CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-658/S-018
19-670/S-018
20-470/S-016
20-641/S-009
20-704/S-008

LABELING REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	OFFICE OF DRUG SAFETY REVIEW	
TO: Robert Meyer, M.D. Director, DPADP	**FROM:** Joyce Weaver, Pharm.D. Safety Evaluator, DDRE (HFD-430)	**PID #** D020159
DATE REQUESTED: 3/29/2002 **DATE RECEIVED:** 3/29/2002	**REQUESTOR:** Charles Lee, M.D.	
DRUG (Est): Loratadine	**NDA** 19-658, 19-670, 20-470, 20-641, 20-704	**SPONSOR:** Schering Corp
DRUG NAME (Trade): Claritin tablets, Claritin RediTabs, Claritin Syrup; Claritin D 12-Hour, Claritin D 24-Hour	**THERAPEUTIC CLASSIFICATION:** antihistamine	
EVENT: Anaphylaxis, anaphylactoid reactions, angioedema, and urticaria		

Executive Summary: Anaphylaxis, anaphylactoid reactions, angioedema, and urticaria were reported more often when the nonsedating antihistamines were used to treat urticaria as compared to their use for all indications. Likewise, death, disability, hospitalization, and life-threatening outcomes were reported more often when the antihistamines were used to treat urticaria. It is not known if the ongoing involvement of a learned intermediary made a difference or would have made a difference in the development, diagnosis, or management of the adverse events.

Reason for Review: The Sponsor has submitted an NDA supplement for the OTC switch for the Claritin products. The proposed indications for the single-ingredient loratadine products include use for the relief and reduction of itching and rash due to recurring or chronic hives of an unknown source. Our purpose in this review is to provide background information from AERS for cetirizine, fexofenadine, and loratadine regarding adverse events when these drugs were used to treat urticaria. Based on data provided by the Sponsor in the NDA Supplement and reviewed by Charles Lee, M.D. (Medical Officer, DPADP), we focused this review on: (1) reports of anaphylaxis, anaphylactoid reactions, angioedema, and urticaria; and (2) the severity of the outcomes of the adverse events. In this review of AERS data, we worked only with raw numbers. We did not perform a "hands-on" review of the case reports because Dr. Lee already has reviewed the cases.

Relevant Product Labeling: Cetirizine, fexofenadine, and loratadine are approved for prescription use to treat chronic idiopathic urticaria (CIU).

Search Date: April 2002	**Search Type:** AERS

Search Strategy—All adverse event (AE) reports of anaphylaxis, anaphylactoid reactions, angioedema, and urticaria for cetirizine, fexofenadine, and loratadine were counted (raw numbers). Additionally, all AE reports for these drugs when used for an urticaria indication were counted. The percentages of AEs reporting anaphylaxis, anaphylactoid reactions, angioedema, and urticaria overall and among reports in which the antihistamine was used to treat urticaria were determined.

Search Results: AERS contains 3724 reports for cetirizine, 2566 reports for fexofenadine, and 4635 reports for loratadine. Reports of AEs occurring when the antihistamine was used to treat urticaria constitute 6.4% of the total reports for cetirizine, 3.1% of the total reports for fexofenadine, and 0.7% of the total reports for loratadine. Reports of anaphylaxis, anaphylactoid reactions, angioedema, and urticaria constitute 5.4% of the total reports for cetirizine, 5.3% of the total reports for fexofenadine, and 2.4% of the total reports for loratadine. Among the reports in which the antihistamines were used to treat urticaria, a higher percentage of reports describe anaphylaxis, anaphylactoid reactions, angioedema, or urticaria: cetirizine—28.6%, fexofenadine—16.5%, and loratadine—25%. This includes cases in which urticaria or angioedema worsened after taking the antihistamine (cetirizine—24, fexofenadine—7, loratadine—4). Among the reports in which the antihistamines were used to treat urticaria, a greater percentage of the reports had serious outcomes (cetirizine—17.2% of all cases had serious outcomes vs. 24.4% of cases with urticaria indication, fexofenadine—11.6% vs. 35.4%, loratadine—15.9% vs. 34.4%).

Discussion / Conclusions: Compared to the other nonsedating antihistamines, AERS contains a smaller percentage of reports for loratadine in which urticaria was the indication for the use of the product. It is not known if loratadine is used less often to treat urticaria compared to cetirizine and fexofenadine. Because loratadine was approved earlier than the other two antihistamines, a larger proportion of the AE reports for loratadine were entered into the Spontaneous Reporting System (SRS). SRS did not capture information on indication for use.

Compared to the use of the antihistamines overall (for any indication), anaphylaxis, anaphylactoid reactions, angioedema, and urticaria were reported more often when the antihistamines were used to treat urticaria. Most likely, these cases are a combination of reactions occurring as consequences of taking antihistamines and ongoing reactions that were not stopped by taking antihistamines. Additionally, serious outcomes were reported more often when the antihistamines were used to treat urticaria. Because the reports were not reviewed in detail, it is not known if the ongoing involvement of a learned intermediary made a difference or would have made a difference in the development, diagnosis, or management of the adverse events.

Reviewer's Signature / Date:	**Team Leader's Signature / Date:**
Division Director Signature / Date:	

Attachments: Attachment 1—Reports of Anaphylaxis, Anaphylactoid Reactions, Angioedema, or Urticaria for Cetirizine, Fexofenadine, and Loratadine

Attachment 1—
Reports of Anaphylaxis, Anaphylactoid Reactions, Angioedema, or Urticaria for Cetirizine, Fexofenadine, and Loratadine

	Cetirizine	Fexofenadine	Loratadine
FDA approval	12/95	7/96	4/93
Total # reports in AERS	3724	2566	4635
# of reports with serious outcomes (% total reports)*	641 (17.2%)	297 (11.6%)	736 (15.9%)
Reports of anaphylaxis, anaphylactoid reactions, angioedema, urticaria (% total reports)	201 (5.4%)	137 (5.3%)	113 (2.4%)
FDA approval for CIU	12/95	2/00	12/96
# AE reports with any entry in "indication(s)" field of AERS (% total reports)[§]	1788 (48%)	1552 (60%)	922 (20%)
AE reports with urticaria as indication for use (% total reports)	238 (6.4%)	79 (3.1%)	32 (0.7%)
# of reports with serious outcomes (% reports with urticaria indications)*	58 (24.4%)	28 (35.4%)	11 (34.4%)
AE reports of anaphylactic or anaphylactoid reactions, angioedema, urticaria (% total reports with urticaria as the indication for use)	68 (28.6%)	13 (16.5%)	8 (25%)
AE reports of anaphylactic or anaphylactoid reactions, angioedema, urticaria **with reports of aggravation of condition excluded** (% total reports with urticaria as the indication for use)	44 (18.5%)	6 (7.6%)	4 (12.5%)

[§] Entries is the "indication(s)" field were not possible prior to the implementation of AERS in 1997; the Spontaneous Reporting System (SRS) did not capture this information.

