Hypospadias is an abnormality that occurs when the urethra is not completely enclosed by the urethral folds. Urethral fold fusion occurs beginning at about 12 menstrual weeks and may not be complete for another month. A direct effect of loratadine on urethral fold fusion would require that the compound be present at 12 weeks or later. This timing appears not to be possible for at least 7 of the Swedish cases. This finding would argue that if loratadine is causally associated with the production of hypospadias, the mechanism would involve an indirect effect, for example, on testicular androgen production or secretion.

2.3. Loratadine may produce testicular toxicity

Male external genital development is believed to occur in response to androgens, probably dihydrotestosterone, which is derived from testicular testosterone through the action of 5α-reductase. To identify whether loratadine has antiandrogenic, estrogenic, or 5α-reductase antagonistic properties, I consulted the FDA pharmacology reviews for desloratadine (Clarinex®), the active metabolite of loratadine. The FDA reviewer concluded that desloratadine and loratadine had nearly identical toxicity profiles, although desloratadine was more potent that the parent compound.

Teratology testing with desloratadine at maternal doses up to 24 mg/kg/day in rats showed a decrease in feed consumption and maternal body weight gain at the highest dose. An increase in preimplantation loss at this dose was consistent with maternal toxicity, but was interpreted by the reviewer as evidence of embryotoxicity. There was no apparent increase in congenital malformations. Administration to adult males, however, was associated with a decrease in testicular and accessory sex organ weight at the highest dose tested (24 mg/kg/day) but also at an intermediate dose (12 mg/kg/day). There was a decrease in feed intake and body weight at the high dose but no such decreases at the intermediate dose, so it is not likely that the antiandrogenic effects are due to generalized toxicity with hypothalalmic hypogonadism. Male fertility parameters were decreased and sperm concentration and testicular histologic evaluation were consistent with antiandrogenic effects. In a separate study, male rats were given desloratadine at 40 mg/kg/day following which some animals were permitted to recover for 18 weeks. In the recovery group, body weight returned to control values but the testicular and accessory sex gland weight remained depressed.

The apparent persistent antiandrogenic effects of high dose desloratadine in adult male rats does not prove human fetal testicular toxicity, but provides a biologically plausible mechanism by which loratadine exposure during the first trimester might have effects on development of the male external genitalia at 12-16 weeks gestation.

3. Data that may increase our ability to evaluate the association

The information I obtained on possible desloratadine antiandrogenic effects was obtained from pharmacology reviews on the FDA web site. The underlying data were not available and the reviews were not necessarily interpreted correctly by me. It is likely

that a re-evaluation of the underlying data on desloratadine and loratadine, perhaps including androgen plasma levels, would add to or detract from the plausibility of the loratadine-hypospadias connection. In addition, plasma androgen levels in human subjects may be available in these submissions.

Rodent hypospadias is not observed in teratology studies, in part because the rodent external genitalia are not entirely differentiated at the time of birth. The difference between the external genitalia of male and female offspring is represented by the anogenital distance, that is, the distance between the anus and the phallus, which is longer in males. Alterations in anogenital distance in newborn rodents may reflect effects analogous to those giving rise to hypospadias in humans. Measurement of anogenital distance may have been performed in the studies submitted to FDA. If so, an evaluation of anogenital distance divided by the body weight or the cube-root of body weight may be useful in predicting the potential for loratadine or desloratadine to interfere with external genital differentiation.

If these data are not in the submissions already in the possession of FDA, it would not be difficult to generate these data. It would be reasonable based on the information that was available to me to ask the manufacturer to sponsor studies to evaluate the possible antiandrogenic effects of loratadine in experimental animal models and in adult men.

Anthony R. Scialli, M.D.
[Department of Obstetrics and Gynecology, Georgetown University Medical Center]

Reviewed by:

/S/

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

/S/

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

cc: Original NDA
HFD-570/Division File
HFD-570/Purucker/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/Zeccola/CSO
HFD-570/Barnes/CPMS
HFD-560/Hu/Medical Reviewer

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/s/

Charles Lee
10/31/02 09:51:55 AM
MEDICAL OFFICER

Mary Purucker
10/31/02 02:19:31 PM
MEDICAL OFFICER
See also TL memo

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

Application Numbers: N19-658, N20-704, N20-641, N19-670, N20-470

Application Type: NDA supplement

Sponsor: Schering Corporation

Proprietary Names: Claritin tablets, RediTabs, and syrup, Claritin D 12 Hour, Claritin D 24 Hour

Category of Drug: Antihistamine
Antihistamine/decongestant

USAN/Established Name: loratadine
loratadine/pseudoephedrine

Route of Administration: Oral

Medical Reviewer: Charles E. Lee, M.D.

Review Date: 9/25/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type and Comments:
N19-658 SE6-018 BL	8/9/02	8/9/02	Labeling, Claritin tablets
N20-704 SE6-008 BL	8/9/02	8/9/02	Labeling, Claritin RediTabs
N20-641 SE6-008 BL	8/9/02	8/9/02	Labeling, Claritin syrup
N19-670 SE6-018 BL	8/9/02	8/9/02	Labeling, Claritin D 12 Hour
N20-470 SE6-016 BL	8/9/02	8/9/02	Labeling, Claritin D 24 Hour

RELATED APPLICATIONS (if applicable):

Application	Document Date:	Application Type:	Comments:

Schering Corporation has submitted 505(b)(2) applications for an OTC switch for the Claritin line of loratadine products. The products are currently approved and marketed as prescription only. The proposed indications for the single ingredient loratadine products are (1) the relief of various symptoms of allergic rhinitis and (2) the relief and reduction of itching and rash due to hives. The submissions reviewed in this document include the most recent proposed OTC labeling for allergic rhinitis indications for the Claritin single ingredient products and for the Claritin D combination products. These submissions have also been reviewed by the Division of Over-the-Counter Drug Products (DOTCDP). This reviewer concurs with the comments and recommendations from DOTCDP. Additional comments were proposed by the Division of Pulmonary and Allergy Drug Products (DPADP) which included changing the name for the dosage form, use in children under from ≥2 to <6 years of age, and use of the Claritin D products in patients with liver disease.

Revised comments to the sponsor are included in this review.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION:

SIGNED:

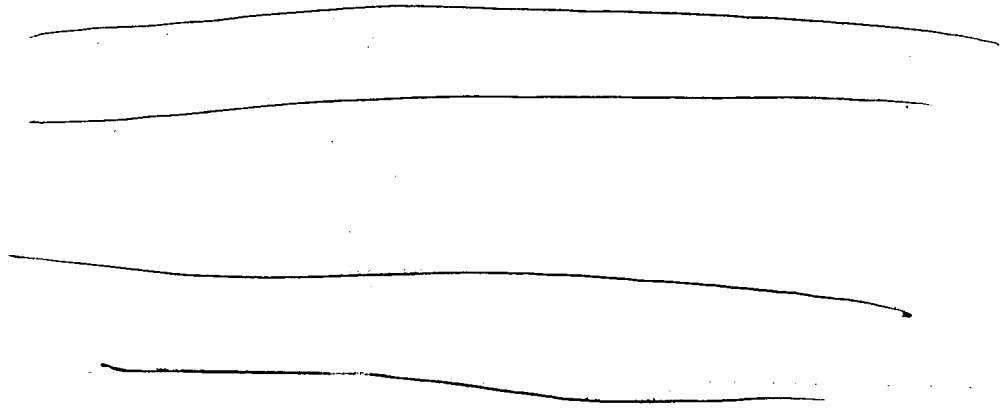
Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

1. INTRODUCTION

The sponsor's proposed OTC labeling for the Claritin D 12-hour and Claritin D 24-hour products instructs consumers with liver or kidney disease to contact a doctor before using the product because a different dose may needed.

The sponsor's current labeling for the prescription products recommends that the Claritin D 12-hour and D 24-hour products be avoided in patients with hepatic insufficiency because hepatic insufficiency results in a greater decrease in loratadine clearance than for PSE, and because the fixed dose combination products cannot be individually titrated [NDA 19-658 SE6-018, 1/25/02, Volume 1, 3.C., pages 98, 108].



