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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-165**

Administrative Documents

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

RE: Desloratadine Tablets for use in the prophylaxis and treatment of symptoms of seasonal allergic rhinitis in adults and adolescents 12 years of age and older.

Trade Name: None
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-b]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.

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 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 for which approval is sought.

Patent Owner: Schering Corporation

1D U.S. Patent No. 5,595,997
Expiration Date: December 30, 2014
Type of Patent: A method of treating allergic rhinitis in a human using desloratadine, the active ingredient in the desloratadine tablet product for which approval is being sought.
Patent Owner: Sepracor, Inc.

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 in a mammal using it (b) that U.S. Patent No. 4,863,931 covers the desloratadine tablet product and (c) that U.S. Patent No. 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, and (d) that U.S. Patent No. 5,597,997 covers a method of using desloratadine to treat allergic rhinitis; and (e) that desloratadine is the active ingredient in desloratadine tablets for which approval is sought and (f) that treating allergic rhinitis 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 5,595,997 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 prophylaxis and treatment of symptoms of seasonal allergic rhinitis in adults and adolescents 12 years of age and older.



Patent Information Pursuant to 21 CFR§314.59

RE: Desloratadine Tablets for use in the prophylaxis and treatment of symptoms of seasonal allergic rhinitis in adults and adolescents 12 years of age and older.

Trade Name: None
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:

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Type of Patent: Desloratadine,
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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 for which approval is sought.

Patent Owner: Schering Corporation

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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 for which approval is sought.

Patent Owner: Schering Corporation

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Patent Owner: Sepracor, Inc.

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 in a mammal using it (b) that U.S. Patent No. 4,863,931 covers the desloratadine tablet product and (c) that U.S. Patent No. 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, and (d) that U.S. Patent No. 5,597,997 covers a method of using desloratadine to treat allergic rhinitis; and (e) that desloratadine is the active ingredient in desloratadine tablets for which approval is sought and (f) that treating allergic rhinitis 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 5,595,997 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 prophylaxis and treatment of symptoms of seasonal allergic rhinitis in adults and adolescents 12 years of age and older.



EXCLUSIVITY SUMMARY for NDA # 21-165 SUPPL # _____

Trade Name Clarinet Generic Name desloratadine

Applicant Name Schering Corporation HFD-570

Approval Date December 21, 2001

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 / X /

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?

FIVE

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 / ___ / NO / X /

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 / / NO / /

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

NDA # _____

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 / /

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 /___/ 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 /___/ 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 /___/ 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 /___/

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 /___/

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 # _____

Investigation #2, Study # _____

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 /___/

Investigation #2 YES /___/ NO /___/

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 /___/

Investigation #2 YES /___/ NO /___/

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 #__, Study # _____

Investigation #__, Study # _____

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.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	:	
IND # _____ YES /___/	!	NO /___/ Explain: _____
	!	_____
	!	_____
Investigation #2	:	
IND # _____ YES /___/	!	NO /___/ Explain: _____
	!	_____
	!	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	:	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
Investigation #2	:	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____



PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021165
Trade Name: DESLORATADINE (SCH 34117) TABLETS
Generic Name: DESLORATADINE (SCH 34117) TABLETS
Supplement Number: 000 **Supplement Type:** N
Dosage Form:
Regulatory Action: AE **Action Date:** 1/19/01
COMIS Indication: ALLERGIC RHINITIS/CHRONIC IDIOPATHIC URTICARIA

Indication #1: for the relief of the nasal and non nasal symptoms of seasonal allergic rhinitis
Label Adequacy: Adequate for some pediatric age groups
Formulation Needed: Other
Comments (if any) Application provides for 12 years of age to adult

Lower Range	Upper Range	Status	Date
0 years	6 months	Waived	
12/18/01			
Comments:			

~~12/18/01: 0-6 months of age is granted a waiver due to the non-existence or difficulty in diagnosis of SAR in this age group.~~

6 months	2 years	Deferred	12/7/02
Comments: 12/18/01: 6 months to 2 years of age is deferred based on			

the potential difficulty of diagnosis and use in this age group, even though the existence of true SAR in this age group is questionable.

12 years	Adult	Completed
2 years	11 years	Deferred
Comments: 12/18/01: ;		

This page was last edited on 12/21/01

/S/

12/21/01
Date

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.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 10101-1001
Expiration Date: 10/31/91

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigator	See Attached Listing	

- 2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- 3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Heribert W. Staudinger, MD		TITLE Vice President, Clinical Research Allergy/Respiratory Diseases/Clinical Immunology	
FIRM/ORGANIZATION		Diseases/Clinical Immunology	
SIGNATURE 		DATE 9/13/91	

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FORM FDA 3454 (7/97)

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Division Director's Memorandum - Addendum

Date: Thursday, December 20, 2001
NDA: 21-165
Sponsor: Schering Plough
Proprietary Name: Clarinex (desloratadine) Tablets, 5 mg

Introduction: This is an NDA for a new molecular entity (NME) – desloratadine (DCL) proposed for the treatment of the symptoms of seasonal allergic rhinitis in patients aged 12 and above. This is the second cycle for this NDA, which had previously been granted an approvable action, due to GMP issues and a withhold recommendation for Schering-Plough's manufacturing sites (specifically the New Jersey and Puerto Rico sites). The Sponsor subsequently withdrew all but their Puerto Rican site (Las Piedras) and has been working to resolve the GMP issues that were the basis of the withhold recommendation (and a 483 letter) with Compliance. These issues are apparently close to being settled and it is expected that Compliance will issue an "acceptable" recommendation for the Puerto Rican site shortly.