* serious outcomes defined as death, disability, hospitalization, or life-threatening reactions

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/s/

Joyce Weaver
4/17/02 11:56:55 AM
PHARMACIST

Julie Beitz
4/19/02 10:36:20 AM
DIRECTOR

Division of Over-the-Counter Drug Products
Labeling Review

NDA:	**20-470 (S019) CBE0**
Sponsor:	**Schering-Plough Corporation**
Drug Product:	**Claritin-D 24 Hour extended release tablet (10 mg loratadine/ 240 mg pseudoephedrine sulfate)**

Submission Dates: February 10, 2003

Receipt Date: February 11, 2003

Type of Submission: NDA Supplement

Pharmacological Categories: Antihistamine

Active Ingredients: Loratadine/Pseudoephedrine Sulfate

Indications: Relief of allergic rhinitis symptoms and nasal and sinus congestion

Review Date: June 3, 2003

Reviewer: Matthew R. Holman, Ph.D.

Background

On December 9, 2002, the Agency approved S017 to allow extension of the expiry date to 24 months for Claritin-D 24 Hour extended release tablets packaged in blister packs and bottles. This approval letter requested that the sponsor revise the storage statement from "Store between 15°C and 25°C (59°F and 77°F)" to "Store between 20°C to 25°C (68°F to 77°F)" at the next printing, or within six months, whichever occurred sooner. The sponsor then submitted S019 as CBE0 to notify the Agency that the expiry date and storage statement were changed as requested.

This supplement contains only carton labels for 5 and 10 count blister packs. The sponsor did not submit blister pack labels for these cartons or the carton and container labels for the [redacted]. However, in a May 28, 2003, telephone conversation, the sponsor indicated that the blister pack label is the same as that approved in the December 9, 2002, approval letter. In addition, the sponsor indicated that the [redacted] was not submitted because this package size is not being marketed

Reviewer's Comments

I. 5 & 10 Count

A. Carton Label

Reviewer's comment: *The sponsor revised **Other information** in the Drug Facts panel to reflect to required temperature range of 20°C to 25°C.*

B. Blister Card Label

Reviewer's comment: *The sponsor did not submit the blister card labels. This is acceptable because the storage conditions are not listed on the blister card.*

II. [redacted]

Recommendations

1. Issue an APPROVAL letter to the sponsor for the 5 and 10 count carton labels with revised storage condition statement per approval letter for S-017.

[redacted]

Matthew R. Holman, Ph.D.
Interdisciplinary Scientist, HFD-560

Marina Chang, R.Ph.
Team Leader, HFD-560

Division of Over-the-Counter Drug Products
Addendum Labeling Review

NDAs:	**19-658 (S018), 20-704 (S008), 20-641 (S009), 19-670 (S018), and 20-470 (S016)**
Sponsor:	**Schering-Plough Corporation**
Drug Products:	**Claritin (loratadine tablets, reditabs®, and syrup)** **Claritin-D 12 and 24 (loratadine/pseudoephedrine XR tablets)**

Submission Dates: November 12, 2002

Type of Submission: NDA Supplement for Rx-to-OTC switch

Pharmacological Categories: Antihistamine

Active Ingredients: Loratadine

Indications: Relief of allergic rhinitis symptoms

Review Date: November 15, 2002

Reviewer: Matthew R. Holman, Ph.D.

Project Manager: Elaine Abraham, R. Ph.

I. Background

On October 31, 2002, the Agency sent a facsimile to the sponsor with recommended changes to the labeling for Claritin tablets, reditabs®, and syrup (NDAs 19-658 (S018), 20-704 (S008), and 20-641 (S009), respectively) and Claritin-D 12 and 24 hr (NDAs 19-670 (S018) and 20-470 (S016), respectively). In response to this facsimile, the sponsor submitted revised final draft labeling for all packaging of these products.

II. Reviewer's Comments

A. NDA 19-658 (S-018) [tablets]

Reviewer's Comment: ***The sponsor revised the labels for 5, 10, 20, 40, and 500 count cartons according agency recommendations. The proposed labeling is acceptable.***

B. NDA 20-704 (S-008) [reditabs]

Reviewer's Comment: ***The sponsor revised the labels for 4 and 10 count cartons according agency recommendations. The proposed labeling is acceptable.***

C. NDA 20-641 (S-009) [syrup]

Reviewer's Comment: ***The sponsor revised the 4 fl. oz. label according agency recommendations. The proposed labeling is acceptable.***

D. NDAs 19-670 (S-018) and 20-470 (S-016) [extended release tablets]

Reviewer's Comment: ***The sponsor revised the labels for 10 and 20 count cartons according agency recommendations. The proposed labeling is acceptable.***

III. Recommendations

The draft labeling submitted for Claritin tablets, reditabs®, and syrup and Claritin-D 12 and 24 hour extended release tablets is acceptable and an approval letter can be issued to the sponsor. Request the sponsor to submit final printed carton and container labels for all products based on this submission.