2. REVISED COMMENTS FOR THE SPONSOR

Revised comments to be communicated to the sponsor follow:

1. *The correct name for the dosage form is "Orally Disintegrating Tablets," not [redacted] Disintegrating Tablets." Labeling should be changed to reflect the appropriate dosage form.*

2. *We note the change in the proposed ages for use of Claritin syrup compared to the original submission. The supplement supporting the use of Claritin syrup for children [redacted] The safety database is inadequate to support the OTC use of this product in children less than [redacted] of age because there has not been a sufficient period of time since approval in the US to collect necessary safety information. Change the proposed ages for use of Claritin syrup to 6 years and older, as was proposed in the labeling and annotated labeling included in the original submission [NDA 19-658 SE06-018, Volume 1, 2.B., page 16 and 3.A. page 26, 1/25/02].*

Reviewed by:

/S/

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

/S/

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

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

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

Application Numbers: N19-658, N20-704, N20-641, N19-670, N20-470
Application Type: NDA supplement

Sponsor: Schering Corporation
Proprietary Names: Claritin tablets, RediTabs, and syrup, Claritin D 12 Hour, Claritin D 24 Hour

Category of Drug: Antihistamine
Antihistamine/decongestant
USAN/Established Name: loratadine
loratadine/pseudoephedrine
Route of Administration: Oral

Medical Reviewer: Charles E. Lee, M.D.
Review Date: 9/20/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type and Comments:
N19-658 SE6-018 BL	8/9/02	8/9/02	Labeling, Claritin tablets
N20-704 SE6-008 BL	8/9/02	8/9/02	Labeling, Claritin RediTabs
N20-641 SE6-008 BL	8/9/02	8/9/02	Labeling, Claritin syrup
N19-670 SE6-018 BL	8/9/02	8/9/02	Labeling, Claritin D 12 Hour
N20-470 SE6-016 BL	8/9/02	8/9/02	Labeling, Claritin D 24 Hour

RELATED APPLICATIONS (if applicable):

Application	Document Date:	Application Type:	Comments:

Schering Corporation has submitted 505(b)(2) applications for an OTC switch for the Claritin line of loratadine products. The products are currently approved and marketed as prescription only. The proposed indications for the single ingredient loratadine products are (1) the relief of various symptoms of allergic rhinitis and (2) the relief and reduction of itching and rash due to hives. These submissions reviewed in this document include the most recent proposed OTC labeling for allergic rhinitis indications for the Claritin single ingredient products and for the Claritin D combination products. These submissions have also been reviewed by the Division of Over-the-Counter Drug Products. This reviewer concurs with the comments and recommendations from DOTCDP. Additional comments by the Division of Pulmonary and Allergy Drug Products (DPADP) include changing the dosage form to "orally disintegrating tablets" and adding text to the Claritin D labels that instructs consumers with liver disease not to use the products. The sponsor changed the proposed ages for use of Claritin syrup from the original submission to include children [redacted] of age. The sponsor must change the proposed ages for use of Claritin syrup to 6 years and older, as was proposed in the labeling and annotated labeling included in the original submission

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION:

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

1. BACKGROUND

Schering Corporation has submitted 505(b)(2) applications for an OTC switch for the Claritin line of loratadine products. The products are currently approved and marketed as prescription only. The proposed indications for the single ingredient loratadine products are (1) the relief of various symptoms of allergic rhinitis and (2) the relief and reduction of itching and rash due to hives. The single ingredient tablets, RediTabs, and syrup are proposed for OTC use in adults and children ages 6 years and older, the same ages for which the currently marketed prescription products are indicated. The proposed indication for the combination loratadine/pseudoephedrine (PSE) products is the relief of various symptoms of allergic rhinitis, including nasal congestion and relief of sinus pressure, among others. The combination loratadine/PSE products are proposed for OTC use in adults and children ages 12 years and older, the same ages for which the currently marketed prescription products are indicated.

2. CONTENTS OF THESE SUBMISSIONS

These submissions reviewed in this document include the most recent proposed OTC labeling for allergic rhinitis indications for the Claritin single ingredient products and for the Claritin D combination products. These submissions have also been reviewed by the Division of Over-the-Counter Drug Products (DOTCDP) [Labeling Reviews, M. Holman NDA 19-658 SE6-018 BL, 8/9/02, and M. Holman and H. Mahayni, NDA 20-470 SE6-016 BL, 8/9/02].

This reviewer concurs with comments and recommendations in the DOTCDP reviews. The following review only contains additional clinical points to be added by the Division of Pulmonary and Allergy Drug Products (DPADP).

3. REGARDING CLARITIN REDITABS

The sponsor's labeling for Claritin RediTabs and Junior Claritin RediTabs includes the phrase [redacted] Disintegrating Tablets" on various locations in labeling, including the principal display panel.

Reviewer comment:
The correct name for the dosage form is "Orally Disintegrating Tablets." Labeling should be changed to reflect the appropriate dosage form.

4. REGARDING CLARITIN SYRUP

The updated labeling in this submission includes directions for use of Claritin syrup in children 2 to up to 6 years of age at the dose of 1 teaspoonful daily (5 mg once daily). The labeling in the original application did not include an indication for children under 6 years of age. The labeling in the original application stated that the consumer is to ask a doctor before using the product in children less than 6 years of age [NDA 19-658 SE06-018, Volume 1, 2.B., page 16 and 3.A. page 26, 1/25/02]. In the sponsor's opinion, this

change is appropriate because of the excellent history of prescription use of this product in this age group, and because the product represents the first non-sedating antihistamine for use in this age group OTC. The sponsor also notes that the product has a wide margin of safety and limited contraindications and warnings for this age group.

Reviewer comment:
The sponsor has changed the proposed ages for use of Claritin syrup from the original submission. Claritin syrup was approved as a prescription product in the US for use in children from 2 to 6 years for the SAR and CIU indications on 12/4/00. The product has been approved in the US for this population for less than two years. The safety database does not support the OTC use of this product in children less than 6 years of age because there has not been a sufficient period of time since approval in the US to collect necessary safety information. The sponsor must change the proposed ages for use of Claritin syrup to 6 years and older, as was proposed in the labeling and annotated labeling included in the original submission [NDA 19-658 SE06-018, Volume 1, 2.B., page 16 and 3.A. page 26, 1/25/02].

5. REGARDING CLARITIN D PRODUCTS

The sponsor's proposed OTC labeling for the Claritin D 12-hour and Claritin D 24-hour products instructs consumers with liver or kidney disease to contact a doctor before using the product because a different dose may needed.

However, the sponsor's current labeling for the prescription products recommends that the Claritin D 12-hour and D 24-hour products be avoided in patients with hepatic insufficiency because hepatic insufficiency results in a greater decrease in loratadine clearance than for PSE, and because the fixed dose combination products cannot be individually titrated [NDA 19-658 SE6-018, 1/25/02, Volume 1, 3.C., pages 98, 108].

Reviewer comment:

The sponsor's current labeling for Claritin D 24-hour notes that patients who have a history of difficulty swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use this product [NDA 19-658 SE6-018, 1/25/02, Volume 1, 3.C., page 108]. This statement is not included in the proposed labeling for the OTC product.

Reviewer comment:
This reviewer checked the AERS database for reports of esophageal obstruction and dysphagia occurring after the reformulation of the product in December 1998. There was a single report of esophageal obstruction reported on 5/3/99 that occurred on 4/7/00 (— #325692). It was not known if the tablet was the initial or revised formulation. There

were no other reports in the AERS of similar events occurring since January 1999. It is acceptable for the sponsor to delete this precaution from the OTC label.

6.

Reviewer comment:

7. COMMENTS FOR THE SPONSOR

Comments to be communicated to the sponsor follow:

1. *The correct name for the dosage form is "Orally Disintegrating Tablets," not "Disintegrating Tablets." Labeling should be changed to reflect the appropriate dosage form.*

2. *We note the change in the proposed ages for use of Claritin syrup compared to the original submission. The supplement supporting the use of Claritin syrup for children 2 to 5 years of age was approved on 12/4/00. The safety database is inadequate to support the OTC use of this product in children less than 6 years of age because there has not been a sufficient period of time since approval in the US to collect necessary safety information. Change the proposed ages for use of Claritin syrup to 6 years and older, as was proposed in the labeling and annotated labeling included in the original submission [NDA 19-658 SE06-018, Volume 1, 2.B., page 16 and 3.A. page 26, 1/25/02].*

3. *The current prescription labeling for the Claritin D 12-hour and D 24-hour products states that these products should be avoided in patients with hepatic insufficiency. Your Integrated Summary of Safety also states that these products should be avoided in patients with hepatic insufficiency [NDA 19-658, Volume 3, 8.H., page 36].*

Reviewed by:

/S/

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

/S/

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

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

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/s/

Charles Lee
9/20/02 04:30:10 PM
MEDICAL OFFICER

Mary Purucker
9/23/02 09:39:43 AM
MEDICAL OFFICER

Medical/IDS Review

NDA #: **19-658**
Drug Name: **Claritin 24 (Loratadine)**
Sponsor: **Schering-Plough**
Subject: **CIU Self-Recognition and Label Comprehension Study**
Reviewer: **Linda Hu, M.D.**
Matthew Holman, Ph.D.
Date: **April 16, 2002**

This label comprehension study was designed to evaluate Claritin ® 24 for over-the-counter (OTC) treatment of chronic idiopathic urticaria (CIU). Claritin ® 24 (loratadine) is currently a prescription medication prescribed for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria (CIU). CIU is not currently an OTC indication for any product marketed in the U.S. The label study was designed to evaluate whether consumers can understand label directions, and in particular the new indication and direction for previously diagnosed, recurring or chronic hives.

The **objectives** of this study were to evaluate if consumers:

- understand the uses, directions and warnings as based on reading the product label
- can accurately self-recognize CIU upon recurrence and appropriately self-select Claritin for use

Study Design

This was an all-comers study enriched with several special populations. Twenty-four marketing research facilities located in twenty-one geographically dispersed markets across the United States were used to complete recruiting and enrollment for this study. Subjects were recruited through advertising, direct mail, and mall intercept for participation. Qualified subjects were asked to read a product label and package insert for Claritin 24 and then were interviewed and asked questions to determine their understanding. Subjects were told that they would be able to refer to the label as needed.