Chemistry/Manufacturing and Controls: Due to most of the sites being withdrawn from the application, the main issue in this review cycle (apart from the overall GMP issues) was to assure that this solitary site had demonstrated the ~~capability to perform all aspects of the manufacturing, packaging and testing.~~ While much of the technology transfer issues for doing so have been a part of the Compliance review of the sponsor's answer to the 483 letter, our CMC staff has received data from the sponsor submitted to their NDA supporting their ability to fully produce this drug product at the remaining, single site. There are some unknown degradants that appear in accelerated testing that occur at sufficient levels that they would need to be qualified, if they occurred in unstressed stability batches. The sponsor will commit to identify the 3 most prevalent unknowns.

Preclinical: No new issues this cycle.

Biopharmaceutics: With some of the other desloratadine (DCL) applications, it became more clear that there were poor metabolizers of DCL who have prolonged half life of the DCL and low levels of the metabolite. This occurs in roughly 7% of adults (higher in blacks). There does not appear to be a major concern with this finding identified in adolescents and adults in either the DCL or loratadine databases. However, there were labeling changes agreed to by the sponsor to explain this potential, as well as the fact that such patients cannot be pre-identified and may suffer more dose-related adverse effects.

A second issue from last cycle was the potential for a phase 4 commitment (if not provided earlier) for the sponsor to do genotyping of the polymorphisms in CYP2D6 isoenzymes to explain some of the racial effects in PK previously seen. The sponsor provided data in the interim on this issue to another DCL application which, although not explanatory of the effects noted in the PK review, are responsive to this issue as described in the approvable letter.

Clinical / Statistical: No new issues of note. The safety updates did include some recent post-marketing data from the EU, and some occurrences of adverse effects bear mentioning in a post-marketing discussion in the labeling. These occurrences include

tachycardia, liver function/enzyme abnormalities and allergic reactions (including anaphylaxis). It should be noted that a part of the safety update for desloratadine as an entity was submitted to the :) and all time periods have been reviewed and accounted for.

Conclusions: This application can be approved once the site is deemed acceptable by Compliance.

/S/

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

Division Director's Memorandum

Date: Friday, October 27, 2000
NDA: 21-165
Sponsor: Schering Plough
Proprietary Name: Clarinex (desloratadine) Tablets, 5 mg

Introduction: This is an NDA for a new molecular entity (NME) – desloratadine (DCL) proposed for the treatment of the symptoms of seasonal allergic rhinitis in patients aged 12 and above. Though this drug is considered an NME, it represents the major metabolite of loratadine or Claritin – a popular second generation H₁-antihistamine. After taking a dose of loratadine, in fact, DCL exerts most of the antihistaminic activity one receives. Given that there are no particularly serious safety implications of giving loratadine as a 'pro-drug' for DCL (note that the parent does have some intrinsic H₁-blocking properties), there is no obvious clinical benefit to the development or approval of DCL. Regardless, the sponsor has stated to FDA that

This NDA is for the first of these products – Clarinex 5 mg tablets. A substantial portion of the preclinical and long-term clinical safety data are being inferred from the loratadine NDA and the resultant post-marketing database. This is acceptable due to pharmacokinetics information (see below).

Note that the original ten month review PUDFA goal date was 8-21-00. However, the sponsor's response to a prior CMC DR letter, was received 8-3-00 and coded as a major amendment, thereby extending both the 10-month and 12-month PDUFA deadlines.

Chemistry/Manufacturing and Controls: While many of the CMC issues have been resolved for this solid oral dosage form, there is a problem with degradation data at accelerated and intermediate conditions that are the subject of on-going communications between the CMC staff and the sponsor. It appears from the CMC evaluation that expiration dating will have to be established and based on primary long-term data, since accelerated data () are out-of-specification by 0 months. A further unresolved issue is the EERs (see below). Amongst the resolved issues is that there are two identified polymorphic forms of DCL drug substance. However, consultation with the biopharmaceutics staff support the bioequivalence of the two morphic forms and therefore the control over the morphic forms and which were used in particular clinical trials appears unimportant from the clinical standpoint.

Preclinical: See Dr. McGovern's primary review and Dr. Sun's team leader memo for details. Essentially, due to DCL being an active metabolite of loratadine, much of the preclinical safety is inferred from the existing preclinical data for loratadine (particularly the carcinogenicity assessment). There were bridging studies done to confirm that no unexpected preclinical issues arise with the DCL formulation compared to loratadine. It should be noted that the exposure to DCL in the mouse carcinogenicity study of

loratadine was not fully satisfactory and the sponsor has agreed to a phase-4 commitment to perform an appropriate mouse DCL study.

Safety pharmacology data showed that DCL would be expected to have little potential to significantly impact on QT intervals in humans. In vitro studies of KV1.5 channels and I_{HERG} channels showed a lower blocking potential for DCL than loratadine in the former studies (7-fold less) and that the IC₅₀ of loratadine and DCL were above 10 micromolar (but about equipotent), compared to terfenadine's and quinidine's IC₅₀ of 0.082 and 0.168 micromolar respectively for the I_{HERG} channels. In vivo studies in rats (single dose) and cynomolgus monkeys (multiple dose) at doses up to 12 mg/kg (as opposed to the clinical dose in humans of 0.1 mg/kg) showed no arrhythmias or QTc effects, though the rats experienced modest tachycardia.