/S/

Matthew R. Holman, Ph.D.
Interdisciplinary Scientist, HFD-560

/S/

Marina Chang, R.Ph.
Team Leader, HFD-560

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/s/

Matthew Holman
11/15/02 01:03:20 PM
INTERDISCIPLINARY

Marina Chang
11/15/02 01:14:16 PM
INTERDISCIPLINARY

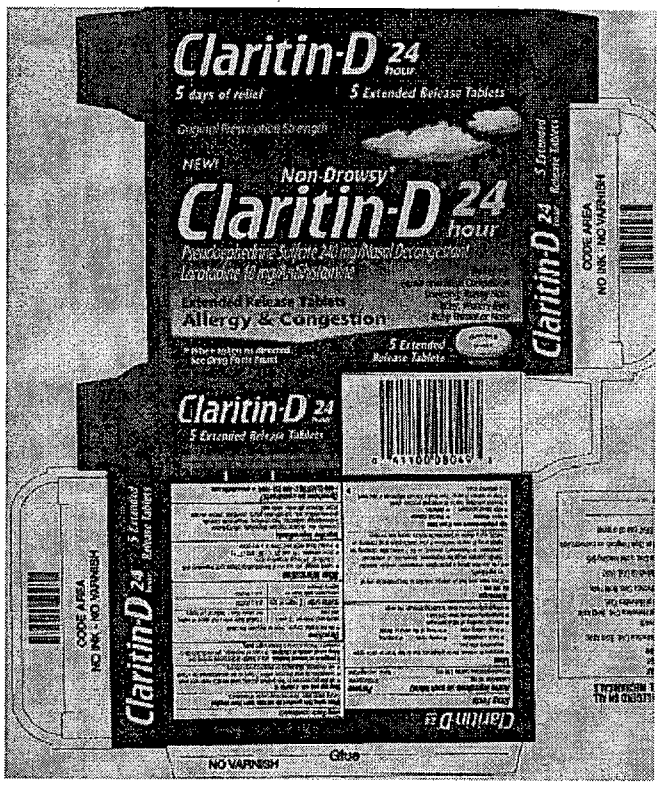
Division of Over-the-Counter Drug Products Labeling Review

NDA:	20-470
Supplement No:	S016
Submission Date:	October 24, 2002
Type of Submission:	Labeling Supplement for Rx-to-OTC switch
Sponsor:	Schering Corporation
Drug Product:	Claritin-D® 24 Hour Extended Release Tablets
Active Ingredient(s):	Loratadine 10 mg and Pseudoephedrine Sulfate 240 mg
Indication:	Relief of allergic rhinitis symptoms and nasal and sinus congestion
Stock Keeping Units	submitted 5 & 10 count (carton & blister pack)
Review Date	October 30, 2002
Reviewer:	Matthew R. Holman
Project Manager	Elaine Abraham, R. Ph.

I. Background

On October 4, 2002, the Agency sent a facsimile to the sponsor with recommended changes to the label for Claritin-D 24 Hour Extended Release Tablets (10 count). In response to this facsimile, the sponsor submitted revised labeling for this product. The revised labeling included carton labels and blister pack for 5 and 10 count packages. This is a review of the revised OTC labeling that was submitted October 24, 2002.

Each tablet contains 10 mg loratadine (antihistamine), and 240 mg pseudoephedrine (decongestant). This NDA was approved November 14, 1994.


Claritin-D 24 hour
5 days of relief
5 Extended Release Tablets
NEW!
Non-Drowsy
Claritin-D 24 hour
Extended Release Tablets
Allergy & Congestion
5 Extended Release Tablets
CODE AREA
NO INK - NO VARNISH
NO VARNISH


CODE AREA
Claritin-D® 24 Hour
(10mg loratadine/240mg pseudoephedrine sulfate)
Extended Release Tablet
Dist. by: Schering-Plough HealthCare Products, Inc.
Memphis, TN 38151 USA
Claritin-D®
24 Hour

II. Reviewer's Comments

A. 10 Count Carton Label

1. Principal Display Panel

Reviewer's comment: ***Proposed labeling is acceptable.***

2. Top and Bottom Panels and Flaps

Reviewer's comment: ***Proposed labeling is acceptable.***

3. Back Panel: Drug Facts Panel

a. Uses

Reviewer's comment: ***The sponsor should revise the statement "• relieves sinus pressure" so that it corresponds to the indication listed in 21 CFR 341.80.***

b. Warnings, Directions, Other information, Inactive ingredients, and Questions

Reviewer's comment: ***Proposed labeling is acceptable.***

c. Format Specifications

Reviewer's comment: ***Leading must be increased from 0 point to 0.5 point as required by 21 CFR 201.66(d)(3).***

B. 10 Count Blister Pack Label

Reviewer's comment: ***Proposed labeling is acceptable.***

III. Recommendations

1. The sponsor should revise the Drug Facts panel on 10 and 20 count carton labels as follows:

   a. Revise the statement "• relieves sinus pressure" to "• temporarily relieves sinus congestion and pressure" in accordance with 21 CFR 341.80.

   b. Leading must be increased from 0 point to 0.5 point as required by 21 CFR 201.66(d)(3).

2. Remind the sponsor that "New!" shall be removed from labeling six months after introduction into OTC market.

/S/

Matthew R. Holman, Ph.D.
Interdisciplinary Scientist, HFD-560

/S/

Marina Chang, R.Ph.
Team Leader, HFD-560

Division of Over-the-Counter Drug Products
Addendum Labeling Review

NDA:	**19-658 (S018)**
Sponsor:	**Schering-Plough Corporation**
Drug Product:	**Claritin (loratadine tablets, 10 mg)**
Stock Keeping Units:	**submitted 5, 10, 20, & 40 count (carton & blister pack) & 500 count (bottle)**

