

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
21-297**

**Administrative Documents**

**Patent Information Pursuant to 21 CFR§314.59 (Section 13)**

RE: CLARINEX™( Brand of Desloratadine) Tablets for use in the treatment of symptoms of chronic idiopathic urticaria in adults 12 years of age and older.

Trade Name: CLARINEX™

Active Ingredient: Desloratadine

Strength: 5 mg.

Dosage Form: Tablet

Pursuant to the provisions of 21 CFR§ 314.53, we hereby supply the patent information for the captioned Schering Corporation NDA:

1A U.S. Patent No. 4,659,716

Expiration Date: April 21, 2004

Type of Patent: Desloratadine, 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2]pyridine, as the compound per se, the active ingredient in desloratadine tablets, pharmaceutical compositions containing it and methods of using it to treat allergic reactions in mammals.

Patent Owner: Schering Corporation.



SCHERING-PLOUGH RESEARCH INSTITUTE

**1B U.S. Patent No. 4,863,931**

**Expiration Date: September 15, 2008**

**Type of Patent: A drug and a drug product patent covering among other things 8-chloro-11-fluoro-6,11-dihydro-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, which is a by-product of the process of making desloratadine, which is the active ingredient in the desloratadine tablet product used for the indication for which approval is sought.**

**Patent Owner: Schering Corporation**

**1C U.S. Patent No. 4,804,666**

**Expiration Date: February 14, 2006**

**Type of Patent: 3-Hydroxy-8-chloro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, which is an active metabolite of desloratadine, as the compound per se which is the active ingredient in the desloratadine tablet and a method of treating allergy mammals by use of the active metabolite of desloratadine**



in the desloratadine tablet product used for the indication for which approval is sought.

Patent Owner: Schering Corporation

1D U.S. Patent No. 6,100,274

Expiration Date: July 7, 2019

Type of Patient: Pharmaceutical compositions suitable for oral administration [1] comprising an anti-allergic effective amount of desloratadine in a pharmaceutically acceptable carrier medium (a) comprising, for example, a DCL-protective amount of a pharmaceutically acceptable basic salt such as a calcium, magnesium or aluminum salt, or (b) wherein the compositions contain less than about 1% by weight of N-formyl-desloratadine; or [2] comprising 5 mg of desloratadine in a pharmaceutically acceptable carrier medium.

Patent Owner: Schering Corporation

The undersigned declares (a) that U.S. Patent No. 4,659,716 covers desloratadine, as the compound per se, pharmaceutical compositions containing it and a method of treating allergic reactions, e.g., chronic idiopathic urticaria, in a mammal using it, (b) that U.S. Patent No. 4,863,931 covers the desloratadine tablet product used for treating chronic idiopathic urticaria, (c) that U.S. Patent No.



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4,804,666 covers an active metabolite of desloratadine as the compound per se, and a method of treating allergy in a mammal using this active metabolite, (d) that U.S. Patent No. 6,100,274 covers the pharmaceutical composition containing desloratadine used for the treatment of chronic idiopathic urticaria, and (e) that desloratadine is the active ingredient in the desloratadine tablet product used for the treatment of chronic idiopathic urticaria, and (f) that the treatment of chronic idiopathic urticaria is the indication for which approval is being sought.

The undersigned further declares that (a) approval of desloratadine tablets is being sought under section 505 of the Federal Food, Drug and Cosmetic Act, 21 USC§355, and that (b) a claim of patent infringement under one or more of U.S. Patent Nos. 4,659,716; 4,863,931; 4,804,666; and 6,100,274 could reasonably be asserted if a person not licensed by the owner of each of the above-listed U.S. Patents engaged in the commercial manufacture, importation, use, sale or offer for sale of desloratadine for the treatment of chronic idiopathic urticaria in adults 12 years of age and older.



EXCLUSIVITY SUMMARY for NDA # 21-297 SUPPL # \_\_\_\_\_  
Trade Name Clarinox Generic Name desloratadine

Applicant Name Schering HFD- 570  
Approval Date February 8, 2002

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ X / NO / \_\_\_/

b) Is it an effectiveness supplement? YES / \_\_\_/ NO / \_\_\_/

If yes, what type(SE1, SE2, etc.)? \_\_\_\_\_

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO / \_\_\_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES / X / NO / \_\_\_ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

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e) Has pediatric exclusivity been granted for this Active Moiety?

YES / \_\_\_ / NO / X /

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / \_\_\_ / NO / X /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES / X / NO / \_\_\_ /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-165 \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / \_\_\_ / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / \_\_\_ /

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X /      NO / \_\_\_ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

\_\_\_\_\_  
\_\_\_\_\_

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / X /      NO / \_\_\_ /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / \_\_\_ /      NO / X /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO / X /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # P00220

Investigation #2, Study # P00221

Investigation #3, Study # \_\_\_\_\_

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_\_\_/ NO / X /

Investigation #2 YES /\_\_\_/ NO / X /

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO / X /

Investigation #2                      YES /\_\_\_/                      NO / X /

Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1, Study # P00220

Investigation # 2, Study # P00221

Investigation #   , Study # \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.



(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/      NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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\_\_\_\_\_  
Signature of Preparer  
Title: Regulatory Management Officer

\_\_\_\_\_  
Date

151

\_\_\_\_\_  
Signature of Office or Division Director

\_\_\_\_\_  
Date

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

## Claim for Exclusivity (Section 20)

1. Pursuant to the provisions of Sections 505(c)(3)(D)(iii) and 505 (j)(4)(D)(iii) of the Food, Drug and Cosmetic Act (FDCA) and 21 CFR 314.108 (b)(4)(iv), the applicant claims three (3) years of exclusivity for its CLARINEX™ (Brand of Desloratadine) Tablets, for use in the treatment of chronic idiopathic urticaria in adults 12 years of age and older.
2. The applicant certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).
3. A list of all published studies or publicly available reports of clinical investigations known to the applicant through a computer-assisted literature search that are relevant to the conditions for which the applicant is seeking approval is provided as **Attachment 1**.
4. The applicant certifies that it has thoroughly searched the scientific literature through a computer-assisted search of the Scholar database, and Dialog database encompassing the subfiles MEDLINE, BIOSIS Previews, EMBASE and SciSearch, for English and non-English literature relating to tablets in humans, covering the period from to July 28, 1999 – to July 28, 2000.
5. To the best of the applicant's knowledge, the list of scientific literature pertaining to desloratadine tablets is complete and accurate, and in the opinion of the applicant, such published studies or publicly available information do not provide a sufficient basis for the approval of the use of desloratadine tablets for the treatment of chronic idiopathic urticaria without reference to the new information contained in the clinical trials in the application. The applicant's opinion that the studies or reports are insufficient is based on the following:



- The literature does not contain adequate characterization of the efficacy and safety profile of desloratadine in the treatment of chronic idiopathic urticaria, which is established by the data from the new clinical studies conducted by the applicant under IND [redacted] and included in this application.
6. The applicant was the sponsor named in the Form FDA-1571 for IND under which the new clinical investigations were conducted.