A total of 565 subjects were interviewed for this study. Five study cohorts were defined as follows:

1) Cohort 1: Self-recognized CIU sufferers (N=196) who indicate that they have been previously diagnosed by a physician as having the condition;

2) Cohort 2: General population (N=116)

3) Cohort 3: Low Literacy (N=96)

4) Cohort 4: Special cohort who should according to the label "Ask a doctor before use", such as those who have liver, kidney disease, are pregnant, or are nursing/breast feeding (N=114)

5) Cohort 5: Special cohort with a history of hives who did not have a diagnosis of chronic hives or CIU by a physician (N=102); this was the acute hive cohort whose members should not use.

Subjects with CIU (Cohort 1) were recruited by first being asked if they had any of a list of health conditions. If they answered they had hives, they were asked "Has a doctor ever told you that you have recurring or chronic hives with an unknown cause, also known as Chronic Idiopathic Urticaria (CIU)?" If they answered affirmatively, they qualified for Cohort 1. If they answered negatively, they qualified for the acute hive group (Cohort 5).

Key label communication objectives were as follows:

- Claritin relieves and reduces itching and rash due to recurring or chronic hives of an unknown source (CIU)

- Claritin should be used only after being diagnosed by a doctor for recurrent or chronic hives

- The consumer should seek emergency medical attention (if rash, hives, insect bite or sting are accompanied with trouble swallowing, fever above 100° F, wheezing or problems breathing, hives or swelling in or around mouth, drooling, trouble speaking, or joint pain); warnings not to use if allergic to loratadine or other antihistamines; and warnings not to use for hives unless previously diagnosed with CIU by a physician and not to use for food allergies or insect bites and stings.

- This product should not be used to treat food allergies or insect bites or stings

Label Comprehension

Label comprehension was assessed by asking both direct and scenario-based questions. First, the participants were asked directly, as an open-ended question (Q1), what the product was used for, and in addition, another question (Q2) as to whether Claritin was intended for use in any of several listed conditions. Second, a series of scenarios was presented, and participants were asked whether Claritin is intended to be used in the scenario described. For Cohorts 1, 2, 3, and 5, some of the scenarios reflected actual sufferers of CIU. Subjects in Cohort 4 answered a shortened questionnaire to test if they understood that they should ask a doctor before use.

Self-Selection

The label comprehension study questionnaire also included questions relating to "self-selection". The purpose of this question was to determine if consumers understood whether they *personally* could use Claritin. Because the intent of Cohort 4 was to determine if subjects with liver/kidney/pregnancy/nursing recognized that they should ask a doctor prior to use, these subjects were asked to assume they had been told by their doctor that they have recurring hives or hives of an unknown source.

As a follow-up to the self-selection question, all cohorts were asked to state reason(s) for their answer. To ascertain whether participants answered correctly regarding self-selection, they were asked a series of medical history/health questions that determined if they had been diagnosed with CIU, had chronic hives, or had contraindications to use.

Self-Recognition

Subjects in Cohort 1 (self-recognized CIU group) were assessed for accurate self-recognition based on a follow-up discussion with a study physician. This assessment was based on a discussion between the subject and the study physician regarding the subject's medical history, and in some cases, subject's selection of a photograph that best represented their skin lesions when they experienced CIU. In other cases, those currently experiencing hives had their hives photographed. In many cases, the photographs of subjects' lesions were of poor quality and were not usable.

Demographics

The demographics of the five study cohorts are summarized in Table 1. An individual participant could be assigned to more than one cohort, so the sum of all cohort totals exceeds the total number of study participants. Two-thirds of the participants were female.

Table 1 Study Populations

Cohort	Male	Female	Total
CIU	49	147	196
General Population	44	72	116
Low Literacy	38	58	96
Contraindicated	47	67	114
Acute Urticaria	35	67	102
Total	193	372	565

The income distribution of the participants in the study cohorts is given in Table 2. The Low Literacy group had a significantly higher proportion of subjects in the lowest annual income group, < $15K. The CIU group had a significantly higher proportion of members in the highest income group (>$75 K annually) than all the other cohorts. Subjects with higher income may be expected to show better label comprehension.

Table 2 Annual Income distribution

	<15K	15K-25K	25K-35K	35K-45K	50K-75K	>75K	Total Responding
CIU	16	22	25	38	45	43	196
General Population	13	20	21	23	19	15	116
Low Literacy	29	20	22	17	3	3	96
Contraindicated	16	19	20	21	19	13	112
Acute Urticaria	12	13	24	25	14	11	102
Total	74	85	101	116	93	76	563

The age distributions of the participants in the study cohorts is given in Table 3. The CIU group had an older population than the general population cohort and the acute urticaria cohort.

Table 3 Age Distribution

	18-34	35-44	45-54	55-64	> 65	Total Responding
CIU	45	47	62	28	14	196
General Population	62	19	18	13	4	116
Low Literacy	32	34	16	10	4	96
Contraindicated	35	22	27	13	17	114
Acute Urticaria	42	23	16	11	10	102
Total	190	132	126	70	47	565

RESULTS

Label Comprehension

Consumer understanding of the product uses was tested by questions 1 and 2 (Q1 and Q2). To be considered "correct", responders had to state specifically that CIU or recurring/chronic hives, not just hives, was the intended use for the product. Answers were considered "acceptable" if respiratory allergies, hay fever, or allergic rhinitis were mentioned along with CIU since Claritin has been used extensively for this indication. Note, however, that these indications were not listed on the label presented to these consumers in this label comprehension study. Answers were considered "incorrect" for those who mentioned CIU along with an incorrect product use, such as for colds/flu, other allergic reactions or if just hives in general were mentioned.

Table 4 summarizes the correct and acceptable response rate to these direct questions and several pertinent scenarios relating to product use across the different cohorts.

Table 4. Product Use – whether consumers understand uses of Claritin (% Correct/Acceptable)

Question #	Tab Pg #	Cohorts- % Correct/ Acceptable				
		C1 CIU Suff.	C2 Gen. Pop.	C3 Low Lit.	C4 "Ask Dr. 1st": Liv/Kid/ Preg/Nsg	C5 "Do not use" Acute Hives
		a	b	c	d	e
Direct Questions:						
1.) Based on the label, what is this product used for? (open-end)	Pg.14	77 bcde	53	55	58	49
2.) List of conditions that prod. is/is not intended to be used for?	Pg.47	71 bcde	41	48	49	38
Scenarios: Correct and Incorrect Use						
5/6.) Scenario Card B: Use on hives from allergic reaction to peanuts - tongue starting to swell/hard to swallow.	Pg.72	91 be	75	87b	88b	80
7/8.) Scenario Card C: Use on rash from bee sting – trouble breathing.	Pg.85	96 bcde	85	87	88	86
9/10.) Scenario Card D:Diagnosed w/CIU (correct use of product)	Pg.94	99 bcde	96	96	97	95
11/12.) Scenario Card E: Use on red rash due to hiking in woods?	Pg.105	85 be	66	80b	80b	73
15/16.) Scenario Card G: Use on first time break out of hives	Pg.118	90 bcde	73	80	82	75

***The proportions/means are compared for statistically significant differences at the 95% confidence level. A lower case letter next to the percent indicates a value significantly greater than the value in the corresponding column.**

Question 1 *Based on the label, what is this product used for?* (open-ended question)

When asked on an open-ended basis what the product was used for, CIU sufferers demonstrated the strongest understanding (77% correct/acceptable). The correct/acceptable response rates for the other cohorts ranged from 49% to 58%. The most common incorrect answer (mentioned by 20% of the total number of subjects) was "hives/itching due to hives" (because the subject did not specify that the hives were chronic). This percentage was 30-40% among the acute hive cohort, depending on how individual responses are classified. It is difficult to elicit specific answers such as chronic hives or hives of an unknown source with an open-ended question. Other common incorrect mentions were "allergies" in general or hay fever. There were also several mentions of asthma, cold/flu, trouble speaking/swallowing, drooling, fever, and joint pain. The Sponsor has been asked to further categorize, summarize and quantify the various responses across the cohorts.

Question 2 *Is this product intended to be used for the following conditions? (Ear infections, hay fever, colds, sinus infections, upper respiratory allergies, food allergies, insect bites/stings, a one time breakout of hives, allergies to animal/pets, recurring or chronic hives of an unknown cause)*

CIU sufferers in Cohort 1 scored the highest (71% correct) for this question, with the other cohorts answering correctly in only 38%-49%. However, for to be considered correct for Q2, the subject had to answer correctly for all conditions listed above.

Table 5 lists the number that responded "yes" to this question for each of the previous conditions. In all cohorts combined, 92% of subjects stated this product was intended for use in recurring or chronic hives of an unknown cause, but not all were considered "correct/acceptable" for Q2 because they also stated it is indicated for other incorrect conditions. The highest proportion (71%) gave the correct response, in the CIU cohort.

When the conditions were examined separately, nearly one-quarter (22%) of all participants stated that the product was intended for hay fever, and 18% thought the product could be used for insect bites/stings. Forty-two percent of the general population cohort, 44% of the acute hive cohort, and 20% of the CIU cohort thought that the product could be used for a one time breakout of hives.

For the general population cohort, 39% thought the product was intended for hay fever, 11% for colds, 16% for food allergies, 27% for insect bites/stings, 29% for allergies to animals/pets and 85% for recurring or chronic hives of an unknown cause.