Submission Dates: October 24, 2002

Type of Submission: NDA Supplement for Rx-to-OTC switch

Pharmacological Categories: Antihistamine

Active Ingredients: Loratadine

Indications: Relief of allergic rhinitis symptoms

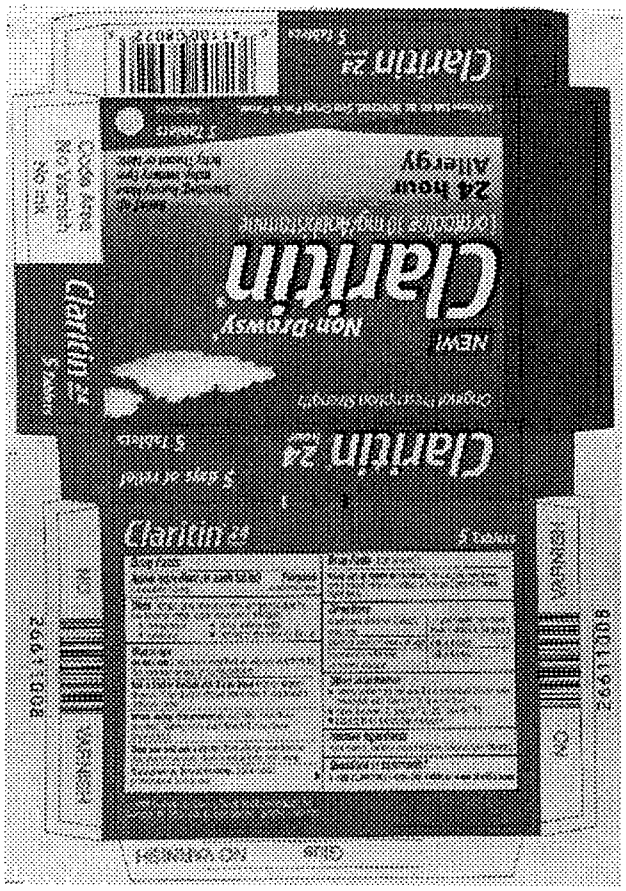
Review Date: October 28, 2002

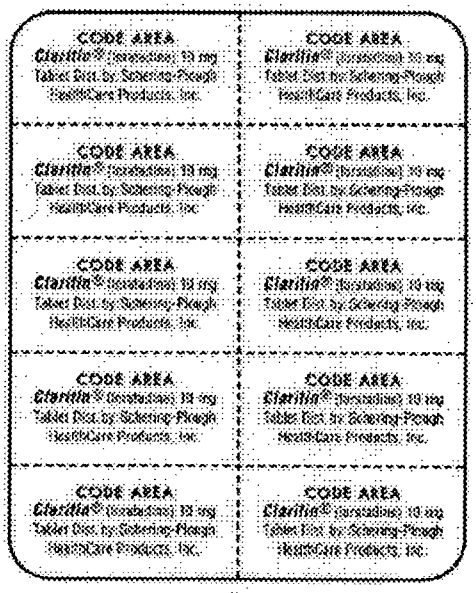
Reviewer: Matthew R. Holman, Ph.D.

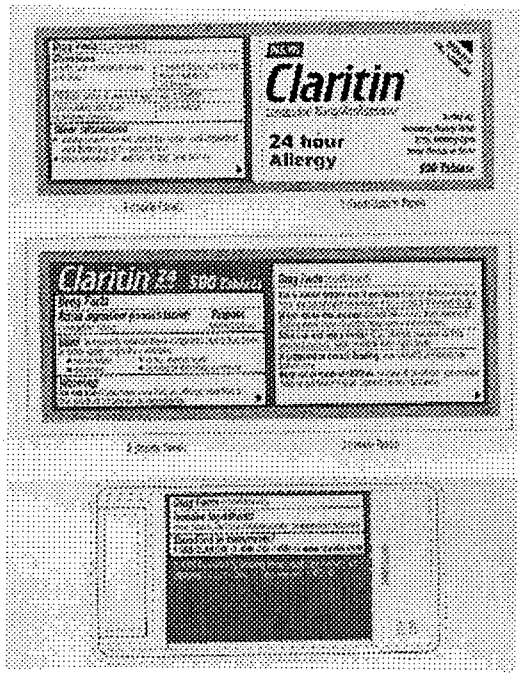
Project Manager: Elaine Abraham, R. Ph.

I. Background

On September 27, 2002, the Agency sent a facsimile to the sponsor with recommended changes to the label for Claritin Tablet (5 count). In response to this facsimile, the sponsor submitted revised labeling for this product. The revised labeling includes carton and blister pack labels for 5, 10, 20, and 40 count packages as well as bottle label for 500 count package. This is a review of the revised OTC labeling to NDA 19-658/S018 that was submitted October 24, 2002.


Claritin 24
24 hour
Allergy
Claritin
NEW!
Non-Drowsy
Claritin 24


CODE AREA
Claritin®
Tablet Dist. by Schering-Plough
HealthCare Products, Inc.



II. Reviewer's Comments

A. Review Content

Reviewer's comment: ***The carton labels for 5, 10, 20, and 40 count packages are identical except for carton size and information directly related to the number of tablets contained in the package. The graphic layout of the PDP panel for 500 count package differs significantly from those of the carton labels (e.g., background color and font color does not resemble that of the carton labels).***

B. 5, 10, 20, and 40 Count Carton Labels

1. Principal Display Panel, Top Panel, Bottom Panel, and Flaps

Reviewer's comment: ***Proposed labeling is acceptable.***

2. Back Panel

Reviewer's comment: ***Under the "Questions" subheading, the word "or" should not appear in bold typeface, but should appear in plain text font.***

C. 500 Count Carton Label

1. Principal Display Panel

Reviewer's comment: ***Proposed labeling is acceptable.***

2. Drug Facts

a. Active Ingredients

Reviewer's comment: ***"Purpose" must be right justified.***

b. Uses, Warnings, Directions, Other Information, and Inactive Ingredients

Reviewer's comment: ***Proposed labeling is acceptable.***

c. Questions

Reviewer's comment: ***The word "or" should not appear in bold typeface, but should appear in plain text font..***

d. Format Specifications

Reviewer's comment: ***The sponsor does not indicate the "Drug Facts" or "Drug Facts (continued)" title font sizes. According to 21 CFR 201.66(d)(2), the font sizes must be at least 9 point and 8 point, respectively. The sponsor must submit this information before label approval. The heading font size must be increased from 7 point to 8 point as required by 21 CFR 201.66(d)(2). The sponsor indicates that leading is 0 point; the sponsor must increase leading to 0.5 point as required by 21 CFR 201.66(d)(3).***

D. 5 and 10 Count Blister Pack Labels

Reviewer's comment: ***Proposed labeling is acceptable.***

III. Recommendations

1. The sponsor should revise the labeling as follows:

A. 5, 10, 20, and 40 Count Carton Labels

Under ***Questions*** subheading, the word "or" should not appear in bold typeface, but should appear in plain text font.

B. 500 Count Carton Label

1. ***Purpose*** subheading must be right justified according to 21 CFR 201.66(d)(6).

2. Format Specifications

   a. Submit font sizes for ***Drug Facts*** and ***Drug Facts (continued)*** titles. According to 21 CFR 201.66(d)(2), the font sizes must be at least 9 point and 8 point, respectively.

   b. The heading font size must be increased from 7 point to 8 point as required by 21 CFR 201.66(d)(2).

   c. Leading must be increased from 0 point to 0.5 point as required by 21 CFR 201.66(d)(3).