**DESLORATADINE USED IN CHRONIC IDIOPATHIC URTICARIA  
FROM 7/28/99 TO PRESENT**

L27 ANSWER 1 OF 4 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 1  
 ACCESSION NUMBER: 2000237082 EMBASE  
 TITLE: The pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup in children aged 2 to 5 years.  
 AUTHOR: Salmun L.M.; Herron J.M.; Banfield C.; Padhi D.; Lorber R.; Affrime M.B.  
 CORPORATE SOURCE: Dr. L.M. Salmun, Allergy/Respiratory Dis. Clin. Res., Schering-Plough Research Institute, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0539, United States. luis.salmun@spcorp.com  
 SOURCE: Clinical Therapeutics, (2000) 22/5 (613-621). Refs: 13  
 ISSN: 0149-2918 CODEN: CLTHDG  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 007 Pediatrics and Pediatric Surgery  
 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 039 Pharmacy  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 AB Objective: We assessed the pharmacokinetics and tolerability of 5 mg loratadine syrup (1 mg/mL) in children aged 2 to 5 years. Methods: Two studies were undertaken. A single-dose, open-label bioavailability study was performed to characterize the pharmacokinetic profiles of loratadine and its metabolite **desloratadine**. Plasma concentrations of loratadine and **desloratadine** were determined at 0, 1, 2, 4, 8, 12, 24, 48, and 72 hours after a single administration of 5 mg loratadine syrup to 18 healthy children (11 male, 7 female; 12 black, 5 white, 1 other; mean age  $\pm$  SD, 3.8  $\pm$  1.1 years; mean weight  $\pm$  SD, 17.4  $\pm$  4.4 kg). In addition, a randomized, double-blind, placebo-controlled, parallel-group study was performed to assess the tolerability of 5 mg loratadine syrup after multiple doses. Loratadine (n = 60) or placebo (n = 61) was given once daily for 15 days to children with a history of allergic rhinitis or chronic idiopathic urticaria. In the loratadine group, 27 boys and 33 girls (52 white, 8 black) were enrolled, with a mean age  $\pm$  SD of 3.67  $\pm$  1.13 years and a mean weight  $\pm$  SD of 17.2  $\pm$  3.8 kg. In the placebo group, 27 boys and 34 girls (53 white, 7 black, 1 Asian) were enrolled, with a mean age  $\pm$  SD of 3.52  $\pm$  1.12 years and a mean weight  $\pm$  SD of 17.3  $\pm$  2.9 kg. Tolerability was assessed based on electrocardiographic results, occurrence of adverse events, changes in vital signs, and results of laboratory tests and physical examinations. Results: The peak plasma concentrations of loratadine and **desloratadine** were 7.78 and 5.09 ng/mL, respectively, observed 1.17 and 2.33 hours after administration of loratadine; the areas under the plasma concentration-time curve to the last quantifiable time point for loratadine and **desloratadine** were 16.7 and 87.2 ng  $\cdot$  h/mL, respectively. Single and multiple doses were well tolerated, with no adverse events occurring with greater frequency after multiple doses of

loratadine than after placebo. Electrocardiographic parameters were not altered by loratadine compared with placebo. There were no clinically meaningful changes in other tolerability assessments. Conclusion: Loratadine was well tolerated in this small, selected group of children aged 2 to 5 years at a dose providing exposure similar to that with the adult dose (ie, 10 mg once daily).

L27 ANSWER 2 OF 4 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 2  
 ACCESSION NUMBER: 2000164381 EMBASE  
 TITLE: Desloratadine Sepracor.  
 AUTHOR: Norman P.  
 CORPORATE SOURCE: P. Norman, Norman Consulting, 18 Pink Lane, Burnham, Bucks SL1 8JW, United Kingdom. Peter.Norman@nationwideisp.net  
 SOURCE: Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs, (2000) 2/2 (117-126).  
 Refs: 90  
 ISSN: 1464-8474 CODEN: COAIF  
 COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 011 Otorhinolaryngology  
 026 Immunology, Serology and Transplantation  
 036 Health Policy, Economics and Management  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

AB The use of the loratadine metabolite, decarboethoxyloratadine (DCL), for the treatment of both allergic rhinitis and diabetic retinopathy is claimed. DCL is claimed to display fewer cardiovascular and tumor promoting side effects than loratadine. DCL was disclosed in US-04659716. DCL and loratadine were compared for antihistamine activity on guinea pig ileum. These gave IC50 values of 0.98 and 18.6 nM, respectively. Inhibition of [3H]mepyramine binding to guinea pig cerebellar membranes was measured and IC50 values of 51.1 and 721 nM were obtained. Mitogenic effects were assessed using a [3H]thymidine uptake assays in mouse splenocytes, and respective IC50 values of 5.6 and 1.0 .mu.M were obtained. The effects of DCL on the inwardly rectified potassium channel of cardiac monocytes were assessed. DCL is stated to be less active than terfenadine in this model. The synthesis of loratadine is described in US-04282233, and of DCL in US-04659716. The conversion of loratadine into DCL is described. Sample tablet and capsule formulations are provided. The only compound for which use is specifically claimed is decarboethoxyloratadine, 8-chloro-6,11-(4-piperadinylidine)-5H-benzo[5,6]cyclohepta[1,2b]pyridine.

L27 ANSWER 3 OF 4 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.  
 ACCESSION NUMBER: 2000113028 EMBASE  
 TITLE: Fexofenadine: A review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria.  
 AUTHOR: Simpson K.; Jarvis B.  
 CORPORATE SOURCE: K. Simpson, Adis International Limited, 41 Centorian Drive, Mairangi Bay, Auckland 10, New Zealand. demail@adis.co.nz  
 SOURCE: Drugs, (2000) 59/2 (301-321).  
 Refs: 78  
 ISSN: 0012-6667 CODEN: DRUGAY

