

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)

15/

2/7/02

\_\_\_\_\_  
Signature of Preparer and Title

\_\_\_\_\_  
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

The requirements of 21 CFR 314.55(a) "Pediatric Use Information" are the subject of \_\_\_\_\_ for CLARINEX \_\_\_\_\_, which was filled on \_\_\_\_\_. In addition, a second NDA for the use of CLARINEX Syrup in children down to the age of 6 months will be submitted on or before December 7, 2002 and will be responsive the official pediatric Written Request, issued on June 6, 2000, and all subsequent amendments.



Division of Pulmonary and Allergy Drug Products

PROJECT MANAGER ADMINISTRATIVE REVIEW

**Application Number:** 21-363

**Name of Drug:** Clarinex (desloratadine) Tablet

**Indication:** Allergic Rhinitis

**Applicant:** Schering

**Material Reviewed**

**Submission Date(s):** April 9, 2001

**Receipt Date(s):** April 10, 2000

**Userfee received:** March 26, 2001

**Review**

User Fee Information:

The userfee for this application was submitted in three payments, with the final payment received by the Agency on March 26, 2001. A fee of \$142,870 was paid on December 26, 2000 (UF ID #4062). This fee was intended for an efficacy supplement to be submitted to NDA 21-165. A fee of \$154,823 was paid on February 15, 2001 (UF ID #4086). This fee was also intended for an efficacy supplement to be submitted to NDA 21-165. Since NDA 21-165 has not yet been approved, the applicant cannot submit supplements. Therefore, they decided instead to submit a new NDA and the Agency agreed that they could combine the two payments already received, and pay the difference in a third payment of \$11,954 (UF ID 4110) which was received on March 26, 2001.

NDA Summary Volume:

1. FDA form 356h - This form was completed, signed, and dated. It includes the relevant DMF numbers and establishment information with CFN numbers.
2. FDA form 3397 (User Fee Cover Sheet) - The form was completed, signed and dated.
3. Volume 1.1 contains an index to the NDA that identifies the starting volume for each section. The index also identifies the "Folder" each section can be located in on the electronic submission. The index does not include any page numbers.
4. The paper submission includes all sections of the electronic submission, with the exception of the case report tabulations and the case report forms.

5. Financial disclosure:

Study P00214

There was a signed form 3454 for numerous investigators who stated that they did not have any financial arrangements that could effect the outcome of the study, nor did the investigators have proprietary interests in the product or were recipients of significant payments.

In addition, there were signed 3454 for the following investigator for whom financial disclosure certification was not received \_\_\_\_\_

Study P00215

There was a signed form 3454 for numerous investigators who stated that they did not have any financial arrangements that could effect the outcome of the study, nor did the investigators have proprietary interests in the product or were recipients of significant payments.

In addition, there were signed 3454 for the following investigators for whom financial disclosure certification was not received \_\_\_\_\_

Study P00216

There was a signed form 3454 for numerous investigators who stated that they did not have any financial arrangements that could effect the outcome of the study, nor did the investigators have proprietary interests in the product or were recipients of significant payments.

In addition, there were signed 3454s for the following investigators for whom financial disclosure was not received: \_\_\_\_\_

Wijeyakumar.  
Study P00217

\_\_\_\_\_

There was a signed form 3454 for numerous investigators who stated that they did not have any financial arrangements that could effect the outcome of the study, nor did the investigators have proprietary interests in the product or were recipients of significant payments.

In addition, there were signed 3454 for the following investigators for whom financial disclosure was not received

\_\_\_\_\_

P00218

==

There was a signed 3454 for numerous investigators who stated that they did not have any financial arrangements that could effect the outcome of the study, nor did the investigators have proprietary interests in the product or were recipients of significant payments.

In addition, there were signed 3454s for the following investigators for whom financial disclosure was not received.

\_\_\_\_\_

P00219

\_\_\_\_\_

There was a signed form 3454 for numerous investigators who stated that they did not have any financial arrangements that could effect the outcome of the study, nor did the investigators have proprietary interests in the product or were recipients of significant payments.