2. Remind the sponsor that "New!" shall be removed from labeling six months after introduction into OTC market.

3. _____

/S/

Matthew R. Holman, Ph.D.
Interdisciplinary Scientist, HFD-560

/S/

Marina Chang, R.Ph.
Team Leader, HFD-560

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/s/

Matthew Holman
11/4/02 10:06:09 AM
INTERDISCIPLINARY

Marina Chang
11/4/02 11:06:36 AM
INTERDISCIPLINARY

Division of Over-the-Counter Drug Products
Addendum- Labeling Review

NDA:	**19-658 (S018)**
Sponsor:	**Schering-Plough Corporation**
Drug Product:	**Claritin (loratadine tablets, 10 mg)**
Stock Keeping Units:	**1 submitted (5 count)** **4 proposed (2, 10, 20, & 40 count)**

Submission Dates: January 25, 2002; March 28, 2002; July 10, 2002 (e-mail); August 9, 2002

Type of Submission: NDA Supplement for Rx-to-OTC switch

Pharmacological Categories: Antihistamine

Active Ingredients: Loratadine

Indications: Relief of allergic rhinitis symptoms

Review Date: August 28, 2002

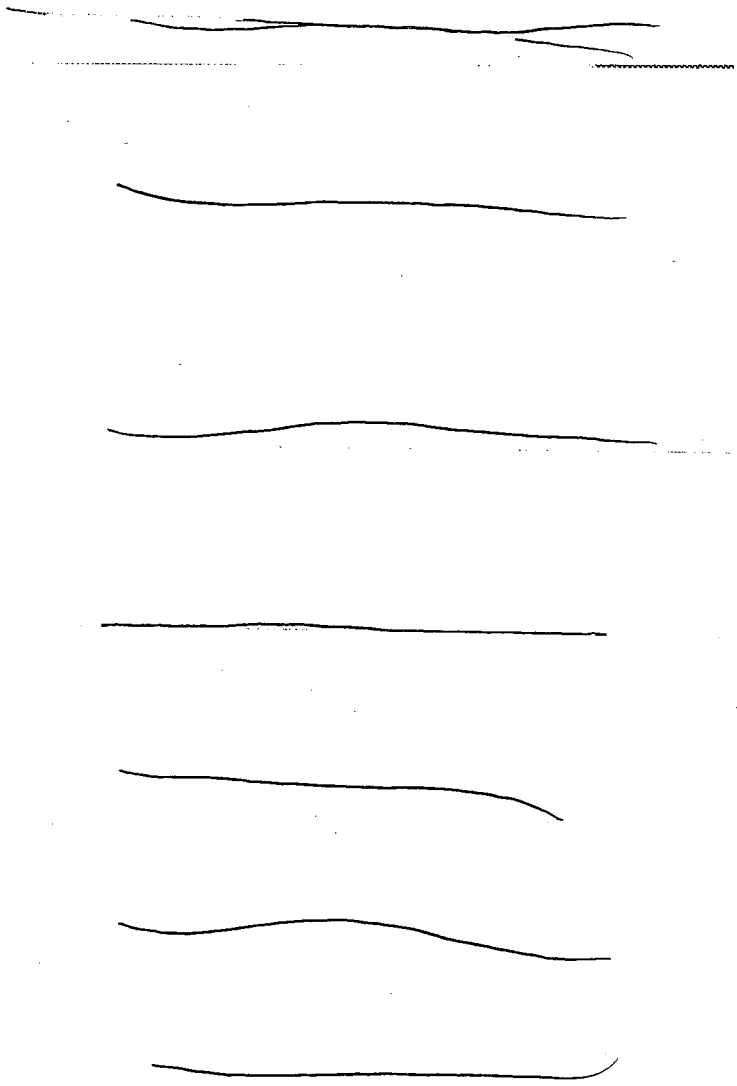
Reviewer: Matthew R. Holman, Ph.D.

Project Manager: Elaine Abraham, R. Ph.

I. Background

On July 23, 2002, the Agency sent a facsimile to the sponsor with recommended changes. In response to this facsimile, the sponsor submitted revised labeling for this product as well as for NDAs 20-641 (Claritin Syrup), 20-704 (Claritin Reditabs), 19-670 (Claritin-D 12 Hour Extended Release Tablets), and 20-470 (Claritin-D 24 Hour Extended Release Tablets) on August 9, 2002. In this submission, the sponsor indicated Claritin 10 mg tablets will be marketed in 2, 5, 10, 20,

and 40 count packages. The sponsor only included the carton and blister pack labels for the 5 count package and the blister pack label for the 10 count package. The sponsor indicated that labeling for all package sizes will be submitted after the sponsor received comments on the labeling submitted August 9, 2002.



II. Reviewer's Comments

Changes recommended by the reviewer are identified by redlining for additions and by ~~strikethrough~~ for deletions.

A. Review Content

Reviewer's comment: ***This review concerns the carton and blister pack labels for the 5 count package as well as the blister pack label for the 10 count package. The agency cannot review and comment on the labeling for the 2, 10, 20, or 40 count packages until such labeling are submitted by the sponsor.***

B. 5 Count Carton Label

1. Principal Display Panel

a. New! — Original Prescription Strength

Reviewer's comment: ***The sponsor added "New!" to the PDP after the initial label review. The sponsor must remove "New!" from labeling six months after introduction to OTC market.***
The sponsor did not remove — from this statement as recommended. The sponsor justifies use of the phrase — Prescription Strength" with the following three argument:

[redacted]

The reviewer recognizes the validity of the sponsor's argument. However, OTC products noted by the sponsor that contain the statement " — Prescription Strength" are no longer available with prescription. In contrast, Claritin has not been approved for OTC marketing for the hives indication, and, thus, Claritin may be available both with and without a prescription. To avoid consumer confusion and deter the use of OTC Claritin for the treatment of hives, the sponsor should reword the statement to read "Original Prescription Strength".

b. Non-Drowsy*

Reviewer's comment: ***The sponsor must place an asterisk immediately after the statement "Non-Drowsy". The asterisk refers consumers to the following statement: "*When taken as directed. See Drug Facts Panel." This statement must appear at the bottom of the PDP in conspicuous print. The sponsor did not make***

this change following the initial label review. ***The Agency is requiring this asterisk and reference statement on the PDP because this is not a non-drowsy product. Drowsiness may occur when not taken as directed. Therefore, the sponsor must add the recommended labeling.***

c. Relief of:
Sneezing, Runny Nose
Itchy, Watery Eyes
Itchy Throat or Nose

Reviewer's comment: ***The sponsor is encouraged to increase font size and change font color to increase contrast with background to make indication more conspicuous.***

2. Top Panel

a. Non-Drowsy*
*When taken as directed. See Drug Facts Panel.

Reviewer's comment: ***See comment 1b above.***

3. Bottom Panel and Flaps

a. Non-Drowsy*
*When taken as directed. See Drug Facts Panel.