COUNTRY: New Zealand  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis  
038 Adverse Reactions Titles  
030 Pharmacology  
011 Otorhinolaryngology  
013 Dermatology and Venereology  
036 Health Policy, Economics and Management  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB Fexofenadine, the active metabolite of terfenadine, is a selective histamine H1 receptor antagonist that does not cross the blood brain barrier and appears to display some anti-inflammatory properties. Fexofenadine is rapidly absorbed (onset of relief .ltoreq.2 hours) and has a long duration of action, making it suitable for once daily administration. Clinical trials (.ltoreq.2 weeks' duration) have shown fexofenadine 60mg twice daily and 120mg once daily to be as effective as loratadine 10mg once daily, and fexofenadine 120mg once daily to be as effective as cetirizine 10mg once daily in the overall reduction of symptoms of seasonal allergic rhinitis. When given in combination, fexofenadine and extended release pseudoephedrine had complementary activity. Fexofenadine was effective in relieving the symptoms of sneezing, rhinorrhoea, itchy nose palate or throat, and itchy, watery, red eyes in patients with seasonal allergic rhinitis. There were often small improvements in nasal congestion that were further improved by pseudoephedrine. Fexofenadine produced greater improvements in quality of life than loratadine to an extent considered to be clinically meaningful, and enhanced patients' quality of life when added to pseudoephedrine treatment. Although no comparative data with other H1 antagonists exist, fexofenadine 180mg once daily was effective in reducing the symptoms of chronic idiopathic urticaria for up to 6 weeks. Fexofenadine was well tolerated in clinical trials in adults and adolescents and the adverse event profile was similar to placebo in all studies. The most frequently reported adverse event during fexofenadine treatment was headache, which occurred with a similar incidence to that seen in placebo recipients. Fexofenadine does not inhibit cardiac K<sup>+</sup> channels and is not associated with prolongation of the corrected QT interval. When given alone or in combination with erythromycin or ketoconazole, it was not associated with any adverse cardiac events in clinical trials. As it does not cross the blood brain barrier, fexofenadine is free of the sedative effects associated with first generation antihistamines, even at dosages of up to 240 mg/day. Conclusions: fexofenadine is clinically effective in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria for which it is a suitable option for first-line therapy. Comparative data suggest that fexofenadine is as effective as loratadine or cetirizine in the treatment of seasonal allergic rhinitis. In those with excessive nasal congestion the combination of fexofenadine plus pseudoephedrine may be useful. In clinical trials fexofenadine is not associated with adverse cardiac or cognitive/psychomotor effects.

L27 ANSWER 4 OF 4 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.  
ACCESSION NUMBER: 1999198363 EMBASE  
TITLE: Clinical pharmacology of new histamine H1 receptor antagonists.  
AUTHOR: Simons F.E.R.; Simons K.J.  
CORPORATE SOURCE: Dr. F.E.R. Simons, Children's Hospital of Winnipeg, 820

Sherbrook Street, Winnipeg, Man. R3A 1R9, Canada.  
lmcniven@hsc.mb.ca

SOURCE: Clinical Pharmacokinetics, (1999) 36/5 (329-352).  
Refs: 164  
ISSN: 0312-5963 CODEN: CPKNDH

COUNTRY: New Zealand

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 011 Otorhinolaryngology  
012 Ophthalmology  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The recently introduced H1 receptor antagonists ebastine, fexofenadine and mizolastine, and the relatively new H1 antagonists acrivastine, astemizole, azelastine, cetirizine, levocabastine and loratadine, are diverse in terms of chemical structure and clinical pharmacology, although they have similar efficacy in the treatment of patients with allergic disorders. Acrivastine is characterised by a short terminal elimination half-life (t1/2.beta.) [1.7 hours] and an 8-hour duration of action. Astemizole and its metabolites, in contrast, have relatively long terminal t1/2.beta. values; astemizole has a duration of action of at least 24 hours and is characterised by a long-lasting residual action after a short course of treatment. Azelastine, which has a half-life of approximately 22 hours, is primarily administered intranasally although an oral dosage formulation is used in some countries. Cetirizine is eliminated largely unchanged in the urine, has a terminal t1/2.beta. of .apprx. 7 hours and a duration of action of at least 24 hours. Ebastine is extensively and rapidly metabolised to its active metabolite; carebastine, has a half-life of .apprx. 15 hours and duration of action of at least 24 hours. Fexofenadine, eliminated largely unchanged in the faeces and urine, has a terminal t1/2.beta. of .apprx. 14 hours and duration of action of 24 hours, making it suitable for once or twice daily administration. Levocabastine has a terminal t1/2.beta. of 35 to 40 hours regardless of the route of administration, but is only available as a topical application administered intranasally or ophthalmically in patients with allergic rhinoconjunctivitis. Loratadine is rapidly metabolised to an active metabolite ~~descarboethoxyloratadine~~ and has a 24-hour duration of action. Mizolastine has a terminal t1/2.beta. of .apprx. 13 hours and duration of action of at least 24 hours. Most orally administered new H1 receptor antagonists are well absorbed and appear to be extensively distributed into body tissues; many are highly protein-bound. Most of the new H1 antagonists do not accumulate in tissues during repeated administration and have 3 residual action of less than 3 days after a short course has been completed. Tachyphylaxis, or loss of peripheral H1 receptor blocking activity during regular daily use, has not been found for any new H1 antagonist. Understanding the pharmacokinetics and pharmacodynamics of these new H1 antagonists provides the objective basis for selection of an appropriate dose and dosage interval and the rationale for modification in the dosage regimen that may be needed in special populations, including elderly patients, and those with hepatic dysfunction or renal dysfunction. The studies cited in this review provide the scientific foundation for using the new H1 antagonists with optimal effectiveness and safety.

## PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 21-297 Supplement # \_\_\_\_\_ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-570 Trade and generic names/dosage form: Clarinet (desloratidine) Action: AP AE NA

Applicant Schering Corporation Therapeutic Class \_\_\_\_\_

Indication(s) previously approved Chronic Idiopathic Urticaria

Pediatric information in labeling of approved indication(s) is adequate \_\_\_ inadequate X

Proposed indication in this application Perennial Allergic Rhinitis

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION. IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? \_\_\_ Yes (Continue with questions) \_\_\_ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

\_\_\_ Neonates (Birth-1month) X Infants (6month-2yrs) X Children (2-12yrs) \_\_\_ Adolescents(12-16yrs)

\_\_\_ 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

\_\_\_ 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

X a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

\_\_\_ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

\_\_\_ c. The applicant has committed to doing such studies as will be required.

\_\_\_ (1) Studies are ongoing,

\_\_\_ (2) Protocols were submitted and approved.

\_\_\_ (3) Protocols were submitted and are under review.

\_\_\_ (4) If no protocol has been submitted, attach memo describing status of discussions.

\_\_\_ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

\_\_\_ 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

\_\_\_ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? \_\_\_ Yes  No  
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Team Leader (e.g.,  
medical review, medical officer, team leader)

JS  
Signature of Preparer and Title

2/7/02  
Date

cc: Orig NDA #21-363  
HFD-570/Div File  
NDA/BLA Action Package  
HFD-960/ Peds Team  
(revised 1-14-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 4-7337

## **Debarment Certification**

Schering Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



SCHERING-PLOUGH RESEARCH INSTITUTE

# MEDICAL TEAM LEADER REVIEW

## Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #: NDA 21-297

APPLICATION TYPE: Original NDA

SPONSOR: Schering Plough

PRODUCT/PROPRIETARY NAME: Clarinex

INDICATION: Chronic Idiopathic  
Urticaria (CIU)

USAN / Established Name: Desloratadine (DCL)

AGE: 12 yrs and older

Proposed Dose: One 5 mg tablet QD

CATEGORY OF DRUG: Antihistamine

ROUTE OF ADMINISTRATION: Oral

MEDICAL REVIEWER: Purucker

REVIEW DATE: 13 June 2001

### SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	Document ID #:	Submission type/Comments:
31 August 2000	NDA 21-297	Data in support of the CIU indication

### RELATED APPLICATIONS

Document Date:	Document ID	Comments:
21 October 1999	NDA 21-165	Initial NDA for desloratadine for SAR indication; The application received an approvable action pending resolution of GMP issues.