Biopharmaceutics: See Dr. Choi's review for details. Comparative data for DCL exposure and metabolism following the administration of DCL 5 mg tablets vs. 10 mg loratadine tablets suggest a very similar level of exposure (by AUC) and pattern of further metabolism. The major metabolite of DCL is the 3-OH form of DCL, which then is further glucuronidated. It is unclear what microsomal enzymes are most crucial for this metabolism, though CYP2D6 and CYP3A4 appear to be significant. Special studies have shown accumulation of DCL and its metabolites in both renal and hepatic disease (at anything more than mild impairment), which should be reflected in dosing recommendations. Further, there appears to be a racial effect in metabolism, perhaps related to polymorphisms in CYP2D6 isoenzymes. Biopharmaceutic reviewers recommend that this effect and its genotyping deserve further exploration. Drug-drug interactions showed some increase in DCL and 3-OH DCL when DCL is co-administered with CYP3A4 inhibitors (erythromycin and ketoconazole), but of clinically inconsequential amounts.

Clinical / Statistical: See Dr. Nicklas' primary review and Dr. Chowdhury's team leader memo for details of the clinical program and DPADP's review findings. The sponsor submitted four RCTs in seasonal allergic rhinitis patients ages 12 and above involving more than 1800 subjects exposed to DCL. This exceeds the expected exposure data as outlined in ICH guidance for NMEs. Dose-ranging data from a two week, parallel group RCT of DCL administered in once-daily doses of 0, 2.5, 5, 7.5, 10 and 20 mg supported efficacy for all doses above 2.5 mg, but with no apparent dose response for efficacy. (There was a clear dose-response for sedation, somnolence and dry mouth, however, particularly at 10 and 20 mg). Of the three "confirmatory" trials (225, 223, 224), there were mixed results, with one trial showing efficacy for 7.5 mg, but not 5 mg (225), one showing efficacy for 5 mg, but not 7.5 mg (224) and one showing efficacy of both doses (223). These inconsistent and somewhat anomalous results appear to be due to chance variability in outcome for a drug and drug-class where showing consistent efficacy is difficult. Taken overall, there is adequate substantial evidence from these studies that 5 mg of DCL once-daily has efficacy in SAR, albeit modest. It should be noted that these mixed results, with modest overall effect sizes, are typical for the parent drug – loratadine – as well.

The sponsor examined onset-of-action in a number of ways, including a failed day-in-the-park study (no separation from placebo during the day), and three EEU chamber studies. While the EEU chamber studies showed an apparent onset in the separation from placebo

by 1.75 hours after a single 5 mg dose of DCL, there appeared to be a paradoxical longer onset for a 7.5 mg dose (examined and "replicated" in 2 of the 3 studies), leading to some appropriate skepticism on behalf of the primary reviewer on the validity of these findings. In the clinical studies, there are data to support the onset-of-effect of 5 mg DCL at or before 24 hours in two studies (001, 225). It should be noted that one of these studies – 225 – did not ultimately support the efficacy of 5 mg (i.e., the separation from placebo was not durable over the full duration of the study). These data taken together do not support a specific claim of onset-of-effect.

In the standard safety assessments, DCL appears to have a very acceptable safety profile. Given its close structural relationship to azatadine, it was unclear if DCL given as DCL would have different sedation/anticholinergic safety profile compared to loratadine. There appears to be low level, dose-related occurrences of sedation, somnolence and dry mouth. At the 5 mg dosage, these were each within a percentage point or so above the reported rates for placebo. Though there are no definitive head-to-head data for DCL and loratadine, cross-study comparisons would suggest a very similar routine safety profile (i.e., no apparent advantage or disadvantage to giving DCL as DCL) between the two.

Cardiac studies included a high dose trial (45 mg daily repeat-dose study, achieving an AUC for DCL 10 times that of the clinical dose), biopharm. studies for drug-drug interactions, as well as ECGs in the clinical trials, including the dose-ranging study. Though the sponsor did not optimally analyze the data (e.g., the ECGs were not hand-read), there appeared to be little or no effect on QTc by DCL. ~~The high dose study showed perhaps a prolongation of 4 msec on mean corrected QT and no notable outlier values.~~ These studies did show a small, but dose-related, increase in ventricular rate suggestive of some anticholinergic activity at higher doses. The sum total data for DCL – including the prior loratadine data, the in vitro channel data, the animal data and the clinical data – suggest that there should be little or no concern over QTc effects with DCL, even with doses significantly exceeding the approvable dose. However, to be more definitive in labeling, it would be useful to have the high-dose cardiac study reanalyzed using acceptable methods so that a more definitive statement can be made in the label. This is not an approvability issue, however.

Dr. Gebert performed the statistical review of the clinical trials and did not find any noteworthy statistical issues, but also felt the data provided do support the efficacy of the proposed 5 mg daily dose. Dr. Gebert confirmed concerns over any definitive onset of effect claims, including any effect at trough following the first dose (i.e., instantaneous symptom scoring before the second dose).

Data Integrity Issues: Four sites were audited by DSI – all found to be acceptable, with findings of either VAI or NAI. Neither the clinical nor the statistical reviewers identified issues with data integrity during their review process.

Due to the multicenter nature of these studies and the lack of significant center-driven effects, the disclosed are not expected to have significant implications for the interpretability of these studies.

EER: The final drug product is produced in Kenilworth, NJ and in Las Piedras, Puerto Rico. Acceptable decisions for all drug substance and product/packaging/testing sites were received, including the Kenilworth and Las Piedras sites. However, the Kenilworth recommendation was based on GMP profile that is now 2 years passed for solid oral dosage forms. Given the repeated Warning letters issued to the sponsor related to this site in recent years, and other known issues with this site, we are currently discussing with Compliance whether this acceptable decision for this site based on a profile done some time ago is still appropriate.