Reviewer's comment: ***See comment 1b above. If space is limited, the reference statement is not required.***

4. Back Panel

b. Drug Facts

i. Uses

Reviewer's comment: ***The sponsor revised labeling under this heading as suggested in initial labeling review.***

ii. Warnings

iii. Directions

Adults and children 6 years and over	1 tablet daily; not more than 1 tablet in 24 hours
Children under 6	Ask a doctor
Consumers with liver or kidney disease	Ask a doctor

Reviewer's comment: ***The sponsor should add directions for individuals with liver or kidney disease. When 3 or more direction statements are listed, the direction statements generally appear in a table. This change was outline in the initial labeling review,*** ***" This may be true, however, in the prescription labeling, there is dose adjustment for these patients. Thus, the OTC label must include directions for consumers with liver or kidney disease. This direction reiterates the point that these consumes can take the product, but only after consulting a physician.***

iv. Questions?

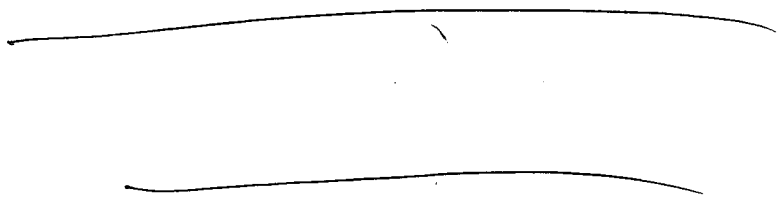
Reviewer's comment: ***The word "or" should not appear in bold typeface, but should appear in plain text font.***

C. 5 Count Blister Pack

CODE AREA
Claritin®
(loratadine)10mg
Tablet
Dist. by: Schering-Plough
HealthCare Products, Inc.
Memphis, TN 38151 USA

Reviewer's comment: ***dosage strength to follow the established name or the proprietary name.***

D. 10 Count Blister Pack



E. Package Insert

Reviewer's comment: ***The sponsor indicated that they are not including a package insert for Claritin because the product is no longer labeled for a hives indication, and this is acceptable.***

III. Recommendations

1. Remind the sponsor that the agency cannot review and comment on labeling for the 2, 10, 20, or 40 count packages until the sponsor submits such labeling. The sponsor should revise the labeling as follows:

I. 5 Count Carton Label

A. Principal Display Panel

1. Reword the phrase "Prescription Strength" to "Original Prescription Strength". The Agency reviewed the sponsor's justification against revising the statement. The Agency recognizes the examples of OTC drug products using the proposed phrase. In contrast to those examples, Claritin may be available with and without a prescription for the treatment of allergic rhinitis and hives, respectively. And, the agency agrees that consumers should understand that OTC Claritin is the same dosage strength as prescription Claritin. Using the word "Original" should prevent consumer confusion about the dosage strength and deter the use of OTC Claritin for the treatment of hives.

2. Add an asterisk ("*") following the phrase "Non-Drowsy". In addition, the following statement must appear at the bottom of the PDP in conspicuous print: "*When taken as directed. See Drug Facts Panel." The agency reviewed the sponsor's argument against this change, however, the Agency has determined that this labeling be required on all loratadine drug products to ensure consumers understand that drowsiness may result at dosages above 10 mg daily.

B. Top Panel

1. Add an asterisk ("*") following the phrase "Non-Drowsy". Add the statement in conspicuous print "*When taken as directed. See Drug Facts Panel." See IB above for explanation.

C. Bottom Panel and Flaps

1. Add an asterisk ("*") following the phrase "Non-Drowsy". Add the statement in conspicuous print "*When taken as directed. See Drug Facts Panel." if space allows.

D. Back Panel

1. Add an asterisk ("*") following the phrase "Non-Drowsy". Add the statement in conspicuous print "*When taken as directed. See Drug Facts Panel." See IB above for explanation.

2. Remove [redacted] heading from second column of Drug Facts panel.

3. Add directions for individuals with liver or kidney disease with directions listed in a table as shown below:

Adults and children 6 years and over	1 tablet daily; not more than 1 tablet in 24 hours
Children under 6	Ask a doctor
Consumers with liver or kidney disease	Ask a doctor

[redacted] however, in the prescription labeling, there is dose adjustment for these patients. Thus, the OTC label must include directions for consumers with liver or kidney disease. This direction reiterates the point that these consumes can take the product, but only after consulting a physician.

4. Remove bold typeface from "or" in the *Questions?* heading so that "or" is in plain text font.

II. 5 Count Blister Pack Label

A. Move the dosage strength to follow the established name (i.e., "(loratadine)10 mg") or proprietary name (i.e., "Claritin® 10 mg").

III. 10 Count Blister Pack

[redacted]

2. Inform the sponsor that the Agency recommends the sponsor increase font size and change font color to accentuate contrast with background and make indications more conspicuous on PDP.

3. Inform the sponsor that "New!" shall be removed from labeling six months after introduction into OTC market.

4. Request that the chemist verify the storage conditions are accurate.

/S/

Matthew R. Holman, Ph.D.
Interdisciplinary Scientist, HFD-560

/S/

Marina Chang, R.Ph.
Team Leader, HFD-560

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Matthew Holman
8/28/02 02:57:43 PM
INTERDISCIPLINARY

Marina Chang
8/28/02 03:26:15 PM
INTERDISCIPLINARY

Division of Over-the-Counter Drug Products Labeling Review

NDA:	20-470
Supplement No:	S016
Submission Date:	January 25, 2002; March 28, 2002; July 10, 2002 (e-mail); August 9, 2002
Type of Submission:	Labeling Supplement for Rx-to-OTC switch
Sponsor:	Schering Corporation
Drug Product:	Claritin-D® 24 Hour Extended Release Tablets
Active Ingredient(s):	Loratadine 10 mg and Pseudoephedrine Sulfate 240 mg
Indication:	Relief of allergic rhinitis symptoms and nasal and sinus congestion
Stock Keeping Units	1 submitted (10 count) 1 proposed (5 count)
Review Date	August 23, 2002
Reviewer:	Houda Mahayni and Matthew R. Holman
Project Manager	Elaine Abraham