**Overview of Application/Review:** This application is intended to support of the safety and efficacy of DCL for the treatment of CIU. The CMC and Preclinical sections cross-reference NDA 21-165, to which this submission could appropriately have been submitted as an efficacy supplement, had the original NDA been approved.

The application includes the results of two 6-week, randomized, double-blind, placebo-controlled clinical trials of identical design (P00220, P00221) conducted with 416 patients age  $\geq 12$  years with CIU. The primary efficacy parameter was change-from-baseline in pruritus symptom score measured at one week and reflective of symptoms experienced over the preceding 24 hours. Relevant secondary endpoints included size and number of hives, interference with sleep, "instantaneous" pruritus scores, and survival-in-study. Safety endpoints included AEs, clinical laboratory profiles, and ECGs. A single dose of DCL was studied. Several pre-specified subset analyses (by gender, age, and ethnicity) were performed for both efficacy and safety parameters.

The results of the two pivotal clinical studies demonstrated that DCL was statistically superior to placebo on the primary efficacy endpoint and numerically superior on most secondary endpoints, including survival-in-study. Subset analyses were generally consistent with the findings in the study population as a whole, although numbers were too small for inferential testing. With regard to safety, DCL demonstrated an AE profile similar to but not identical with the SAR population studied in NDA 21-165. AE's that tended to be more prevalent in the CIU population included headache, dyspepsia, diarrhea, and dizziness. Conclusions regarding the impact of DCL on the ECG will be based primarily on data submitted with NDA 21-165, since the numbers of patients studied in this application did not add substantially to the totality of exposure to DCL, and ECG's were not performed at a time corresponding to  $C_{max}$ . No clinically meaningful prolongation of  $QT_c$  was reported for any individual.

The application also includes data from a 28-day clinical pharmacology study (P01196) conducted to assess the PK/PD relationship of DCL on histamine-induced wheal and flare in normal volunteers (N=28). The clinical review of this trial was comprised of a safety assessment only, which found no new safety concerns unique to this study or population. The OCBP review concluded that DCL showed antihistamine activity by one hour (as measured by inhibition of wheal and flare), that seemed to persist for up to 24 hours, and absence of tachyphylaxis to this effect. The clinical significance of this finding is not known.

Overall, the application is complete and convincing of the safety and efficacy of DCL in CIU.

**Outstanding Issues:** The sponsor must resolve the GMP issues identified in the approvable letter for NDA 21-165. The sponsor must incorporate the changes to the PI identified in the MO and OCBP reviews.

Recommended Regulatory Action:

N drive location:

NDA's:

Efficacy / Label Supp.:  X  Approvable   Not Approvable

Signed: Medical Reviewer: \_\_\_\_\_

Date: \_\_\_\_\_

Medical Team Leader: \_\_\_\_\_

Date: \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

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

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Mary Purucker  
6/15/01 12:13:33 PM  
MEDICAL OFFICER

Robert Meyer  
6/18/01 10:28:53 AM  
MEDICAL OFFICER

## Division Director's Memorandum

Date: Thursday, June 28, 2001  
NDA: 21-297  
Sponsor: Schering Plough  
Proprietary Name: Clarinex (desloratadine) Tablets, 5 mg for Chronic Idiopathic Urticaria

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**Introduction:** This is an NDA for a new molecular entity (NME) – desloratadine (DCL) proposed for the treatment of the chronic idiopathic urticaria in patients aged 12 and above. This same drug product is the subject of NDA 21-165 and this current submission would ordinarily be an efficacy supplement. However, due to timing issues and due to the non-approval of Clarinex because of GMP issues at several Schering-Plough facilities, this was submitted as an NDA instead (since Schering cannot supplement an unapproved NDA).

This NDA then carries new clinical data, but no new CMC or Pharm-Tox data. For the latter, it refers to NDA 21-165, the Clarinex Seasonal Allergic Rhinitis application.

The regulatory due date for this application is 6/30/2001.

**Chemistry/Manufacturing and Controls:** No new issues. Unfortunately, there is still no acceptable EER since the recent site inspections showed continuing and new problems. Until there is an acceptable inspection, this NDA and the related NDA cannot be approved.

**Preclinical:** No new issues, since the population and dose are the same as those reviewed in 21-165.

**Biopharmaceutics:** See Dr. Suarez-Sharp's review for details. The PD assessment for CIU was done via histamine skin testing, a test which directly measures antihistaminic properties of the moiety, but which is not well validated in terms of predicting clinical response. In this model, there is reasonable antihistaminic activity seen within the first hour, lasting throughout the dosing interval (though not always statistically significant in comparison to placebo at all time points. There was no tachyphylaxis seen in this model over 28 days.

**Clinical / Statistical:** See Dr. Rosebraugh's primary review for details. The sponsor conducted two adequate and well-controlled trials in 416 patients with CIU that establish the efficacy of 5 mg once-daily of desloratadine in the treatment of the signs (number and size of hives) and symptoms (pruritus as the primary variable) of chronic idiopathic urticaria.

**Labeling:** There are a number of modifications to the labeling needed to better describe the data and to limit excessively promotional claims. These will be included in the action letter, since there cannot be an approval this cycle.

**Conclusions:** This NDA is approvable, and can be approved and then subsumed under NDA 21-165 when all cGMP issues are resolved and fully acceptable labeling is submitted.

**RS**

Robert J. Meyer, MD  
Director,  
Division of Pulmonary and Allergy Drug Products.

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

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/s/

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Robert Meyer  
6/28/01 10:23:47 AM  
MEDICAL OFFICER

**Division of Pulmonary and Allergy Drug Products  
CONSUMER SAFETY OFFICER REVIEW**

**Application Number: NDA 21-165/S-001**

**NDA 21-363**

**NDA 21-297**

**Name of Drug: Clarinex® (desloratadine) Tablets**

**Sponsor: Schering Corporation**

**Materials Reviewed**

- Approved Labeling for Clarinex® (desloratadine) Tablets, indicated for Seasonal Allergic Rhinitis, dated December 21, 2001.
- Faxes to Schering, dated January 31 and February 4, 2001 indicating changes suggested by the Division
- Final Draft Labeling incorporating two new indications, Perennial Allergic Rhinitis (NDA 21-363) and Chronic Idiopathic Urticaria (NDA 21-297), dated February 6, 2002.

**Background**

Following initial review of the labeling submitted with NDA 21-363 and NDA 21-297, the Division provided suggested changes via facsimile dated January 31, 2002, relating to NDA 21-363. On Friday, February 1, 2002, Schering representatives agreed to the suggestions with minor editorial changes.

On Monday February 4, 2002, the Division provided Schering with a facsimile that incorporated the changes agreed to on February 1, 2002, with the addition of information pertaining to the Chronic Idiopathic Urticaria (CIU) indication.