Labeling / Naming: There have been several rounds of communication with the sponsor with regard to the label. DPADP has significantly limited the proposed labeling regarding clinically unsubstantiated in vitro/in vivo effects of DCL, we have removed claims, and otherwise refined the label to not overstate effects nor to inappropriately discount carcinogenicity findings for loratadine.

The proposed tradename "Clarinet" was found by the division and OPDRA to be acceptable. It is noted that loratadine-pseudoephedrine is marketed as Clarinet in two European countries. Other than some implications for Micromedex, which the sponsor can address, this is not expected to present clinically important drug safety issues.

Pediatric Considerations: The sponsor was issued a written request for pediatric studies in patients down to 6 months of age on June 6th, 2000 and amended on Oct 19th, 2000.

Given that loratadine is approved down to age 2, there certainly is no public health imperative for a quicker submission. Therefore, a deferral of pediatric data below the age of 12 until 12-7-02 is appropriate for this NDA.

Conclusions: The division recommends approving this NDA, following resolution of the EER situation and identification of an appropriate expiration dating period. DPADP recommends phase 4 commitments to explore the genotyping of CYP2D6 in relationship to accumulation in African Americans and a commitment to perform a DCL-mouse carcinogenicity study.

ISI
Robert J. Meyer, MD
Director,
Division of Pulmonary and Allergy Drug Products. 10/27/00

cc Original
Division File
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HFD570/Borders

MEDICAL TEAM LEADER MEMORANDUM

DATE: September 29, 2000

TO: NDA 21-165

FROM: Badrul A. Chowdhury, MD, PhD
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

SUBJECT: Secondary medical review of Desloratadine Tablet NDA

CC: HFD-570: Meyer, Nicklas, McGovern, Choi

Administrative

NDA 21-165 was submitted by Schering Corporation on October 20, 1999. The twelve-month goal date for action on this application is October 20, 2000. Desloratadine (DCL) has not been approved for marketing in any foreign country. DCL is an active metabolite of loratadine. Loratadine is currently marketed in the US and internationally as the active component of Claritin® line of products. DCL and loratadine are second-generation histamine H1-receptor antagonists. Schering has proposed two trade names for DCL - Clarinex® and [redacted]. OPDRA does not have an objection to any of the names; however, we prefer the Clarinex® name, because this lacks the qualifier [redacted] in the [redacted] name. The proposed dose of DCL for adults and children down to 12 years is 5 mg PO QD. The proposed indications are relief of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR), [redacted]. Symptoms claimed to be effectively treated by DCL are stuffiness/congestion, rhinorrhea, nasal itching, sneezing, itchy/burning eyes, tearing/watery eyes, redness of the eyes, and itching of the ears/palate. Some of these label claims are exaggerated and will be commented upon in the recommendation section of this memorandum.

Chemistry and manufacturing

DCL tablets are light blue, round, film coated tablets containing 5 mg DCL, and various inactive ingredients. The [redacted] will be manufactured at Schering facilities in Rathdrum, Ireland, and in Singapore. All [redacted] will be done at Schering facilities either in Kenilworth, NJ, or in Las Piedras, Puerto Rico. [redacted] will be done at Schering facilities either in Union, NJ, or in Las Piedras, Puerto Rico. Twelve months [redacted] data on two lots [redacted] in NJ and in Puerto Rico was submitted with the NDA. These lots [redacted] in Ireland. Two other batches [redacted] from Singapore were [redacted], and these data were submitted during the review. There are major CMC outstanding issues that are detailed in Dr. Swiss's reviews.

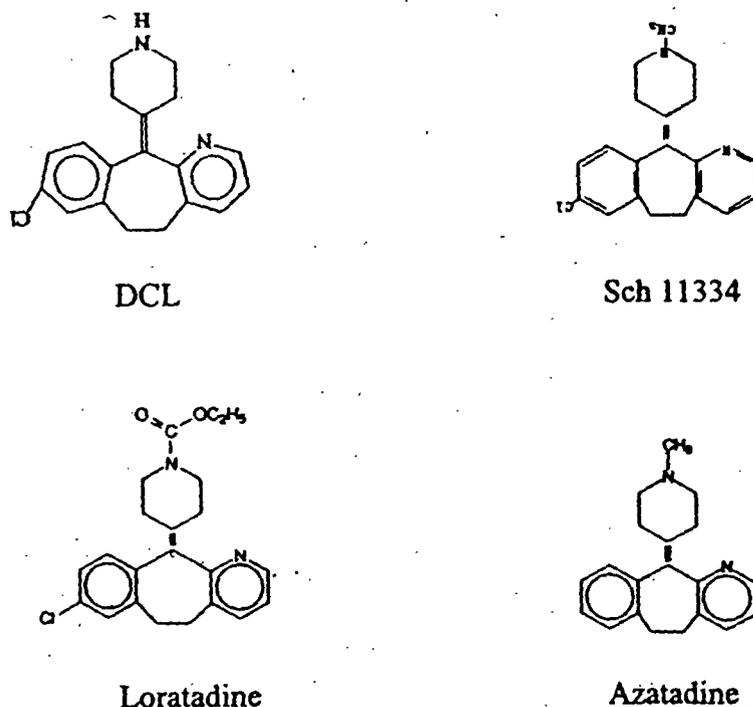


Figure 1. Structure of DCL and some related molecules

DCL is a tricyclic H₁-receptor antagonist. Structurally DCL is closely related to its precursor loratadine, which was studied by Schering in 1960s under IND [] and to a first-generation sedating H₁-receptor antagonist azatadine (Figure 1). Schering dropped development because of high incidence of sedation and anti-cholinergic effects.