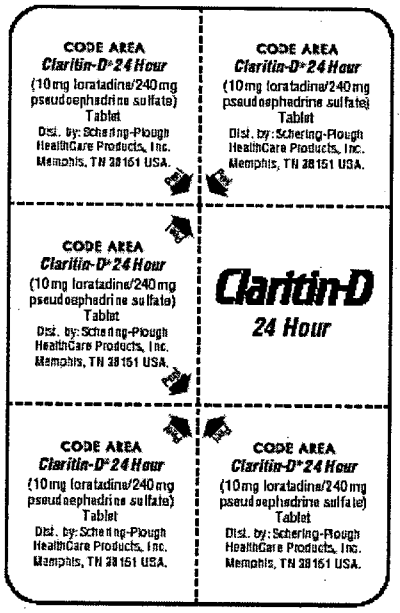
I. Background

On January 25, 2002, the sponsor submitted supplement 016 to the Agency requesting the change from a prescription to an over-the-counter (OTC) status for both the allergic rhinitis (AR) and chronic idiopathic urticaria (CIU) indications. As the result of this request, a joint advisory committee (Non-Prescription Advisory Committee (NDAC) and Pulmonary Advisory Committee) was convened on April 22, 2002 to discuss an urticaria indication for OTC use. CIU currently is not an OTC indication. AR is currently a monograph indication for OTC antihistamine drug products. Loratadine as an OTC antihistamine for AR use was discussed in a previous NDAC meeting. During the April 2002 meeting, the joint advisory committee concluded that CIU is an indication that is not easily recognized by the consumer and, thus, should not be an OTC indication unless more data has demonstrated that consumers can recognize and self-treat CIU.

Because the labels submitted for all five NDAs are similar, the tablet carton label was reviewed for use as a template to revise all labeling. Thus, on July 23, 2002, the Agency sent a facsimile to the sponsor with recommended changes to the label for Claritin Tablets (NDA 19-658). In response to this facsimile, the sponsor submitted revised labeling for this product as well as NDAs 20-641 (Claritin Syrup), 20-704 (Claritin Reditabs), 19-670 (Claritin-D 12 Hour Extended Release Tablets), and 20-470 (Claritin-D 24 Hour Extended Release Tablets) on August 9, 2002. This is a review of the revised OTC labeling to NDA 20-470/S016, for Claritin-D® 24 Hour Extended ReleaseTablets, received August 9, 2002. Claritin-D® 24 Hour is a tablet indicated for the relief of allergic rhinitis symptoms and nasal and sinus congestion. The product is packaged in a blister card. Two package sizes are proposed: 5 count (1 blister card of 5) and 10 count (2 blister cards of 5). The sponsor only included the carton label for the 10 count and blister pack label for the 5 count. The sponsor indicated that labeling for all package sizes will be submitted after the sponsor received comments on the labeling submitted August 9, 2002.

Each tablet contains 10 mg loratadine (antihistamine), and 240 mg pseudoephedrine (decongestant). This NDA was approved November 14, 1994.

1 page(s) of draft labeling has been removed from this portion of the review.



II. Reviewer's Comments

Changes recommended by the reviewer are identified by redlining for additions and by ~~strikethrough~~ for deletions.

A. Reviewer's content

Reviewer's comment: ***This review concerns the 10 count carton and the 5 count blister pack labels. The agency cannot review and comment on the labeling for the 5 count carton label until such label is submitted by the sponsor.***

B. 10 Count Carton Label

1. Principal Display Panel

a. New! —Original Prescription Strength

Reviewer's comment: ***The sponsor added "New!" to the PDP after the initial label review. The sponsor must remove "New!" from labeling six months after introduction to OTC market.***
The sponsor did not remove — ' from this statement as recommended.
The sponsor justifies use of the phrase —Prescription Strength" with the following three argument:

The reviewer recognizes the validity of the sponsor's argument. However, OTC products noted by the sponsor that contain the statement — Prescription Strength" are no longer available with prescription. It is requested that the sponsor reword the statement to read "Original Prescription Strength".

b. Non-Drowsy*

Reviewer's comment: ***The sponsor must place an asterisk immediately after the statement "Non-Drowsy". The asterisk refers consumers to the following statement: "*When taken as directed. See Drug Facts Panel." This statement must appear at the bottom of the PDP in conspicuous print. The sponsor did not make this change following the initial label review. The sponsor argues that this information appears in "Warnings" and is not required on the PDP. The Agency is requiring this asterisk and reference statement on the PDP because this is not a non-drowsy product. Drowsiness may occur when not taken as directed. Therefore, the sponsor must add the recommended labeling.***

c. ~~24 hour~~ Extended Release Tablets
Allergy & Congestions

Reviewer's comment: ***The sponsor may delete "24 hour" because it is redundant and deletion may make PDP easier to read.***

d. 10 Extended ReleaseTablets'

Reviewer's comment: ***The should should include entire dosage form in net quantity of content to prevent consumers from confusing this product with other products, such as Claritin 10 mg tablets.***

2. Top Panel

a. Non-Drowsy*
*When taken as directed. See Drug Facts Panel.

Reviewer's comment: ***See comment 1b above.***

3. Bottom Panel and Flaps

a. Non-Drowsy*
*When taken as directed. See Drug Facts Panel.

Reviewer's comment: ***See comment 1b above. If space is limited, the reference statement is not required.***

4. Back Panel

a. Non-Drowsy*
Claritin-D 24 Hour
10 Extended Release Tablets
*When taken as directed. See Drug Facts Panel.

Reviewer's comment: ***See comment 1b above.***

b. Drug Facts

i. Uses

- reduces swelling of nasal passages
- temporarily relieves sinus congestion and pressure
- temporarily restores freer breathing through the nose

Reviewer's comment: ***The sponsor should revise the statement "• relieves sinus pressure" so that it corresponds to the indication listed in 21 CFR 341.80. The sponsor should align bulleted statements in accordance with 21 CFR 201.66(d)(4), which states ". . . Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line."***

ii. Warnings

(a) ~~***Warnings (continued)***~~

Reviewer's comment: ***The sponsor should delete "Warnings (continued)" because the continuation arrow and "Drug Facts (continued)" mark continuation of Drug Facts in the second panel.***

(b) **Do not use**

~~• for treatment of hives~~

Reviewer's comment: ***The sponsor should delete reference to hives because it is not a contraindication and there is no OTC product with this indicaton.***

(c) **When using this product do not take more than directed**

Reviewer's comment: ***The sponsor should bold the statement "do not take more than directed" as required by 21 CFR 341.80(c)(1)(ii)(A).***

iii. Directions

~~• adults and children 12 years and over: take 1 tablet with a full glass of water daily~~
~~• do not take more than 1 tablet in any 24 hour period~~
• do not divide, crush, chew, or dissolve the tablet
~~• not for use in children under 12 years of age.~~

Adults and children 12 years and over	1 tablet daily with a full glass of water; not more than 1 tablet in 24 hours
Children under 12 years of age	Ask a doctor
Consumers with liver or kidney disease	Ask a doctor

Reviewer's comment: ***The sponsor should add directions for individuals with liver or kidney disease. When 3 or more direction statements are listed, the direction statements generally appear in a table. This change was outline in the initial labeling review, but the sponsor did not concur. The sponsor argues that the liver and kidney disease direction are not necessary "because there are no specific dose adjustment***

recommendations for self-treatment." This may be true, however, in the prescription labeling, there is dose adjustment for these patients. Thus, the OTC label must include directions for consumers with liver or kidney disease. This direction reiterates the point that these consumers can take the product, but only after consulting a physician.

iv. Questions?