Table 5. (Question 2) Is the product intended to be used for following conditions: (those answering yes)

	Total	CIU	Gen Pop	LL	Preg/Liver /Kidney	Acute Hives
Total Responding	565	196	116	96	114	102
Ear Infections	1.9%	--	1.7%	8.3%	0.9%	2.0%
Hay Fever	21.6%	11.7%	38.8%	22.9%	16.7%	35.3%
Colds	7.6%	0.5%	11.2%	15.6%	4.4%	18.6%
Sinus Infections	9.2%	1.0%	17.2%	13.5%	7.0%	17.6%
Upper Respiratory Allergies	18.1%	8.2%	31.0%	16.7%	13.2%	33.3%
Food Allergies	11.7%	7.1%	16.4%	13.5%	13.2%	20.6%
Insect Bites/Stings	18.4%	9.2%	26.7%	18.8%	23.7%	29.4%
One Time Breakout of Hives	32.0%	19.9%	42.2%	36.5%	37.7%	44.1%
Allergies to Animals/Pets	17.7%	9.7%	29.3%	21.9%	14.0%	31.4%
Recurring or Chronic Hives of an Unknown Cause	91.7%	99.0%	85.3%	84.4%	89.5%	92.2%

A series of scenarios was also presented to study participants. These questions and the percent correct in each cohort is also summarized in Table 4. The scenarios from this table are provided in their entirety as follows.

Scenario B "Jane is allergic to peanuts, and she accidentally ate a candy bar that had peanuts in it. Her arms have broken out into hives. Her tongue has started to swell and it is getting hard for her to swallow. She wants to take something to help her."

"Based on the label, is this product intended to be used for this situation, or not?"

Scenario C "Pam was working in the garden and got stung by a bee. She suddenly developed a rash and is having trouble breathing."

"Based on the label, is this product intended to be used for this situation, or not?"

Scenario D "For the past several months, Ted has broken out in hives about every week. His doctor told him he has a condition called "Chronic Idiopathic Urticaria" or recurrent hives of an unknown source or no known cause."

"Based on the label, is this product intended to be used for this situation, or not?"

Scenario E "Bill is on a hiking trip through the woods and developed an itchy red rash on his legs. He wants to take something to relieve his symptoms"

"Based on the label, is this product intended to be used for this situation, or not?"

Scenario G "Sue broke out in hives on her arms and legs for the first time in her life. She would like to take a product to treat the hives."

"Based on the label, is this product intended to be used for this situation, or not?"

Self-Selection

Questions (Q17/18) *Considering everything on the package label, is this product intended* ***for you, personally****, to take home and start using? Why do you say that?*

The purpose of the "self-selection" series of questions was to determine if consumers understood whether they *personally* could use Claritin based on their personal history of hives, as well as their current medications and medical conditions. Using this information, the Sponsor classified subjects as belonging to one of three categories: "OK to use", "Ask a doctor first", and "Do not use".

For the self-selection question, a high proportion of previously diagnosed CIU sufferers (Cohort 1) gave correct or acceptable answers (Table 6). However, a significant proportion of those in the general population (Cohort 2) and acute hive population (Cohort 5), 30% and 46% respectively, gave incorrect responses.

Table 6. Self-Selection Question (Q17/18)

SELF-SELECTION: Whether consumers understand if they can personally use Claritin®.							
			Cohorts - % Correct/ Acceptable				
Objective	Question #	Tab Pg #	C1 CIU Suff. (OK to use)	C2 Gen. Pop. (Do not use)	C3 Low Lit. (Do not use)	C4 "Ask Dr. 1st": Liv/Kid/ Preg/Nsg	C5 "Do not use" Acute Hives
Whether consumers understand if they can personally use Claritin®.	17/18/19/20.) Considering everything on the package label, is this product intended for you, personally, to take home and start using?	Pg.152	100	70	65	80	54

In the general population (Cohort 2), the large majority of whose members should not use, there were 73 correct or acceptable answers from 104 responding (70%) in the group. Of those in Cohort 2 who should ask a doctor first, 7/8 (87%) answered correctly or acceptably, while all of those who evaluated as OK to use did self-select to use, 4/4 (100%). The fraction of general population participants who decided correctly not to use is marginal. Of those who answered incorrectly, 19% stated the product was intended for allergic rhinitis or allergies, 19% stated it relieved itching/rash, 16% stated it relieved hives, and 9% said it relieved chronic/recurrent hives.

In the acute urticaria group (cohort 5) who should not use or should ask a doctor, 55/102 (54%) gave correct or acceptable answers. They stated that the product was not intended for their use or that they would "ask their doctor" prior to use. This is a low percentage of correct answers. Of those who answered incorrectly, at least 23% stated that the product could be used to relieve hives, 21% stated the drug relieves chronic/recurring hives, 15% stated relieves itching/rash, and 11% responded that the product can be taken for allergies or allergic rhinitis. The respondents that answered the product is intended to treat chronic/recurring hives did not have a physician diagnosis of CIU (although this is not explicitly stated in the submission). The Sponsor has been asked to categorize, summarize and quantify the responses to this question.

The results of this question indicate that 46% of consumers with acute urticaria will incorrectly decide to self-treat with Claritin. Over 90% of consumers with a physician diagnosis of CIU will accurately self-treat with Claritin. Seventy-one percent (12/17) of those in the CIU group who should ask a doctor before use will self-treat inappropriately. Of consumers in the general population who should not use, about 30% will self-select to use the drug.

Self-Recognition

Only subjects in Cohort 1, CIU Sufferers (self-reported), participated in this arm of the study. In order for the subjects to be evaluated on the ability to self-recognize chronic idiopathic urticaria, they spoke with a nurse and a study physician at West™s Central Medical Operations Group (CMOG). Nearly all of the subjects (94%) who self-reported having CIU were confirmed by the physician as having CIU.

DISCUSSION

The study results suggest that over 90% of consumers with a previous diagnosis of CIU, about 30% of consumers from the general population without a previous diagnosis, and about 46% of those with acute hives believe that the product is intended for their use. Incorrect reasons for self-selecting to use the drug included: the product was to be used for hives without specifying chronic, acute hives, allergic rhinitis, itching/rash, or chronic/recurrent hives without a prior physician diagnosis. There were also several mentions of asthma, cold/flu, trouble speaking/swallowing, drooling, fever, and joint pain. Question 2 showed that in the general population cohort, 39% thought the product was intended for hay fever, 11% for colds, 16% for food allergies, 27% for insect bites/stings, 42% for a one time break out of hives, 29% for allergies to animals/pets.

The study suggests that some consumers who do not have a prior diagnosis of CIU will not make the distinction between general hives, acute hives, and chronic urticaria when deciding whether this product may be right for them to use. Others will use for generally accepted indications for Claritin. An important issue is whether consumers with symptoms of anaphylaxis recognize that they should seek immediate medical attention. Although study participants were shown scenarios describing anaphylaxis, they were not asked specifically whether or when to seek medical attention.

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

Application Numbers: N19-658, N20-704, N20-641, N19-670, N20-470
Application Type: NDA supplement
Sponsor: Schering Corporation
Proprietary Names: Claritin tablets, RediTabs, and syrup, Claritin D 12 Hour, Claritin D 24 Hour
Category of Drug: Antihistamine
Antihistamine/decongestant
USAN/Established Name: loratadine
loratadine/pseudoephedrine
Route of Administration: Oral
Medical Reviewer: Charles E. Lee, M.D.
Review Date: 4/4/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type	Comments:
N19-658 SE6-018 BM	3/28/02	3/28/02	Response to IR	Claritin tablets
N20-704 SE6-008 BM	3/28/02	3/28/02	Response to IR	Claritin RediTabs
N20-641 SE6-009 BM	3/28/02	3/28/02	Response to IR	Claritin syrup
N19-670 SE6-018 BM	3/28/02	3/28/02	Response to IR	Claritin D 12 Hour
N20-470 SE6-016 BM	3/28/02	3/28/02	Response to IR	Claritin D 24 Hour

RELATED APPLICATIONS (if applicable):

Application	Document Date:	Application Type:	Comments:
N19-658 SE6-018	1/25/02	NDA supplement	ISS, Volume 1.3

Schering Corporation has submitted NDA supplements for an OTC switch for the Claritin line of loratadine products, including the chronic idiopathic urticaria (CIU) indication. In their NDA supplement, the sponsor addresses SAEs occurring in patients with CIU who were treated with loratadine. The proportion of SAEs due to anaphylaxis was higher in patients taking loratadine for urticaria (14%, 5/37) than in patients taking loratadine for allergic rhinitis (2%, 4/222). One case in which the patient self-medicated for a condition related to urticaria resulted in fatality.

Since completion of the previous review [Medical Officer Review, NDA 19-658 SE6-018 BM, 4/4/02], an additional report from AERS of anaphylaxis in a patient with was noted by the Joyce Weaver, Office of Drug Safety. This case was not among those submitted by the sponsor, and represents an additional case. The case (Mfr., [redacted] #1959723) was an 18 year-old US female who developed hives one hour after ingesting a hot dog. She was treated at the ER with diphenydramine 50 mg po and received a prescription for loratadine tablets. The patient took a single dose of loratadine, and 3 to 4 hours later, developed difficulty breathing and her throat "closed down." She was treated in the ER with epinephrine and prednisone. Hives reportedly returned after taking hydroxyzine. The patient was not hospitalized. A copy of this case report and the previously reviewed fatal case report in included in this review. If included with previously reviewed SAEs, the proportion of SAEs due to anaphylaxis in patients taking loratadine for urticaria is 16% (6/38) compared with 2% (4/222) for allergic rhinitis. As noted in the previous review, the differences in the proportion of SAE reports for anaphylaxis may represent a safety signal, and there may be a higher safety risk for anaphylaxis in patients who are taking loratadine for urticaria than for other indications.