Preclinical pharmacology and toxicology studies

DCL has favorable preclinical efficacy and safety profile. Preclinical studies submitted in the NDA are reviewed in Dr. McGovern's excellent review. Relevant preclinical data are briefly commented upon below.

In *in vitro* studies on cloned human histamine receptors DCL demonstrated selectivity to H₁-receptor over H₂- or H₃-receptors, and a 14-fold greater affinity for the H₁-receptor than loratadine (IC₅₀ of 51 and 721, respectively). The sponsor claims that DCL also inhibits

experimental systems. The sponsor proposes to include this information in the label to support claims that DCL has Unless supported by convincing data, claims regarding of DCL should be removed from the label.

The sponsor has conducted extensive preclinical studies to support cardiac safety of DCL. *In vivo* whole animal studies in rats, monkeys, and guinea pigs, DCL (doses up to 12 mg/kg oral, 10 mg/kg intraperitoneal, or 25 mg/kg intravenous, respectively) demonstrated no significant cardiovascular effects. *In vitro* studies on guinea pig ventricular papillary muscles DCL at concentrations of 100 microM showed no effect on action potential duration. In whole-cell patch clamp studies in rat or guinea pig ventricular myocytes, DCL at doses up to 1000 nM (about 350 ng/ml) had no effect on I_{ki} , I_{to} , I_{ped} , and I_{ks} channels. DCL at concentrations between 30 nM and 1 microM had no effect on human HERG channel expressed in *Xenopus* oocytes. At concentrations greater than 3 microM, DCL inhibited HERG current by 10-15%. For comparison, terfenadine inhibits HERG current starting at 10 nM with an IC_{50} value of 82 nM. One study conducted at Georgetown University, Washington, DC, reported similar results¹. These pre-clinical data suggest that DCL may not have the potential to cause serious cardiac arrhythmia that has been seen with some second-generation H1-antihistamines. Loratadine also has had a very favorable cardiac safety profile.

Human pharmacokinetics and bioavailability studies

The sponsor has submitted results from 15 clinical pharmacology studies involving 525 subjects. From these studies the sponsor has reached the following major conclusions: (a) ~~Maximum plasma concentration of DCL is reached at about 2-4 hours post dose;~~ (b) Plasma elimination half-life of DCL is approximately 27 hours; (c) Oral bioavailability of DCL is not affected by food; (d) Age, gender, race, hepatic or renal dysfunction have no significant effect on the DCL pharmacokinetic parameters; (d) Coadministration of DCL with CYP3A4 inhibitors such as ketoconazole and erythromycin does not significantly increase plasma DCL and its 3-OH metabolite; and (e) Nine times the recommended dose of DCL does not cause QTc prolongation. With the exception of DCL metabolism in patients with liver and kidney dysfunction, and effect on QTc at high doses, the sponsor's conclusions are generally supported by the submitted data.

Studies submitted in the biopharmaceutics section of the NDA are reviewed in detail by Dr. Choi. In the following sections, two drug interaction studies and one high dose safety study are briefly reviewed from cardiac safety standpoint. One study evaluating the comparative PK of DCL and loratadine is also briefly reviewed because the results has implications on the requirement for long term clinical safety data on DCL. The Division has agreed that long-term safety data would not be necessary if the proposed clinical dose of DCL did not give a higher bioavailability compared to that from loratadine at the approved 10 mg QD dose for the same age range (Telecon minutes August 27, 1998; Telecon minutes September 30, 1998).

¹ Ducic et.al. Comparative effects of loratadine and terfenadine on cardiac K⁺ channels. J Cardiovasc Pharmacol 1997; 30: 42-54.

C98-352: DCL plus ketoconazole PK interaction and cardiac safety study

This was a randomized, multi-dose, placebo-controlled, third-party blind, two-way cross-over study in 24 healthy subjects (12 males and 12 females, ages 19 to 50 years, mean age 36.9 years, baseline QTc \leq 420 msec) that evaluated the PK interaction and cardiac safety of DCL 7.5 mg QD AM administered with ketoconazole 200 mg BID. This study was conducted in a single US center (Jerry Herron, MD, Little Rock, Arkansas). There were two treatment phases of 10 days each, with 7 days wash-out in between. Treatment in one phase was DCL and placebo, and in the other phase was DCL and ketoconazole. Serial ECGs were done over 16 hour period at baseline (day -1) and on day 10. The ECGs were read by machine for QT interval, and correction for heart rate was by Bazett's formula. The sponsor only provided analyses using maximum QTc data and not mean and AUC QTc data.

Administration of DCL with ketoconazole caused a mild increase in DCL and DCL metabolite (Table 1). QTc interval did not change appreciably on DCL and ketoconazole coadministration (Table 2). The mean increase in QTc was 2.3 msec after administration of DCL, and 5.4 msec after administration of DCL plus ketoconazole. At day 10 the maximum QTc for DCL+placebo arm was 431 msec, and for the DCL+ketoconazole arm was 435 msec. The maximum prolongation of the QTc following DCL+ketoconazole treatment was 22 msec.