On Wednesday, February 6, 2002, Schering representatives agreed to the suggestions relating to CIU but requested the addition of a new table, titled, "Pruritus Symptom Score". The proposed new table was discussed internally and it was suggested that rather than a table with data from study P00221, the Division would prefer that it reflect the results of study P00220. Schering agreed to this suggestion and agreed to submit final draft labeling to NDAs 21-363 and 21-297 based on the agreements reached on February 1 and 6, 2002. Schering also agreed to submit a labeling supplement to NDA 21-165 as a means of maintaining a single label for the product.

**Review**

Electronic submission of the Final Draft Label received February 7, 2002. A visual line-by-line comparison with the currently approved label as well as the changes discussed above found that this version contained all items agreed to as of February 6, 2002.

**Conclusions**

All appropriate changes have been implemented as discussed above.

/s/ - 2/7/02

Anthony M. Zeccola  
Regulatory Management Officer

**MEDICAL OFFICER'S LABELING COMMENTS**

**(Ref: Medical Officer's Review: June 15, 2001)**

2 pages redacted from this section of  
the approval package consisted of draft labeling

**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS**

**LABELING COMMENTS**

(Ref: May 22, 2001 Review)

1 pages redacted from this section of  
the approval package consisted of draft labeling

**PHARMACOLOGY/TOXICOLOGY REVIEWER'S**

**LABELING COMMENTS**

**(Ref: June 12, 2001Review)**

**Communication Review:**

Labeling review:

The additional wording added to the label concerning the new indication of chronic idiopathic urticaria is based upon clinical data and is, thus, not subject to review from a preclinical perspective.

**RECOMMENDATIONS:**

**Internal comments:**

1. The NDA for descarboethoxyloratadine for the treatment of chronic idiopathic urticaria is approvable from a preclinical standpoint.
2. The sponsor should submit the final study report for the Phase 4 mouse carcinogenicity study within three years of the NDA 21-165 approval or study initiation, whichever occurs first. This comment was communicated to the sponsor following review of NDA 21-165.

**Reviewer signature:**

  
\_\_\_\_\_  
Timothy J. McGovern, Ph.D.

**Team leader signature:**

  
\_\_\_\_\_  
C. Joseph Sun, Ph.D.

Attachments: NDA 21-165 Original Review  
NDA 21-165 Label Review #1  
Addendum to NDA 21-165 Label Review #1

**DDMAC REVIEWER'S LABELING COMMENTS**

1 pages redacted from this section of  
the approval package consisted of draft labeling

**DRAFT PACKAGE INSERT FROM SPONSOR**

**February 16, 2001**

13 pages redacted from this section of  
the approval package consisted of draft labeling

**DRAFT PACKAGE INSERT (ANNOTATED) FROM SPONSOR**

**Original NDA Submission  
August 30, 2000**

18 pages redacted from this section of  
the approval package consisted of draft labeling

**DRAFT CARTON & PACKAGING LABELING FROM SPONSOR**

Original NDA Submission

August 30, 2001.

*(see NDA 21-165 for Carton Proofs)*

8 pages redacted from this section of  
the approval package consisted of draft labeling

**INFORMATION REQUEST**

**March 20, 2001**

## MEMORANDUM OF TELECON

DATE: March 20, 2001

APPLICATION NUMBER: NDA 21-297, Clarinex (desloratadine) for CIU

BETWEEN:

Name: Dan McHugh, R.Ph., Manager, Regulatory Affairs (CMC)  
Phone: 908-740-6744  
Representing: Schering Corp.

AND

Name: Craig Ostroff, Pharm.D., Project Manager  
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Medical Officer request

Ref: March 16, 2001 submission

The medical officer requested the missing data for the lab results as detailed in the sponsor's March 16, 2001 submission. The sponsor offered to supply replacement pages for the paper copies and a revised computer file.

/s/

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Craig Ostroff, Pharm.D.  
Project Manager

/s/

-----  
Craig Ostroff

4/5/01 04:52:00 PM

CSO

**MINUTES FROM PNDA MEETING**

**January 18, 2000**

Memorandum of Telephone Facsimile Correspondence

Date: February 24, 2000

To: Bernadette Knott  
Regulatory Affairs

Fax: 908-740-6500

From: Gretchen Trout *GT*  
Project Manager

Subject: IND   
January 18, 2000 Meeting

Reference is made to the meeting held between representatives of your company and this Division on January 18, 2000. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-1058.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

## INDUSTRY MEETING MINUTES

DATE: January 18, 2000

IND:  

PRODUCT: desloratadine

SPONSOR: Schering

### FDA PARTICIPANTS:

Young-Moon Choi, Clinical Pharmacology and Biopharmaceutics Reviewer

Badrul Chowdhury, Acting Medical Team Leader

Jim Gebert, Biometrics Reviewer

Shawn Khorshidi, Chemistry Reviewer

Tim McGovern, Pharmacology Reviewer

Robert Meyer, Division Director

Dick Nicklas, Medical Reviewer

Prasad Peri, Chemistry Reviewer

Guirag Poochikian, Chemistry Team Leader

Joe Sun, Pharmacology Team Leader

Kevin Swiss, Chemistry Reviewer

Gretchen Trout, Project Manager

Ramana Uppoor, Clinical Pharmacology and Biopharmaceutics Team Leader

Steve Wilson, Biometrics Team Leader

### SPONSOR PARTICIPANTS:

Dr. Affrime, Clinical Pharmacology

Ms. Albrecht, Project Management

Ms. Blazovic, Regulatory Affairs – Technical Support

Ms. Boyle, Regulatory Affairs

Dr. Cayen, Drug Safety and Metabolism

Dr. Chambers, Analytical Development

Ms. Knott, Regulatory Affairs

Mr. Locinsky, Development Operations

Dr. Lamendola, Regulatory Affairs

Dr. Lorber, Clinical Research

Dr. Mirro, Drug Safety

Ms. Perniciaro, Regulatory Affairs, CMC

Dr. Saillot, Clinical Data Management

Ms. Shneyer, Biostatistics

Dr. Staudinger, Clinical Research

Dr. Zezza, Regulatory Affairs, CMC

**BACKGROUND:** Schering requested a meeting on August 25, 1999, to discuss the development program for the desloratadine (DCL) product line. Due to the timing of the submission of the DCL 5 mg tablet NDA (NDA 21-165) and the scheduling of the meeting, it was agreed to postpone the scheduling of the meeting and to hold a pre-NDA style meeting. However, Schering requested that the Division address two questions (see submission dated October 27, 1999, and the Division's facsimile dated November 12, 1999). The pre-NDA meeting request was submitted on November 5, 1999. Reference is made to the submission dated December 22, 1999.

The Division began by stating that some of the answers we will be providing at this meeting are based on the presumption that the current NDA (21-165) will be reviewed and approved within the first cycle. Otherwise, it might affect some of our answers (especially with regard to regulatory issues, but some of the scientific issues as well).

Pharmacology/Toxicology

The Division has no specific issues. Schering's proposal to cross-reference is acceptable.