OUTSTANDING ISSUES:

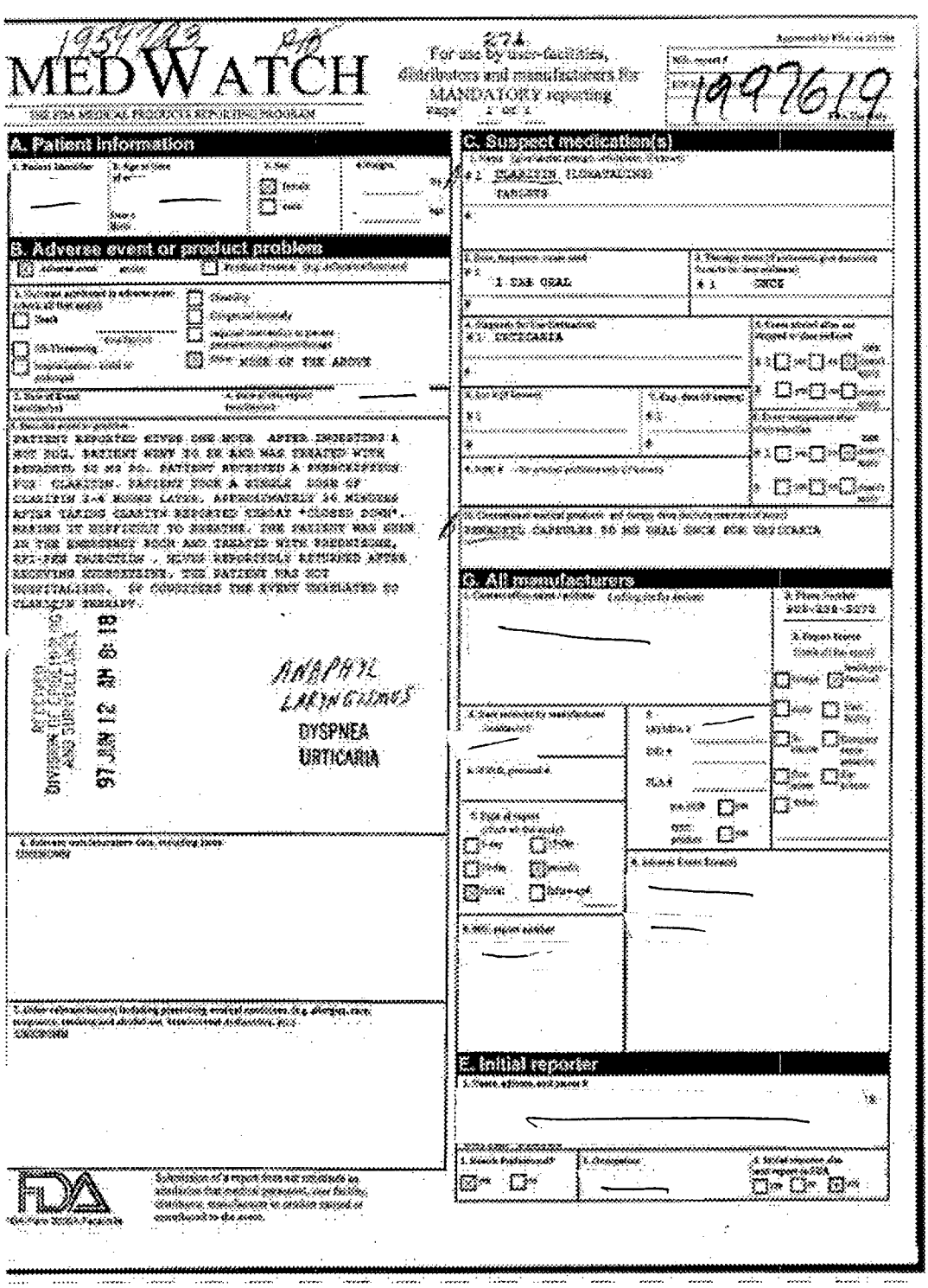
RECOMMENDED REGULATORY ACTION:

NAI: X

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**



MEDWATCH

1997619

A. Patient information

B. Adverse event or product problem

PATIENT REPORTED HIVES ONE HOUR AFTER INGESTING A NEW PILL. PATIENT WENT TO ER AND WAS TREATED WITH BENADRYL IV AT 2A. PATIENT RECEIVED A PRESCRIPTION FOR CLARITIN. PATIENT TOOK A SINGLE DOSE OF CLARITIN 3-4 HOURS LATER, APPROXIMATELY 24 HOURS AFTER TAKING CLARITIN REPORTED SUDDEN "CLOSED DOWN", MAKING IT DIFFICULT TO BREATHE. SHE PATIENT WAS SEEN IN THE EMERGENCY ROOM AND TREATED WITH PREDNISONE, EPI-PEN INJECTION . PATIENT REPORTEDLY RETURNED AFTER RECEIVING MEDICATIONS. THE PATIENT WAS NOT HOSPITALIZED. IT CONSIDERS THE EVENT UNRELATED TO CLARITIN THERAPY.

97 JAN 13 AM 8:19

ANAPHYL
LARYNGITIS
DYSPNEA
URTICARIA

C. Suspect medication(s)

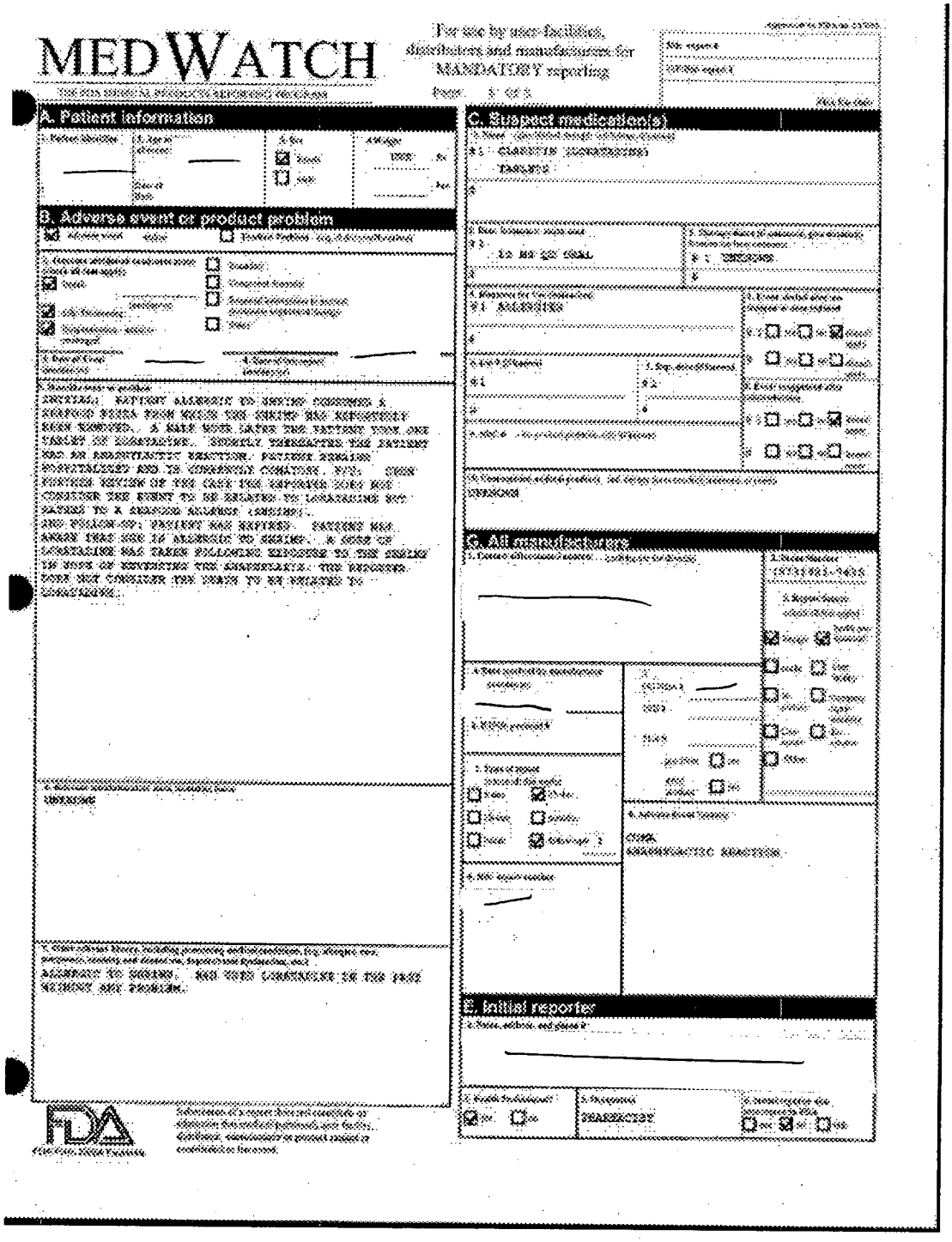
1. CLARITIN

SINCE

C. All manufacturers

E. Initial reporter

FDA



MEDWATCH

For use by user facilities, distributors and manufacturers for MANDATORY reporting

A. Patient information

B. Adverse event or product problem

C. Suspect medication(s)

D. Suspect manufacturer

E. Initial reporter

FDA

Reviewed by:

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

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

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

Medical Review
NDA #: 19-658/S-018
Drug Name: Claritin (loratadine)
Sponsor: Schering Corporation
Reviewer: Charles J. Ganley, M.D.
Correspondence Date: January 25, 2002
Date: March 26, 2002

In support of their supplemental NDA for the switch of the Chronic Idiopathic Urticaria (CIU) indication for Claritin from prescription to OTC, the sponsor has submitted a consumer survey, a physician survey, an expert panel report and a labeling comprehension study. This review summarizes the results of the consumer and physician surveys and comments on the Expert Panel report. The labeling comprehension study is reviewed in a separate FDA document.