Table 1. Mean PK parameters on day 10 following DCL and ketoconazole treatment

Parameters	DCL + Placebo		DCL + ketoconazole	
	DCL	3-OH DCL	DCL	3-OH DCL
C max (ng/mL)	12.4	2.06	15.8	3.09
Tmax (hr)	6.10	4.98	5.94	5.00
AUC _{0-24hr} (ng.hr/mL)	225	29	272	55

Source: vol 1, p 38; vol 89, p 3

Table 2. Mean difference between maximum ECG parameters on day 10 from baseline (day -1)

Parameters	All subjects (n=24)		Female subjects (n=12)		Male subjects (n=12)	
	DCL + Pbo	DCL + Keto	DCL + Pbo	DCL + Keto	DCL + Pbo	DCL + Keto
Vent rate	12.2	5.6	10.6	2.8	13.8	8.4
QT (msec)	-7.2	-3.7	4.3	2.3	-18.7	-9.7
QTcB (msec)	2.3	5.4	3.2	4.8	1.3	6.0

B is Bazett's correction for heart rate

Source: vol 89, p 33, 34

C98-353: DCL plus erythromycin PK interaction and cardiac safety study

This was a randomized multi-dose, placebo-controlled, third-party blind, two-way cross-over study in 24 healthy subjects (12 males and 12 females, ages 19 to 46 years, mean age 37.4 years, baseline QTc \leq 420 msec) that evaluated the PK interaction and cardiac safety of DCL 7.5 mg QD AM coadministered with erythromycin 500 mg BID. This study was conducted in a single US center (Thomas Hunt, MD, Austin, Texas). The study design, treatment duration, ECG timing, ECG reading, and data analyses methods were identical to DCL-ketoconazole interaction study C98-352.

Administration of DCL with erythromycin caused a mild increase in DCL and DCL metabolite (Table 3). QTc interval did not change appreciably on DCL and erythromycin coadministration (Table 4). At day 10 maximum QTc was 445 msec for both groups, and maximum prolongation of the QTc following DCL+erythromycin treatment was 31 msec.

Table 3. Mean PK parameters on day 10 following DCL and erythromycin treatment

Parameters	DCL + Placebo		DCL + erythromycin	
	DCL	3-OH DCL	DCL	3-OH DCL
C max (ng/mL)	6.51	2.98	8.07	4.30
Tmax (hr)	2.88	4.71	2.77	4.31
AUC _{0-24hr} (ng.hr/mL)	100	51	114	73

Source: vol 1, p 43; vol 95, p 3

Table 4. Mean difference between maximum ECG parameters on day 10 from baseline (day -1)

Parameters	All subjects (n=24)		Female subjects (n=12)		Male subjects (n=12)	
	DCL + Pbo	DCL + EES	DCL + Pbo	DCL + EES	DCL + Pbo	DCL + EES
Vent rate	9.5	11.5	NA	NA	NA	NA
QT (msec)	-8.9	-8.3	NA	NA	NA	NA
QTcB* (msec)	7.8	9.8	NA	NA	NA	NA

* B is Bazett's correction for heart rate

Source: vol 95, p 33

C98-357: High dose DCL cardiac safety study

This was a randomized multi-dose, placebo-controlled, third-party blind, two-way cross-over study in 24 healthy subjects (12 males and 12 females, ages 20 to 48 years, mean age 35.6 years, baseline QTc \leq 420 msec) that evaluated the cardiac safety and PK parameters of DCL administered at a dose of 45 mg QD AM. This study was conducted in a single US center (Jerry Herron, MD, Little Rock, Arkansas). There were two treatment phases of 10 days each, with 7 days wash-out in between. Treatment in one phase was placebo, and in the other phase was DCL 45 mg QD. Serial ECGs were done over 16 hour period at baseline (day -1) and on day 10. The ECGs were read by machine for QT interval, and correction for heart rate was based on Bazett's formula. The sponsor only provided analyses using maximum QTc data and not mean and AUC QTc data.

Results of the PK data are shown in Table 5. DCL 45 mg caused marked increase in DCL and DCL metabolite compared to the ketoconazole and erythromycin interaction studies. Mean QTc interval increased by 4 msec over placebo on DCL treatment based on the sponsor's analysis (Table 6). At day 10 the maximum QTc for placebo arm was 429 msec, and DCL arm was 433 msec. The maximum prolongation of the QTc following DCL treatment was 24 msec.

Table 5. Mean PK parameters on day 10 following DCL treatment

Parameters	Placebo		DCL 45 mg QD	
	DCL	3-OH DCL	DCL	3-OH DCL
C max (ng/mL)	ND	ND	63.8	12.2
Tmax (hr)	ND	ND	4.54	4.04
AUC _{0-24hr} (ng.hr/mL)	ND	ND	1057	185

Source: vol 115, p 4

Table 6. Mean difference between maximum ECG parameters on day 10 from baseline (day -1)

Parameters	All subjects (n=24)		Female subjects (n=12)		Male subjects (n=12)	
	Placebo	DCL	Placebo	DCL	Placebo	DCL
Vent rate	4.2	13.6	NA	NA	NA	NA
QT (msec)	3.8	-17.8	NA	NA	NA	NA
QTcB* (msec)	0.3	4.3	NA	NA	NA	NA

* B is Bazett's correction for heart rate

Source: vol 115, p 32

P00117: Comparative PK of DCL and loratadine

This was a single center, open-label, multi-dose, three-way cross-over study in 25 healthy subjects (18 males and 7 females, ages 19 to 41 years, mean age 26 years) to characterize the PK profile of DCL and its metabolites following 10 day treatment with DCL 5 mg, DCL 7.5 mg, and loratadine 10 mg. Results show that the exposure from DCL 5 mg QD and loratadine 10 mg QD to DCL and its major metabolites are comparable (Table 7). This study supports that safety data from loratadine 10 mg QD can be extrapolated to DCL 5 mg QD, therefore obviating the need for long-term safety data for DCL 5 mg.