Reviewer's comment: ***Debold the word "or" between the phone number and website URL.***

C. 5 Count Blister Pack Label

CODE AREA
Claritin-D® 24 Hour
(10 mg loratadine/240 mg
pseudoephedring sulfate)
Extended Release Tablet
Dist. by: Schering-Plough
HealthCare Products, Inc.
Memphis, TN 38151 USA

Reviewer's comment: ***The sponsor must include dosage form ("Extended Release Tablet") as part of the statement of identity.***

D. Format Specifications

Reviewer's comment: ***This reviewer finds the format specifications, such as font, type size, or barline/hairline thickness for the 10 count carton label as specified in 21 CFR 201.66 and, thus, acceptable as proposed.***

III. Recommendations

1. Remind the sponsor that the agency cannot review and comment on labeling for the 5 count carton label until the sponsor submits such label. The sponsor should revise the labeling as follows:

I. 10 Count Carton Label

A. Principal Display Panel

1. Reword the phrase —Prescription Strength" to "Original Prescription Strength". The Agency reviewed the sponsor's justification against revising the statement. The Agency recognizes the examples of OTC drug products using the proposed phrase. In contrast to those examples, Claritin may be available with and without a prescription and the agency agrees that consumers should understand that OTC Claritin is the same dosage strength as prescription Claritin. Using the word "Original" should prevent consumer confusion about the dosage strength.

2. Add an asterisk ("*") following the phrase "Non-Drowsy". In addition, the following statement must appear at the bottom of the PDP in conspicuous print: "*When taken as directed. See Drug Facts Panel." The agency reviewed the sponsor's argument against this change, however, the Agency has determined that this labeling be required on all loratadine drug products to ensure consumers understand that drowsiness may result at dosages above 10 mg daily.

3. Delete "24 hour" in statement "24 hour Extended Release Tablets" to avoid redundancy on PDP.

4. Amend the declaration of contents to read "10 Extended Release Tablets" so that entire dosage form is listed.

B. Top Panel

1. Add an asterisk ("*") following the phrase "Non-Drowsy". Add the statement in conspicuous print "*When taken as directed. See Drug Facts Panel." See A2, above for discussion.

C. Bottom Panel and Flaps

1. Add an asterisk ("*") following the phrase "Non-Drowsy". Add the statement in conspicuous print "*When taken as directed. See Drug Facts Panel." if space allows.

D. Back Panel

1. Add an asterisk ("*") following the phrase "Non-Drowsy". Add the statement in conspicuous print "*When taken as directed. See Drug Facts Panel." See A2, above for discussion.

2. Drug Facts

a. Revise the statement "• relieves sinus pressure" to "• temporarily relieves sinus congestion and pressure" in accordance with 21 CFR 341.80. Also, align the bulleted statements in accordance with 21 CFR 201.66(d)(4), which states ". . . Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line."

b. Remove "*Warnings* (continued)" heading from second column of Drug Facts panel.

c. Delete the bulleted statement ——— under **Do not use** subheading.

d. Bold entire statement under **When using this product** subheading as required by 21 CFR 341.80(c)(1)(ii)(A).

e. Revise ***Directions*** by incorporating dosing information into a table as follows:

• do not divide, crush, chew, or dissolve the tablet

Adults and children 12 years and over	1 tablet daily with a full glass of water; not more than 1 tablet in 24 hours
Children under 12 years of age	Ask a doctor
Consumers with liver or kidney disease	Ask a doctor

The sponsor may be correct in asserting that there are not specific doses for consumers with liver or kidney disease, however, in the prescription labeling, there is dose adjustment for these patients. Thus, the OTC label must include directions for consumers with liver or kidney disease. This direction reiterates the point that these consumes can take the product, but only after consulting a physician.

f. Debold "or" between phone number and website URL under ***Questions?*** heading.

II. 5 Count Blister Pack Label

A. Include the entire dosage form (Extended Release Tablet) on the label.

2. Inform the sponsor that "New!" shall be removed from labeling six months after introduction into OTC market.

/S/

Houda Mahayni, R.Ph., Ph.D.
Interdisciplinary Scientist, HFD-560

/S/

Matthew R. Holman, Ph.D.
Interdisciplinary Scientist, HFD-560

/S/

Marina Chang, R.Ph.
Team Leader, HFD-560

Division of Over-the-Counter Drug Products
Labeling Review Addendum

NDA:	**19-658 (S018)**
Sponsor:	**Schering-Plough Corporation**
Drug Product:	**Claritin (loratadine tablets, 10 mg)**
Stock Keeping Units:	**2 (Allergy & Recurring Hives)**

Submission Dates: January 25, 2002
July 10, 2002 (via e-mail)

Type of Submission: NDA Supplement

Pharmacological Categories: Antihistamine

Active Ingredients: Loratadine

Indications: Relief of allergic rhinitis symptoms & chronic hives

Review Date: July 24, 2002

Reviewer: Matthew R. Holman, Ph.D.

Project Manager: Elaine Abraham, R. Ph.

Reviewer's Comments

Carton Label, Principal Display Panel:

— Prescription Strength 10 Tablets

Reviewer's comment: ***The word — must deleted because it implies that there is a less-than-prescription strength product available.***

Recommendations

Inform the sponsor to delete — from the phrase —Prescription Strength" on the principal display panel. This change is in addition to the labeling comments that were provided to the sponsor on July 24, 2002 via facsimile.

/S/

Matthew R. Holman, Ph.D.
Interdisciplinary Scientist, HFD-560

/S/

Marina Chang, R.Ph.
Team Leader, HFD-560