Consumer Survey

Design

The consumer survey was conducted through the National Family Opinion Interactive Panel. This is a website-based group that allows any Internet user to register for their survey participant list. Registered users are informed of survey opportunities via e-mail and can decide in which surveys they choose to participate. Participation in a survey allows users to accumulate points that can be used for prizes or cash.[1] In this case, an e-mail was sent to over 500,000 households each for two consecutive weeks in October-November 2001. A screening survey was used to help identify a chronic urticaria population by asking, "Have you ever been diagnosed by a medical doctor as having chronic or recurrent hives that have no known discernable cause (also known as chronic urticaria)." Each e-mail mailing yielded approximately 15,000 qualified adult subjects (older than 18 years of age).

A more detailed interactive survey was conducted in 845 subjects randomly sampled from the pool of subjects. The sample size was chosen so that 300 chronic idiopathic urticaria sufferers would complete the survey. This would allow for an error of +/- 6% at a 95% confidence interval. Questions in the survey were either open ended or multiple choice.

The objectives of the survey were as follows:

- To obtain information on the frequency and severity of symptoms from a patient perspective;
- To obtain information on the patient interaction with their physician;
- To obtain information on treatment modalities;
- To obtain information on a patient's perspective on the ability of patients to recognize symptoms and determine what actions should be taken during an attack.

Results

Of the 845 subjects, 388 subjects completed the survey[2]. The average age was 45 years, 66% were female and 84% were white. The majority of subjects had experienced recurring hives for greater than 3 years (68%). Thirteen percent had the condition for less than one year. Most were diagnosed with chronic hives more than three years prior to the survey (59%). Approximately 39% had episodes "all of the time" or at least every month. A majority of subjects had four or more episodes each year (58%). The episodes resolve within a week for 66%. Approximately 51% experienced an episode in the past month.

Itching (81%), hives or wheals (77%) and redness (68%) were the most common symptoms. Itching (56%) and hives (25%) were listed as the most prominent symptoms during an attack. Individuals were more likely to have hives in multiple areas simultaneously (62% had 8 or more hives at one time). Most did not view the condition as serious (73%). During an attack, most use a prescription or OTC medication.

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[1] 1000 points is equivalent to approximately $10. Up to 1500 points can be obtained for taking a survey.

[2] 457 subjects did not complete the survey for the following reasons: 192 did not respond, 95 logged on after the survey closed, 81 did not suffer from CIU on requalification, 81 worked in sensitive occupations (e.g. advertising, pharmaceuticals), 1 was not > 18 years old, 7 did not want to take the survey

Approximately 20% of the subjects contact their physician when they have an attack (78 of 388). Only 21% of these subjects contacted the physician immediately and an additional 33% waited a day or less before contacting the physician.

Most subjects (94%) felt it was easy to identify the condition when it appeared. Prior to seeing a physician, over 90% used an OTC medication to treat the condition. The majority of these subjects used an OTC antihistamine (62%). There was no consensus for the name given the condition by the physician at the initial visit. Chronic idiopathic urticaria was used less than 10% of the time.

When asked what they would do if they developed difficulty breathing, fever or trouble swallowing during an attack, 95% would go to the emergency room or visit their doctor. Only 5% would use the medicine already prescribed. This was a multiple-choice question. An open-ended question in this instance would be more appropriate to decrease the chance of biasing the respondent.

Discussion

It is difficult to interpret these surveys for the following reasons:

- It is difficult to validate whether the subjects who participated actually have the underlying condition;
- Because many of the questions are multiple choice and not open-ended, this limits the range of answers that would have been provided by the respondents and may influence the respondents answer;
- The results of this survey are not reproduced in another cohort of subjects with chronic urticaria; and
- It assumes that the population who participated are representative of the overall population of chronic urticaria sufferers.

If it is assumed that the majority of subjects have the underlying condition, then there are some interesting observations.

- It is not surprising that the majority of subjects, after the initial diagnosis by a physician, would self-identify the condition and not call the doctor. They were given either prescription medication or instructed to use OTC medication by the physician for the next attack.
- It is not surprising that many attempted to treat the symptoms with an OTC topical product indicated for itching prior to seeing a physician. Itching was the most common symptom (in 81%) and the most prominent (in 56%) in this group of respondents. What is surprising is that 62% used OTC anti-histamines prior to seeing a physician. OTC anti-histamines are not indicated for this condition or for the symptoms associated with a rash. It is unclear whether they sought the advice of another health provider, pharmacist or used alternative resources (e.g. the Internet) in deciding to use an anti-histamine before seeking the opinion of a physician.
- The screening question for continuing in the survey used the descriptor "chronic or recurrent hives that have no known/discernable cause (also know as chronic urticaria)." The responses to subsequent questions on how the physician described the condition at the initial visit (page 25 of the report) may have been influenced by this screening question. In any event, there was no consensus descriptor for this condition. Chronic Idiopathic Urticaria was used infrequently. The most common descriptors included the word hives. Clearly, the most important descriptor on any label would have to include the word hives. It is unclear what other defining terms should be included.
- The answers to the question regarding what the consumer would do if they experienced symptoms such as difficulty breathing, fever or trouble swallowing is difficult to interpret because multiple choices were given. It is not clear how they would have responded had it been an open-ended question. Aside from the answer regarding a visit to the emergency room, the sense of urgency is not discernable. For those who responded that they would call or visit a physician, the timing of this call or visit was not elicited.

Physician Survey

The physician survey used Internet based databases as their source of respondents[3]. The survey was conducted between November 13, 2001 to November 15, 2001 by Marketing Measures, Inc. Physicians were pre-screened for their specialty and whether they treated patients with CIU. The survey

[3] databases: Medical Marketing Conference, Medscape or ePocrates

included 359 qualified Internet interviews from physicians with backgrounds in Primary Care (151), Dermatology (75), Allergy (55) and Pediatrics (78)[4].

The survey collected information on the practice patterns of these physicians regarding the diagnosis and treatment of patients with hives. The deficiencies of the survey are similar to those described in the consumer use study. The information is anecdotal and is generally not helpful in assessing the use of loratadine in the OTC setting.

Expert Panel Report

The sponsor organized a panel of expert consultants to address two questions:

1) Can a patient self-recognize and safely self-treat a recurring episode of chronic idiopathic urticaria with OTC loratadine after initial diagnosis by a physician?
2) Are there serious medical consequences from a patient self-treating hives with OTC loratadine without prior consultation with a physician? If so, can these consequences be mitigated with labeling?

Based on personal experience, the panel believed that patients diagnosed with chronic idiopathic urticaria could self treat their condition because most already do it after the initial diagnosis by a physician. Although they provided no data to support this position, it certainly is not unrealistic if one can be assured that the patient would get the diagnosis in the first place.

The panel also felt that this population was not at greater risk than the general population for more serious conditions (e.g. anaphylaxis). Despite this, they recommend labeling instructing subjects to seek immediate medical help for symptoms such as "difficulty breathing, faintness, swelling of the tongue or in the throat, or gastrointestinal distress". This is somewhat contradictory unless the purpose is to reinforce what is already told to them by a physician at the time of diagnosis.

They also recommend that the indication be limited to the CIU population because 1) patients with recurring hives should have an evaluation by a physician; and 2) "data are not now available for a broader urticaria indication". This position and recommendation are perplexing in view of the information available from the consumer survey of patients with "chronic urticaria" and the label comprehension study. Presumably, the sponsor made this information available to them. If the consumer survey is to be believed, consumers are already using OTC anti-histamines for the treatment of hives and physicians are not adequately evaluating them for other conditions[5]. The broader use of anti-histamines for hives already appears to be prevalent in the general population based on the consumer survey. It would be very difficult to reverse that practice if it is accurate.

One of the major deficiencies of the report is that it fails to address the issue of accurate self-selection in the general population. Although this was not one of the questions they were asked to answer, it should have come up in the course of discussion. Because of the failure to address the accuracy of self-selection, there is an underlying assumption that whatever is written on a package will be adhered to by consumers. The data in the sponsor's database do not support this.