Table 7. Mean PK parameters on day 10 following treatment

	DCL 5 mg QD	DCL 7.5 mg QD	Loratadine 10 mg QD
DCL			
C max (ng/mL)	4.89	7.30	6.03
AUC _{0-24hr} (ng.hr/mL)	71.9	104	74.9
3-OH DCL			
C max (ng/mL)	1.62	2.30	1.73
AUC _{0-24hr} (ng.hr/mL)	23.1	34.3	23.4
3-OH DCL glucuronide			
C max (ng/mL)	29.4	46.0	29.9
AUC _{0-24hr} (ng.hr/mL)	488	735	489

Source: vol 1, p 63-67

Clinical studies

The sponsor has submitted efficacy and safety data from studies conducted in 3282 patients with SAR. Of these, 2346 patients were treated with DCL, and 1044 patients were treated with placebo. This includes 108 patients in two cross-over studies who received both DCL and placebo. The submitted studies are one dose-ranging study, three phase 3 efficacy and safety studies, one day-in-the park onset of action study, and three environmental exposure

unit (EEU) onset of action studies. Detail review of the clinical studies can be found in Dr. Nicklas's medical review. In the subsequent sections, the clinical studies are briefly reviewed.

C98-001: Multi-dose dose-ranging efficacy and safety study

This was a six-arm, 1:1:1:1:1:1 randomized, multicenter, double-blind, placebo-controlled, parallel-group study that evaluated dose-ranging efficacy and safety of various doses of DCL versus placebo. Treatment arms were placebo, or DCL 2.5 mg, 5 mg, 7.5 mg, 10 mg, or 20 mg. The study enrolled 12 to 75 year old (overall mean age about 34 year) patients with SAR in 29 US centers during the spring allergy season of 1998. The study had a one-week screening period followed by a two-week double-blind treatment period. Follow-up visits were at days 4, 8, and 15. Study drug was administered daily in the morning at approximately the same time each day.

Efficacy assessment was primarily based on patients scoring of four nasal symptoms (rhinorrhea, congestion, itching, and sneezing) and four non-nasal symptoms (itchy or burning eyes, tearing, redness of eyes, and itchy ears or palate) on 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) recorded daily in diary card in the morning before dosing and approximately 12 hours later in the evening. Scoring was reflective (status over previous 12 hours), and instantaneous (status at the time of recording). ~~The protocol specified primary efficacy variable was the change from baseline in the patient assessed AM plus PM total reflective symptoms score (four nasal plus four non-nasal symptoms described above) averaged over the 2-week treatment period.~~ Secondary efficacy variables included total symptom score without nasal congestion (seven symptoms), nasal symptom score (four symptoms), non-nasal symptom score (four symptoms), individual symptom scores, overall condition of SAR jointly assessed by patient and investigator, and response to treatment jointly assessed by patient and physician. Safety assessment included recording of adverse events, physical examination, clinical laboratory tests, and ECGs.

A total of 1036 patients were randomized, 172 to 174 patients in each group. Over 90% of patients completed the study. The ITT population, defined as patients who received at least one dose of study drug and had baseline and some follow-up data, included 1026 patients. Results of change from baseline in the patient assessed AM plus PM total reflective symptoms score averaged over the 2-week treatment period (primary efficacy variable), and other efficacy measures are shown in Table 8 and Table 9. The results support efficacy of all doses except the 2.5 mg dose. Efficacy was seen on day 2 onwards (data not shown). End of dosing interval efficacy is also supported for 5 mg and higher doses based on total instantaneous scores (Table 9). There was no clear dose-response for doses 5 mg and higher. Individual symptom scores suggest that DCL 5 mg and higher were effective on various nasal and non-nasal symptoms. All doses of DCL were well tolerated in the study. The adverse events fatigue and somnolence had some dose ordering. Fatigue was reported by <1%, 2%, 3%, 3%, 4%, and 5% in placebo, and DCL 2.5 mg, 5 mg, 7.5 mg, 10, and 20 mg treated patients, respectively. Somnolence was reported by <2%, 3%, 3%, 4%, 5%, and 8% in placebo, and DCL 2.5 mg, 5 mg, 7.5 mg, 10, and 20 mg treated patients, respectively. The

QT interval did not change meaningfully on treatment. Based on the results of this study the sponsor tested the 5 mg and 7.5 doses in further studies.

Table 8. Mean change from baseline in patient assessed total reflective AM and PM symptom score

Time	Treatment	N	Baseline (mean)	Mean change (%)	P vs Pbo
Day 2-15	Placebo	173	13.7	-2.5 (-12.5 %)	0.19
	DCL 2.5 mg	171	13.4	-3.2 (-20.0 %)	
	DCL 5.0 mg	171	14.2	-4.3 (-28.0 %)	
	DCL 7.5 mg	172	13.9	-4.3 (-26.7 %)	
	DCL 10 mg	172	13.7	-3.9 (-24.8 %)	
	DCL 20 mg	169	13.9	-4.8 (-32.5 %)	
Day 2	Placebo	173	13.7	-1.6 (-3.8 %)	0.12
	DCL 2.5 mg	171	13.4	-2.3 (-13.0 %)	
	DCL 5.0 mg	171	14.2	-3.7 (-25.1 %)	
	DCL 7.5 mg	172	13.9	-3.6 (-22.5 %)	
	DCL 10 mg	172	13.7	-3.1 (-20.2 %)	
	DCL 20 mg	169	13.9	-3.6 (-23.4 %)	

Source: v 120, p 52, 53

Table 9. Mean change from baseline in various efficacy measures for two DCL doses