Chemistry, Manufacturing and Controls

A summary of the CMC questions are provided below, followed by the Division's comments.

Questions common for [redacted]

**Confirm acceptance of the following proposals:**

**1. Referencing NDA 21-165 for the manufacturing, control, specifications and methods for the Desloratadine drug substance.**

This will be contingent on approval of N21-165. Once the NDA is approved, cross-referencing is acceptable. The Division recommends that Schering provide all corrections and responses in one amendment. [redacted]

Schering stated that [redacted] prior to approval of N21-165 and asked if they had to wait until the tablet is approved. The Division replied that they can submit, but we cannot approve them. The Division suggested that Schering keep in mind that if there are issues with the drug substance in NDA 21-165 this will have to be addressed. We want the final package of drug substance used for reference; i.e., a consolidated drug substance package.

**2. Test regimen listed for release and stability.**

In general, the Division accepts Schering's proposal.

**3. Stability protocols presented.**

In general, the Division accepts Schering's proposal.

**4. A quantitative color test is not planned since it has not been observed to change in color.**

The Division requested that Schering submit adequate data at the time of submission, on release and stability, to show that environmental factors (e.g., temperature, humidity, and light) do not effect color. If these factors do not adversely impact on the parameter being studied, than the test for this parameter may not be needed.

**5. Use of ICH identification and qualification thresholds for assessing impurities and degradation products.**

In principal, Schering's proposal is acceptable. Impurities  $\geq 0.1\%$  need to be qualified.

Schering stated that \_\_\_\_\_, and additional work may show that it is not \_\_\_\_\_. The Division replied that they should submit the data.

**6. Electronic data format, stability data will be provided as SAS data and excel spreadsheets.**

This is acceptable.

Question common for \_\_\_\_\_

**Confirm acceptance of the following proposal:**

**7. Rationale of not performing additional characterization or bioequivalence studies for \_\_\_\_\_ with regard to polymorphs referencing the data supplied in NDA 21-165 showing characterization and bioequivalence of the two polymorphs.**

This will be addressed by the Biopharmaceutics reviewer. Schering will not need to characterize the \_\_\_\_\_ if data submitted to NDA 21-165 are acceptable.

Questions common for \_\_\_\_\_

8. \_\_\_\_\_

\_\_\_\_\_ However, we need additional information. \_\_\_\_\_

[Redacted]

9. [Redacted] has updated its process to use [Redacted]

[Redacted] To qualify this process, a large-scale batch of the [Redacted] manufactured with this material will be monitored for stability. One month data will be available at the time of NDA submission.

The Division stated that the [Redacted] will have to be adequate, and Schering should provide more stability data as soon as they have it (including accelerated data).

10. [Redacted]

[Redacted]

[Redacted]

**ADDITIONAL CMC COMMENTS**

- The Division stated that we also want individual dissolution data.
- Schering needs to provide drug product stability data from the Singapore site (in addition to Ireland).

### Clinical Pharmacology and Biopharmaceutics

The Division presented overheads with comments (see attachment 2).

The Division agreed that this was acceptable.

### Clinical

The Division made the following comments.

- All responses to issues raised in the submission and the proposed labeling are dependent on demonstration of efficacy and safety of the 5 mg tablet formulation.
- If the data for the urticaria, SAR/asthma, and PAR studies are submitted under the same NDA, a subanalysis of each condition in regard to efficacy and safety will be necessary.
- If there is a labeling claim for “nasal and non-nasal symptoms”, it must be possible to separate the data on nasal and non-nasal symptoms in order to support the claim.
- The Division questioned what was the basis for using different techniques in terms of the PAR and SAR/asthma studies for combining 3 studies into 2 studies.

Schering replied that the PAR proposal was changed at the time of the Division's comments on the protocol. They changed the primary parameter to instantaneous average over total symptom score, which changed the sample size. Therefore they proposed to combining the studies. Schering indicated that they had significant difficulty recruiting for SAR and they wanted the two studies to have approximately equal sample sizes. The Division replied that this was fine.

### Statistics

The Division requested that Schering provide a statement in their write-up indicating why the analysis they chose was appropriate.

The Division also provided the following comments.

- The CANDAs for DCL tablets (NDA 21-165) was very helpful, and the CANDAs for the remaining NDAs should be similar.
- Schering had stated that for SAR and asthma some patients having less than 1 week of data will be excluded. The Division stated that FEV<sub>1</sub> will be the most important variable, and patients who have a baseline FEV<sub>1</sub> and 1 on-treatment FEV<sub>1</sub> should be included.

NOTE: In a follow-up conversation, Ms. Knott informed Ms. Trout that this is in the SAR prophylaxis protocol only, not asthma.

The Division requested that Schering include any patients with any post-baseline data in the ITT.

Regulatory Issues

The Division made the following comments.

- To support the rhinitis indication, Schering must provide explicit nasal and non-nasal data.
- The NDA must be complete and reviewable at the time of submission.
- The Additional indications may be submitted prior to the DCL tablet NDA (N21-165) being approved, in which case they could be submitted as a single NDA. If the tablet NDA is already approved prior to submission, each indication will be a separate efficacy supplement.
- For each indication, Schering should submit one document with an integrated discussion of safety from all of the indications, and an individualized discussion for each separate indication.

151

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Gretchen Trout  
Project Manager

Cc: Orig. IND —  
Div. File  
HFD-570/Nicklas  
HFD-570/Chowdhury  
HFD-570/Choi  
HFD-570/Uppoor  
HFD-570/Swiss  
HFD-570/Peri  
HFD-570/McGovern  
HFD-570/Wilson  
HFD-570/Sun  
HFD-570/Meyer  
HFD-570/Gebert  
HFD-570/Poochikian  
HFD-570/Trout

Drafted: GST/February 3, 2000

Rd accepted by: Choi/2-16-00  
Uppoor/2-16-00  
McGovern/2-16-00  
Peri/2-17-00  
Poochikian/2-17-00

File name: n:\staff\troutg\ — min

MINUTES/CORRESPONDENCE

**MINUTES FROM PNDA MEETING**

**May 11, 1999**

Memorandum of Telephone Facsimile Correspondence

Date: June 7, 1999

To: Mary Jane Boyle  
Regulatory Affairs

Fax: 908-740-2982

From: Gretchen Trout  
Project Manager

Subject: IND.   
May 11, 1999, meeting

Reference is made to the meeting held between representatives of your company and this Division on May 11, 1999. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-1058.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.** If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.



BACKGROUND: Reference is made to the meeting request dated March 10, 1999, and the background package dated March 29, 1999.

CHEMISTRY, MANUFACTURING, and CONTROLS

The following issues were identified by Schering for discussion:

Drug Substance

1. Drug Substance test regimen
2. Drug Substance stability plans

Drug Product

1. Drug Product Stability plans
2. Adherence to ICH degradation product qualification guideline

Data format for the Drug Product stability report

The Division made the following comments.