Summary

The sponsor notes that "urticaria is a rather common condition with an estimated incidence of 10 - 20 percent of the U.S. population". "About one-fifth of the urticaria cases are chronic- - persisting more than six weeks and the vast majority of chronic sufferers have an idiopathic disorder." Based on this information, the majority of consumers who experience urticaria will not have chronic hives. One of the important issues to be addressed for this indication is accurate self-selection, de-selection and use by all consumers likely to use this product. The consumer survey and physician surveys do not provide sufficient information on the ability of consumers to accurately select and use this product.

The Expert Panel Report is also deficient in providing supporting information for the accurate self-selection and use of the product. There appears to be an underlying assumption in their recommendation that simply writing instructions on the label limiting use to the CIU population will lead to consumer compliance. Contrary to the recommendation of the panel, the Agency should also consider a more general hives indication in the general population and determine what information should be provided to support this claim.

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[4] "Qualified " interview was not defined

[5] In the consumer survey, 7% had skin testing and 39% had blood testing.

Charles J. Ganley, M.D.

cc: orig.
HFD-570/meyer/mann/lee/chowdhury/zeccola
HFD-560 /merritt/ganley/katz/hilfiker/chang/hu/holman

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

Application Numbers: N19-658, N20-704, N20-641, N19-670, N20-470

Application Type: NDA supplement

Sponsor: Schering Corporation

Proprietary Names: Claritin tablets, RediTabs, and syrup, Claritin D 12 Hour, Claritin D 24 Hour

Category of Drug: Antihistamine
Antihistamine/decongestant

USAN/Established Name: loratadine
loratadine/pseudoephedrine

Route of Administration: Oral

Medical Reviewer: Charles E. Lee, M.D.

Review Date: 3/5/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type	Comments:
N19-658 SE6-018	1/25/02	1/25/02	NDA supplement	Claritin tablets
N20-704 SE6-008	1/25/02	1/25/02	NDA supplement	Claritin RediTabs
N20-641 SE6-008	1/25/02	1/25/02	NDA supplement	Claritin syrup
N19-670 SE6-018	1/25/02	1/25/02	NDA supplement	Claritin D 12 Hour
N20-470 SE6-016	1/25/02	1/25/02	NDA supplement	Claritin D 24 Hour

RELATED APPLICATIONS (if applicable):

Application	Document Date:	Application Type:	Comments:

These NDA supplements are 505(b)(2) applications for an OTC switch for the Claritin line of loratadine products. The sponsor is the Schering Corporation. The products are currently approved and marketed as prescription only. The proposed indications for the single ingredient loratadine products are (1) the relief of various symptoms of allergic rhinitis and (2) the relief and reduction of itching and rash due to recurring or chronic hives of an unknown source. The single ingredient tablets, RediTabs, and syrup are proposed for OTC use in adults and children ages 6 years and older; the same ages for which the currently marketed prescription products are indicated. The proposed indication for the combination loratadine/pseudoephedrine (PSE) products is the relief of various symptoms of allergic rhinitis, including nasal congestion and relief of sinus pressure, among others. The combination loratadine/PSE products are proposed for OTC use in adults and children ages 12 years and older, the same ages for which the currently marketed prescription products are indicated. There currently are no OTC products approved in the US for the treatment of CIU, urticaria, or itching due to hives. Public advisory committee opinion will be sought regarding the appropriateness of an OTC indication for CIU. The applications are appropriately indexed and organized to allow clinical review. No subgroup analysis of efficacy by gender, race, or age >65 years for AR or CIU was provided in the Integrated Summary of Efficacy. The sponsor should provide an analysis of efficacy for these subgroups. The Integrated Summary of Safety (ISS) does not include a subgroup analysis of safety by gender or by race. The ISS does not include a review of the medical literature regarding the safety of the products. Preliminary review of proposed product labeling reveals concerns about the appropriateness of an OTC indication for CIU and the OTC use for CIU in children. The sponsor will be asked to submit an analysis of the safety of the products by gender and race, and a review of the medical literature regarding the safety of the products. With the above exceptions, the submission is adequate to allow clinical review. The submission is fileable.

OUTSTANDING ISSUES: Analysis of safety by gender and race and a review of the medical literature regarding the safety of loratadine and loratadine/PSE.

RECOMMENDED REGULATORY ACTION:

NDA is: **Fileable: X** **Not Fileable:**

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

1. GENERAL INFORMATION AND BACKGROUND

These NDA supplements are 505(b)(2) applications for an OTC switch for the Claritin line of loratadine products. The sponsor is the Schering Corporation. The products and their NDA application numbers follow:

- NDA 19-658, SE6-018, Claritin tablets (loratadine 10 mg)
- NDA 20-704, SE6-008, Claritin RediTabs (loratadine 10 mg)
- NDA 20-641, SE6-009, Claritin Syrup (loratadine 5 mg/5 mL)
- NDA 19-670, SE6-018, Claritin D 12-Hour tablets (loratadine 5 mg/pseudoephedrine HCl 120 mg)
- NDA 20-470, SE6-016, Claritin D 24-Hour tablets (loratadine 10 mg/pseudoephedrine HCl 240 mg)

The products are currently approved and marketed as prescription only. The proposed indications for the single ingredient loratadine products are (1) the relief of various symptoms of allergic rhinitis and (2) the relief and reduction of itching and rash due to recurring or chronic hives of an unknown source. The single ingredient tablets, RediTabs, and syrup are proposed for OTC use in adults and children ages 6 years and older, the same ages for which the currently marketed prescription products are indicated.

The proposed indication for the combination loratadine/pseudoephedrine (PSE) products is the relief of various symptoms of allergic rhinitis, including nasal congestion and relief of sinus pressure, among others. The combination loratadine/PSE products are proposed for OTC use in adults and children ages 12 years and older, the same ages for which the currently marketed prescription products are indicated.

Loratadine is a tricyclic antihistamine, and is one of the second-generation antihistamines. Second generation antihistamines tend to be less sedating and less likely to have anticholinergic side effects than first generation antihistamines. There has been much recent public interest in a switch for loratadine from prescription status to OTC status. The California Blue Cross submitted a Citizen's Petition requesting OTC status for "non-sedating" (second generation) antihistamines, including loratadine. The petition was based on a review of approximately 300 relevant publications, and included meta-analyses of data extracted from these publications. In addition, the Agency solicited information from the public on the regulation of OTC drug products at a recent Public Hearing on over-the-counter drug products [Docket 00N-1256, 6/28/00-6/29/00, http://www.fda.gov/ohrms/dockets/dockets/00n1256/00n1256xx.htm].
The Agency also heard opinions on the suitability of second generation antihistamines such as loratadine for OTC switches in a joint meeting of the Nonprescription Drugs and Pulmonary and Allergy Drugs Advisory committees on 5/11/01 [http://www.fda.gov/ohrms/dockets/ac/cder01.htm#Nonprescriptio]. The Advisory Committee concluded that loratadine demonstrated a risk/benefit profile suitable for an OTC antihistamine.

Information regarding the safety and efficacy of loratadine for these indications has been previously submitted to the approved NDAs. The sponsor points out in their cover letter

that they are supportive of the switch only if both indications and all dosage forms are approved for OTC marketing. There were no pre-IND, End-of-Phase 2, or pre-NDA meetings for these applications, although the sponsor met with Drs. Temple, Meyer, Ganley, and Mann on 12/20/01 to discuss the submission.

These are paper NDA submissions. The applications for the loratadine products are identical and consist of 63 paper volumes. Some of the data are also submitted in electronic form. The applications for the loratadine/PSE products are identical and consist of 61 paper volumes. Some of the data are also submitted in electronic form. The submissions for the loratadine products and the loratadine/PSE products are identical, except for 2 additional volumes in the loratadine application, Volumes 1.62 and 1.63. These volumes contain information supporting the OTC switch of the CIU indication.

There currently are no OTC products approved in the US for the treatment of CIU, urticaria, or itching due to hives. CIU, urticaria, and itching due to hives are not an OTC monograph indication. At the time of this review, it appears that public advisory committee opinion will be sought regarding the appropriateness of an OTC indication for CIU. A combined Nonprescription Advisory Drugs and Pulmonary and Allergy Drugs Advisory Committee meeting tentatively is scheduled for 4/22/02.

2. FOREIGN MARKETING AND REGULATORY HISTORY

The five dosage forms of loratadine (tablets, RediTabs, syrup, D-12 Hour tablets, D-24 Hour tablets) are marketed worldwide. In most countries, the single ingredient loratadine products are indicated for the relief of symptoms of seasonal and perennial allergic rhinitis (SAR and PAR), allergic skin disorders, and chronic idiopathic urticaria (CIU). Loratadine tablets and RediTabs are indicated for patients 6 years of age and older; loratadine syrup is indicated in patients 2 years of age and older. The loratadine/PSE combination products are generally indicated for the treatment of symptoms of SAR in patients 12 years of age and older [NDA 19-658, Volume 1.1, Section 3.C., page 3].

The numbers of countries in which each of the products is approved for prescription and non-prescription use is displayed in Table 1.

Table 1. Worldwide marketing of loratadine products [[NDA 19-658, Volume 1.1, Section 3.C., page 3].