Measures Time	Placebo	DCL 5 mg	DCL 7.5 mg	p-value, placebo vs	
				DCL 5 mg	DCL 7.5 mg
Total symptom score, AM instantaneous					
Day 2-15	-2.4 (-12.0 %)	-3.8 (-24.8 %)	-2.8 (-15.6 %)	<0.01	<0.01
Total nasal symptom score, AM + PM prior 12 hours reflective					
Day 2-15	-1.4 (-12.4 %)	-2.2 (-27.1 %)	-2.3 (-25.2 %)	<0.01	<0.01
Total non-nasal symptom score, AM + PM prior 12 hours reflective					
Day 2-15	-1.2 (-12.3 %)	-2.1 (-26.2 %)	-2.1 (-27.0 %)	<0.01	<0.01
Rhinorrhea, AM + PM prior 12 hours reflective					
Day 2-15	-0.3 (-8.9 %)	-0.5 (-22.0 %)	-0.5 (-19.3 %)	<0.01	<0.01
Nasal congestion, AM + PM prior 12 hours reflective					
Day 2-15	-0.4 (-14.2 %)	-0.5 (-21.3 %)	-0.5 (-20.4 %)	0.04	0.04
Nasal itching, AM + PM prior 12 hours reflective					
Day 2-15	-0.3 (-8.8 %)	-0.6 (-29.5 %)	-0.6 (-26.9 %)	<0.01	<0.01
Sneezing, AM + PM prior 12 hours reflective					
Day 2-15	-0.4 (-8.3 %)	-0.6 (-32.1 %)	-0.6 (-33.6 %)	<0.01	<0.01
Itchy or burning eyes, AM + PM prior 12 hours reflective					
Day 2-15	-0.3 (-8.9 %)	-0.6 (-27.2 %)	-0.6 (-27.5 %)	<0.01	<0.01
Tearing, AM + PM prior 12 hours reflective					
Day 2-15	-0.3 (-6.5 %)	-0.5 (-25.4 %)	-0.5 (-16.2 %)	<0.01	0.02
Redness of eyes, AM + PM prior 12 hours reflective					
Day 2-15	-0.3 (-8.9 %)	-0.5 (-23.9 %)	-0.5 (-19.7 %)	0.01	<0.01
Itchy ears or palate, AM + PM prior 12 hours reflective					
Day 2-15	-0.3 (-6.0 %)	-0.5 (-25.9 %)	-0.5 (-19.8 %)	<0.01	<0.01

Source: vol 120, p 55-62

C98-223: Multi-dose two-week efficacy and safety study

This was a three-arm, 1:1:1 randomized, multicenter, double-blind, placebo-controlled, parallel-group study that evaluated efficacy and safety of 5 mg and 7.5 mg doses of DCL

versus placebo. The study enrolled 12 to 75 year old (overall mean age about 33 year) patients with SAR in 10 US centers during the fall allergy season of 1998. The study had 4-14 days of screening period followed by a two-week double-blind treatment period. Follow-up visits were at days 4, 8, and 15. Study drug was administered daily in the morning at approximately the same time each day.

Efficacy and safety variables were same as study C98-001 with the following changes. Total symptom score included cough as an added non-nasal symptom. Data analyses were done with and without cough at our request, because cough is not a cardinal symptom of SAR. An added secondary variable in this study was health-related quality-of-life (HQOL) questionnaire self-administered by each patient 18 years of age and above at baseline and at last visit, both with one-week recall. The questionnaire was comprised of the generic instrument SF-36 Health Survey, and Rhinoconjunctivitis HQOL (RQOL) questionnaire. SF 36 covers eight domains – physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. RQOL also covers eight domains – sleep, non-nose and eye symptoms, practical problems, nasal symptoms, eye symptoms, activities, emotions, and overall.

A total of 496 patients were randomized, 165 to placebo, 165 to DCL 5 mg, and 166 to DCL 7.5 mg. Over 90% of the patients completed the study. ITT population, defined as patients who received at least one dose of study drug and had baseline and some follow-up data, included 493 patients. A total of 421 (85%) patients were at least 18 years of age, of these 406 (97%) completed QOL assessment. Results of change from baseline in the patient assessed AM plus PM total reflective symptoms score averaged over the 2-week treatment period (primary efficacy variable), and other efficacy measures are shown in Table 10. Based on the protocol specified primary efficacy variable, the results show efficacy of 5 mg and 7.5 mg doses. Of the two doses, DCL 7.5 mg was numerically superior to DCL 5 mg, however, efficacy for DCL 5 mg was adequately supported. DCL 5 mg was numerically superior to placebo for all measures. There was a large placebo response at the second week of treatment making the differences between DCL 5 mg and placebo less in magnitude and not statistically different for various measures. However, the study was not powered to detect these differences. For DCL 5mg dose, efficacy was seen on day 3 onwards. Analyses of individual symptom score show larger effect sizes for sneezing, and itching of eyes and nose. These are typical histamine mediated symptoms. Analyses of data without cough do not change the conclusion (data not shown). QOL measures showed some differences favoring DCH for some domains; however, there was no clear overall QOL effect. All doses of DCL were well tolerated in the study. The adverse event somnolence had dose ordering. Somnolence was reported by 2%, 3%, and 4% of placebo, DCL 5 mg, and DCL 7.5 mg treated patients, respectively. QT interval did not change meaningfully on treatment. This study supports efficacy for DCL 5 mg and 7.5 mg doses.

Table 10. Mean change from baseline in various efficacy measures

Measures Time	Placebo	DCL 5 mg	DCL 7.5 mg	p-value, placebo vs	
				DCL 5 mg	DCL 7.5 mg
Total symptom score (including cough), AM + PM prior 12 hours reflective					
Day 2-15	-3.94 (-22.1 %)	-5.02 (-28.2 %)	-5.73 (-31.2 %)	0.04	<0.01