DRUG SUBSTANCE

SPECIFICATIONS

1. All relevant DMF, from each site, should be updated.
2. Schering needs a quantitative test for color of solution
3. The Division wants acceptance criteria for loratadine and for total unspecified impurities. The acceptance criteria for impurities \_\_\_\_\_ should be tightened.
4. The acceptance criterion for residual solvent \_\_\_\_\_ ) should be tightened.
5. A particle size distribution specification should be established. Schering proposed setting the specification \_\_\_\_\_  
\_\_\_\_\_ The Division agreed to discuss this proposal internally and provide Schering with a response.
6. The Division wants forms I and II quantitatively identified at the drug substance level and recommends \_\_\_\_\_. However, if Schering provides data which shows that \_\_\_\_\_ is the more sensitive method in this case, the Division will consider \_\_\_\_\_

STABILITY

7. At the time of NDA submission: \_\_\_\_\_ months of long-term \ \_\_\_\_\_ and \_\_\_\_\_ months of accelerated \_\_\_\_\_ stability data on three batches from the primary stability site must be provided. In addition, adequate long-term and accelerated stability data from other proposed site (site specific) must be provided.

Schering stated that at the time of the NDA submission, they will only have release data from the Singapore site and they feel this should be adequate. The Division replied that for a new site stability data needs to be submitted,

release data are not acceptable. The number of batches and length of time will depend on the stability profile from the primary batch.

8. Schering will need to commit that the first 3 drug substance production batches at each site be placed in long term and accelerated stability studies, and adequate number of annual batches thereafter be placed on long term studies using the approved protocol.
9. The color of solution test and specification should be added to the protocol for drug substance stability.

## DRUG PRODUCT

### SPECIFICATIONS

1. Refer to ICH guidelines for impurities.
2. Include test and specification for friability.
3. Provide a specification for hardness range.
4. With regard to dissolution, the method is not discriminatory in controlling the dissolution profiles of the proposed tablets. For batch to batch consistency, the proposed method and specification may be revised. Schering may need to use a different medium. Schering should submit data in multiple media, then we discuss specifications.

### MANUFACTURING

5. Tablets manufacturing and composition should be appropriately modified to target for 100% of assay (active ingredient).

### STABILITY

6. At the time of NDA submission: ~~6~~ months of long-term ~~6~~ and ~~6~~ months of accelerated ~~6~~ stability data on three batches from the primary stability site must be provided. In addition, adequate long-term and accelerated stability data from other proposed site (site specific) must be provided.



The Division will discuss this at the Office level and get back to Schering on this issue.

7. Schering should provide a commitment that the first 3 drug product production batches at each site be placed in long term and accelerated stability studies and adequate number of annual batches thereafter on long term studies using the approved protocol.

### DATA FORMAT

8. In order to make the page numbers easier to locate, please place them at the bottom or top of the page.

9. Present each stability condition separately.

NONCLINICAL PHARMACOLOGY & TOXICOLOGY

Note: The questions from the March 29, 1999, briefing document are reproduced here for ease of review. The answers are taken from overheads shown by the Division at the meeting, with additional discussion as indicated.

1. *Given that loratadine preclinical reports have already been submitted to our approved NDA 19-658 for CLARITIN (loratadine) Tablets we plan to cross-refer to study reports in this NDA rather than resubmitting selected loratadine study reports such as chronic toxicity and carcinogenicity studies which are required to support the bridging strategy. Is this acceptable?*

Yes. However, if the Division needs a study that we cannot easily locate, we will ask Schering to resubmit those particular reports.

2. *Preliminary histological results (report in progress) from the 3 month toxicity study in monkeys as presented in the appended documentation corroborates the appropriateness of the toxicology bridging strategy – Is the Agency in agreement with this assessment.*

- Histology data appear to support bridging based upon preliminary review.
- A final decision on bridging will follow complete review of 3 month studies in rats and monkeys (PK data from these studies are also important and should be submitted to assist in making final decision).
- Final decision should be made prior to NDA submission.

3. *The toxicology program conducted with desloratadine together with the desloratadine preclinical safety information garnered from the loratadine studies provides an extensive safety assessment of desloratadine - is the Agency in agreement with this assessment?*

- Yes, based upon review of submitted summary.
- A final decision will be based upon complete review of studies, especially:
  - Acceptance of the bridging strategy for chronic toxicity in rats and monkeys
  - Definitive Segment I-III reproductive toxicity studies (submitted prior to or in the NDA)
  - In vivo mouse micronucleus study (submitted prior to or in the CAC package)
  - Agreement on bridging strategy with Executive CAC concurrence for carcinogenicity studies (see below)

4. *The oncogenicity studies conducted with loratadine demonstrate the lack of a carcinogenic liability with desloratadine at doses which exceed ICH guidelines since they were conducted at loratadine doses that produced greater than 25-fold animal to human desloratadine exposure multiple – Is the Agency in agreement with this assessment?*

- Package in support of waiver of carcinogenicity studies should be submitted for Carcinogenicity Assessment Committee (CAC) concurrence
  - Package should include:
    - Metabolic profile (PK data for parent compound and metabolites) and protein binding data across humans, mice and rats
    - Rationale for support of 25-fold exposure ratio
    - In vivo mouse micronucleus study (if not already submitted)
- For rats, the carcinogenicity study with loratadine appears to be adequate to support bridging to the desloratadine program provided that the aforementioned information in the CAC package for this species does not significantly alter the exposure ratio.
- For mice, there are currently questions in terms of which clinical dose (5 or 7.5 mg) will eventually be selected, which exposure parameter will be used in support of a 25-fold mouse to human exposure ratio (mean AUC or geometric mean AUC; use of the geometric mean supports a 25-fold ratio while mean AUC does not), and exposure linearity in the clinical setting (5, 7.5 and 10 mg). Furthermore, metabolic profile and protein binding comparisons between humans and mice may add more uncertainty about this approach.
- CAC concurrence should be obtained prior to NDA submission.

Discussion: The CAC requires a 45 day response period, therefore the package should be submitted more than 45 days prior to the submission of the NDA. With regard to metabolic profiling, the Division stated that submission of profile and exposure information across species should be acceptable. The Sponsor should reach agreement with the Division Clinical Pharmacology and Medical review staff in regards to the clinical exposure concerns prior to submission of the CAC package. The Sponsor indicated that, in the future, they would like to discuss in greater detail the elements to be included in the CAC package.

#### HUMAN PHARMACOKINETICS & BIOAVAILABILITY

1. *The levels of SCH 34117 following the administration of desloratadine are comparable to the levels following loratadine administration relative to the acceptability of our preclinical and clinical programs – Is the Agency in agreement with this assessment.*

Yes we agree, but it is a matter of dose. There is some variability, 5 mg and 7.5 mg of desloratadine are comparable to 10 mg of loratadine.

2. *The metabolic profile of SCH 34117 following the administration of SCH 34117 is the same as the downstream metabolic profile of 34117 following administration of loratadine – Is the Agency in agreement with this assessment?*

Yes. Schering should submit the quantitative data (they have only provided qualitative data).