Formulation	Number of Countries approved (marketed)			
	Prescription		Non-prescription	
Loratadine, 10 mg tablets	114	(102)	30	(28)
Loratadine, 10 mg RediTabs	35	(15)	7	(3)
Loratadine, 1 mg/mL syrup	92	(80)	22	(20)
Loratadine D 12 Hour tablets	74	(51)	10	(7)
Loratadine D 24 Hour tablets	34	(15)	4	(3)

Loratadine was first introduced as a prescription product in Belgium in 1988 and as a non-prescription product in Canada in 1988. In most countries where loratadine tablets and syrup are available as a non-prescription products, it is indicated for both AR, allergic skin disorder, and CIU indications, including the UK, Canada, and Australia [NDA 19-658, Volume 1.1, Section 3.C., pages 3-4].

In the US, Claritin tablets (NDA 19-658) were approved for SAR in April 1993 and for CIU in September 1995. Claritin syrup (NDA 20-641) was approved in the US for patients 6 years of age and older in October 1996 and in patients ages 2 to 6 years in September 2000. Claritin RediTabs (NDA 20-704) were approved in the US in December 1996. Claritin D 12 Hour tablets (NDA 19-670) were approved in the US in November 1994 and Claritin D 24 Hour tablets (NDA 20-470) were approved in August 1996 [NDA 19-658, Volume 1.1, Section 3.C., page 4].

3. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)

The following items were included in these submissions:

- Form FDA 356h [Volume 1.1, no page number]
- Statements of Good Clinical Practice [Volume 1.31, Section 8.K., page 2]]
- Integrated Summary of Efficacy (ISE) [Volume 1.2]
  - The ISE consists of summaries of clinical studies conducted by the sponsor in support of the original NDAs and NDA supplements for loratadine and loratadine/PSE combination products. No subgroup analysis of efficacy by gender, race, or age >65 years for AR or CIU was provided. The sponsor should provide an analysis of efficacy for these subgroups.
- Integrated Summary of Safety (ISS) [Volumes 1.3 to 1.31]
  - The bulk of the ISS is line listings of AE reports for the individual products. The line listings are summarized and tabulated to allow review. Safety data includes summaries of data from NDA clinical trials, worldwide postmarketing events for both prescription and OTC use, and abuse and overdose potential. The ISS addresses drug-disease interactions and population subgroups such as children and the elderly, and use in pregnancy, but does not include a subgroup analysis of safety by gender or by race for either AR or CIU indications. The ISS does not include a review of the medical literature regarding the safety of the products. The sponsor should submit an analysis of the safety of the products by gender and race, and the sponsor should provide a review of the medical literature regarding the safety of the products.
- Integrated Summary of Benefits and Risks [Volume 1.31]
- Proposed labeling [Volume 1.1, Section 2]
- Environmental assessment
  - The sponsor has requested a categorical exclusion from this requirement because the Expected Introduction Concentration of loratadine into the aquatic environment is below one part per billion [Volume 1.1, Section 3.D., page 3]

The following items were not included in these submissions because no new clinical studies were performed for this application:

- Debarment certification
- Financial disclosure statement
- Case report forms for patients with SAEs or discontinuing studies

The sponsor has not included a list of referenced DMFs in these submissions. The sponsor references CMC information in NDAs 19-658, 20-641, and 20-704 for loratadine and NDAs 19-670 and 20-470 for loratadine/PSE products.

The sponsor did not include a plan to meet the pediatric study requirement. However, the sponsor has completed pediatric studies for loratadine in children down to 6 months of age to support the approval of loratadine in children down to the age of 2 years. The amount of PSE in the combination products is not appropriate for children under the age of 12 years.

4. CLINICAL STUDIES

There were no clinical studies in these submissions.

5. OTHER STUDIES AND SUPPORTIVE INFORMATION

The single ingredient loratadine applications (NDAs 19-568, 20-704, and 20-641) include information to support the proposed OTC switch of the CIU indication [Volume 1.62, 1.63]. This information includes the following:

- "Habits and Practices of CIU Sufferers" study report [Volume 1.62, Section 20.A., pages 1-56]
- "Physicians' CIU Habits and Practices" study report [Volume 1.62, Section 20B., pages 1-48]
- CIU Label Comprehension Study Report [Volume 1.62, Section 20.C., pages 1-200 and Volume 1.63, Section 20.C., pages 201-422]
- CIU Expert Panel Review [Volume 1.63, pages 1-88]

This information is described briefly below. The information is provided in a form that is acceptable for this clinical reviewer. It should be noted that none of the material supporting the OTC switch of the CIU indication appears to address use of the product in children, an age group in which CIU is unusual.

5.1. "Habits and Practices of CIU Sufferers" study report

The sponsor commissioned a research study to understand fundamental dynamics of CIU from the patient perspective, including frequency of suffering, types of symptoms, and duration and severity of the condition. The study was also to understand the interaction of CIU patients with their physicians, treatment modalities, and ease of patient recognition of the condition once a physician has established the diagnosis. This study was a survey of 1.2 million US households, performed by E-mail over two consecutive weeks, 10/30/01 and 11/6/01. Each survey resulted in approximately 15,000 qualified adult subjects. Data is presented in a descriptive fashion [Volume 1.62, Section 20.A., pages 1-56].

5.2. "Physicians' CIU Habits and Practices" study report

The sponsor also conducted a survey of physicians to understand their diagnostic procedures and approach to the diagnosis of CIU, to determine their perceptions of the patient's ability to recognize an episode of CIU, and to understand their view of patient

self-management practices following establishment of a diagnosis. A total of 359 interviews of medical doctors were completed among an Internet panel of physicians. This group included 151 primary care physicians, 75 dermatologists, 55 allergists, and 78 pediatricians. The survey was conducted in November 2001. Data is presented in a descriptive fashion [Volume 1.62, Section 20B., pages 1-48].

5.3. CIU Label Comprehension Study Report

This was a multicenter label comprehension study designed to evaluate how well the average consumer understood the conditions in which loratadine could be used based on his/her reading of the carton label and package insert. Results are presented in a descriptive fashion [Volume 1.62, Section 20.C., pages 1-200 and Volume 1.63, Section 20.C., pages 201-422].

5.4. CIU Expert Panel Review

The sponsor convened a panel of outside experts to consider whether CIU is an appropriate OTC indication for loratadine. The meeting was held on 1/14/02. The panel included four physicians and a moderator. Three of the four physicians were allergists and one was a dermatologist. A 2 ½-page consensus statement is provided. The bulk of this section contains Curriculum Vitae of panel members [Volume 1.63, pages 1-88].

6. BRIEF REVIEW OF PROPOSED LABELING

Annotated package labeling has been included in this submission. Initial labeling concerns include the following:

- Appropriateness of the OTC indication for CIU
- Different labeling and packaging for both the allergic rhinitis and CIU indications for the identical single ingredient loratadine products
- [redacted]
- Labeling the syrup formulation for use in children under the age of 12 years, an age in which CIU is unusual

The sponsor has provided a copy of labeling and packaging of loratadine single-ingredient products approved for OTC use in Canada and the UK [Volume 1, Section 3.C., pages 109-173].

7. DSI REVIEW/AUDIT

DSI audit will not be requested because no new efficacy or safety studies were included in this application for these drug products.

8. SUMMARY

These NDA supplements are 505(b)(2) applications for an OTC switch for the Claritin line of loratadine products. The sponsor is the Schering Corporation. The products are currently approved and marketed as prescription only. The proposed indications for the single ingredient loratadine products are (1) the relief of various symptoms of allergic rhinitis and (2) the relief and reduction of itching and rash due to recurring or chronic

hives of an unknown source. The single ingredient tablets, RediTabs, and syrup are proposed for OTC use in adults and children ages 6 years and older, the same ages for which the currently marketed prescription products are indicated. The proposed indication for the combination loratadine/pseudoephedrine (PSE) products is the relief of various symptoms of allergic rhinitis, including nasal congestion and relief of sinus pressure, among others. The combination loratadine/PSE products are proposed for OTC use in adults and children ages 12 years and older, the same ages for which the currently marketed prescription products are indicated. There currently are no OTC products approved in the US for the treatment of CIU, urticaria, or itching due to hives. Public advisory committee opinion will be sought regarding the appropriateness of an OTC indication for CIU.

The applications are appropriately indexed and organized to allow clinical review. No subgroup analysis of efficacy by gender, race, or age >65 years for AR or CIU was provided in the Integrated Summary of Efficacy. The sponsor should provide an analysis of efficacy for these subgroups. The Integrated Summary of Safety (ISS) does not include a subgroup analysis of safety by gender or by race. The ISS does not include a review of the medical literature regarding the safety of the products. Preliminary review of proposed product labeling reveals concerns about the appropriateness of an OTC indication for CIU and the OTC use for CIU in children. The sponsor will be asked to submit an analysis of the safety of the products by gender and race, and a review of the medical literature regarding the safety of the products. With the above exceptions, the submission is adequate to allow clinical review. The submission is fileable.

9. TIME LINE FOR REVIEW

Write-up will be concomitant with the review process. The schedule for review is displayed in Table 2. Clinical review will focus primarily on the ISS. Label review will be complete by [redacted] Draft review will be complete by [redacted] 4 weeks before the action date.

Table 2. Proposed schedule for review.

Milestone	Target Date for Completion
CIU Habits and Practices surveys	
CIU Label Comprehension study	
CIU Expert Panel Review	
ISE	
ISS	
Label Review	
Draft Review	
Division Action Date	
Action Date, 10 months	

Reviewed by:

/S/

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

/S/

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

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