL

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Alexander R. Gaquinto, Ph.D.
Senior Vice President
Worldwide Regulatory Affairs

JFL/js
Enclosures

APPEARS THIS WAY
ON ORIGINAL