3. *The sites of hydroxylation on the SCH 34117 molecule show quantitative species differences, with 5- and 6-hydroxylation predominant in laboratory animals, and 3-hydroxylation the major metabolic site in humans (All the hydroxylated metabolites are pharmacologically active). This metabolic species difference will result in low animal/human exposure multiples to 3-OH-SCH 34117. Since the major circulating human metabolite; i.e., the glucuronide conjugate of 3-OH-SCH 34117, is formed in similar amounts from both loratadine and SCH 34117, this finding does not impact the bridging strategy. – Is the Agency in agreement with this perspective?*

The Division agrees that there is a species difference.

The Division then requested that Schering include the following information in item 6 of the NDA submission.

1. Metabolism studies; e.g., CYP450, in vitro enzyme induction/inhibition
2. Protein binding data
3. Dissolution data in three media  
Dissolution profile comparison for 2 manufacturing sites
4. Formulation
5. Assay validation data
6. Relative BA or absolute BA (Note: the Division is not requesting an absolute BA study, however if Schering has conducted a study they should provide the results or a justification for not conducting the study.)
7. Food effect on 7.5 mg tab/5 mg (Note: The Division is asking for the results of a food effect study, or a rationale for not conducting a study).

Schering informed the Division that they have a 7.5 mg food effect study, however they had not planned a 5 mg food effect study. The Division replied that they may not need to, they should look at the differences in the formulation and if they can rationalize that the two are proportional, they won't need to do a 5 mg study. The sponsor was referred to the draft food effect guidance for further details.

Discussion: The Division pointed out that there is a high variability in the pharmacokinetics of DCL and questioned about the polymorphism. Schering replied that they have conducted a battery of tests, however, they have not been able to identify the drug metabolizing enzyme. They will continue to work on this, even after they have submitted the NDA, but currently they do not know the reason for the polymorphism. Schering showed an overhead (see attachment) which shows the studies they have conducted to date.

There was also discussion regarding whether it is appropriate to use arithmetic mean or geometric mean, especially in light of a bimodal distribution (polymorphism) in calculating the human-animal exposure ratios. The Agency felt that in looking at exposure ratios, especially for carcinogenicity studies, the issue may not be arithmetic or geometric mean, rather a question of safety. Therefore, the highest human exposure (in slow metabolizers for example) may be

more appropriate. However, this will be reviewed when the carcinogenicity package is submission to Pharm/Tox group.

## CLINICAL

1. *The efficacy and safety of SCH 34117, desloratadine tablets has been established in the following four clinical trials supporting the indication – the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR): C98-001, C98-223, C98-224, & C98-225. These studies support the fact that both the 5.0 mg and the 7.5 mg doses of desloratadine tablets are effective in relieving symptoms of SAR with comparable safety profiles. Based on these results we are proposing that 5.0 mg be the recommended dose for the administration of desloratadine tablets. We believe the clinical program supports the dosing recommendation of 5.0 mg once daily and seek your general agreement with our conclusions.*

The Division cannot comment on the relative merits of the 5.0 and 7.5 mg doses based on the synopses of efficacy submitted with the package. This will be a review issue.

The Division requested the following:

- Results without cough in TSS
- Results of TSS & TNSS without congestion
- Preclinical and exposure requirements must be met to bridge to loratadine database.

With regard to the proposed data analysis and presentation, analyses without cough must be done for individual studies. In addition, congestion is not typically included as part of TSS and TNSS for antihistamines. Analysis of TSS and TNSS should be performed with and without congestion.

Schering replied that they are conducting analyses with and without cough, which had been previously requested by the Division, but they were not aware of the need to look at data with and without congestion. Schering questioned if they show efficacy with congestion, will this be an issue. The Division replied that this may be an issue for promotional claims.

2. *Onset of Action analysis: In previous communications with the Agency with regard to loratadine a specific definition of onset of action has been suggested when conducting statistical analysis on the data. This definition of onset of action is the first timepoint that the drug is significantly superior to placebo in change from baseline in total symptoms score and consistently significantly different thereafter. We have become aware, through certain publications (e.g., Annals of Allergy, Asthma and Immunology Volume 79, December 1997) and promotional activity (e.g., involving fexofenadine hydrochloride), that another analysis seems to have been accepted by the Agency which is different than what we have utilized. This analysis defines onset of action on a per-patient basis. THE primary endpoint of the study was time to onset for clinically important relief which was defined as time to the first of three consecutive timepoints where the subject experienced "slight" to "complete" relief. Analysis was performed using the Kaplan-Meier method. To that end,*

*we wish to get clarification on the Agency's position with respect to the acceptability of more than one type of analysis based upon the definition of onset of action.*

Onset of action for the Division is the first timepoint the drug is significantly superior to PBO in change from baseline in TSS (without cough) and consistently significantly different thereafter. We have not accepted per-patient Kaplan-Meier methods for labeling, and are not aware of the fexofenadine promotional activity that Schering cites.

The Division agreed to review an argument from Schering for Kaplan-Meier, if they submit one, but they would need substantial data to support their approach.

#### Comments on DATA PRESENTATION:

Sample efficacy tables did not include all the analyses we typically require. The Division requested the following.

1. Efficacy variables every 12 hours during the first days of therapy (before day 4) particularly as they may relate to onset of effect and end of dosing interval (EODI ) efficacy.
2. Separate AM & PM reflective scores.
3. Efficacy for individual weeks of therapy as well as combined.
4. TSS, TNSS, TNNSS collectively and by individual components.

#### ELECTRONIC SUBMISSION

1. *Is the electronic submission plan as outlined in the appended documentation acceptable to the Agency?*

Yes.

The Division questioned if the SAS files will be similar to those submitted in support of mometasone. Schering replied that they will provide all data files and clinical studies in SAS. They will provide the key programs for running data.

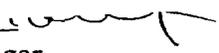
#### FOLLOW-UP:

May 20, 1999. Jim Walker, of Schering, telephoned Anne Trontell, of the Division, and asked several follow-up questions. Dr. Trontell provided preliminary answers, then on June 7, 1999, Gretchen Trout, of the Division, telephoned Mary Jane Boyle, of Schering, with the Division's final answers. The questions and answers were as follows.

1. Do the analyses without congestion need to be done for the onset-of-action studies?
  - A. Yes, Schering needs to do the analyses without (and with) congestion for the onset-of-action studies.
  
2. Since the analyses without congestion will appear as appendices to the individual study reports, would the Division prefer any special cross-referencing?
  - A. No, the standard cross-referencing is acceptable.
  
3. How should they do the analyses for the ISE with regard to congestion?
  - A. Schering should also do this analyses without congestion.

na

/S/



Gretchen Trout, Project Manager

cc: IND. \_\_\_\_\_  
Div. File

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Rd accepted by: Johnson/5-26-99  
Gebert/5-27-99  
Trontell/5-28-99  
Choi/6-2-99  
Uppoor/6-2-99  
McGovern/6-3-99  
Sun/6-3-99  
Jenkins/6-7-99

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