In addition, there were signed 3454 for the following investigators for whom financial disclosure was not received:

\_\_\_\_\_

**NOTE: The medical officer should take these financial arrangements into consideration when determining if there is a need for a scientific audit of these investigators data. In addition, the medical officer should evaluate whether Schering showed due diligence in following up on investigators who did not provide financial information.**

**Review Discipline Volumes:**

1. The first volume for each discipline contains an index identifying sections and the volume number in which the section begins. Page numbers are not included in the index, each identified section can be located behind a tab identifying the section.

**General Information:**

1. Patent information

There was no patent information contained in this submission. Patent information was included in NDA 21-165 for Clarinex (desloratadine) Tablets.

2. Exclusivity

The applicant claims exclusivity in accordance with Section 505©(3)(D)(iii) and 505(j)(4)(D)(iii).

3. Debarment certification

The applicant certifies that they did not and will not knowingly 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.

**Conclusion(s):**

1. The application is fileable from an administrative perspective.

---

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

---

/s/

-----  
Gretchen Trout  
4/25/01 02:34:06 PM  
CSO

**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.



## Division Director's Memorandum

Date: Friday, February 08, 2002  
NDA: 21-363  
Sponsor: Schering Plough  
Proprietary Name: Clarinex (desloratadine) Tablets, 5 mg for Allergic Rhinitis

---

Introduction: This is an NDA for desloratadine (DCL), which has previously been approved for the treatment of Seasonal Allergic Rhinitis at a dose of 5 mg once daily. This NDA (which would have been a supplement to NDA 21-165 if that had been approved on the first cycle) is intended to support the efficacy of DCL in the treatment of Perennial Allergic Rhinitis (PAR) and therefore allowing a change in the indication to allergic rhinitis in general.

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 2/10/02.

Chemistry/Manufacturing and Controls: No new issues. An acceptable EER for the sole site of manufacture is in place (Las Piedras, PR).

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.

Clinical / Statistical: See Dr. Nicklas' primary review and Dr. Chowdhury's secondary review for details. The sponsor conducted two adequate and well-controlled 4-week trials patients with PAR, and also submitted two trials in patients with concomitant asthma and SAR to support some labeling on the safety of DCL in asthma patients with allergic rhinitis. Essentially, of the 2 PAR studies, only one clearly supports efficacy, but given the previous data (and the data on concomitant asthma) for SAR, this is enough to establish efficacy under the Division's current policy regarding the development of allergic rhinitis treatments. The asthma trials basically showed no safety issues with DCL given to AR patients with asthma, but no clear data revealing a benefit for asthma itself with DCL.

Labeling: There are a number of modifications to the labeling that were needed to better describe the data and to limit excessively promotional claims. These have been incorporated and agreed to by the sponsor. The labeling is also incorporating changes to 21-165's approved label to respond to NDA 21-297 for chronic idiopathic urticaria.

Conclusions: This NDA will be approved. Concomitantly, we will also approve a labeling supplement to NDA 21-165 and related NDA 21-297 (for chronic urticaria) so that there is one, unified approved label for this drug. Administratively, the original 21-165 should become the NDA of record.

/S/

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

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

/s/

-----  
Robert Meyer  
2/8/02 01:57:37 PM  
MEDICAL OFFICER

## MEDICAL TEAM LEADER MEMORANDUM

DATE: January 28, 2002

TO: NDA 21-363

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

SUBJECT: Secondary medical review of Clarinex 5mg Tablets (desloratadine 5mg) NDA for Perennial Allergic Rhinitis

CC: HFD-570: Meyer, Mann, Nicklas, Zeccola

### Administrative

NDA 21-363 for Clarinex (desloratadine) 5mg Tablets was submitted by Schering Corporation on April 9, 2001 (letter date). The PDUFA action due date on this application is February 10, 2002. The use of Clarinex Tablet 5mg in seasonal allergic rhinitis in patients 12 years and older was approved on December 21, 2001 (NDA 21-165). The applicant is now seeking to broaden the indication of Clarinex 5mg Tablets to allergic rhinitis, which is inclusive of seasonal allergic rhinitis and perennial allergic rhinitis, and to support the use of Clarinex 5mg Tablets in patients with allergic rhinitis and concurrent asthma in patients 12 years and older.

These are: NDA 21-297 for use of Clarinex Tablet 5mg in chronic idiopathic urticaria in patients 12 years of age and older,

### Chemistry and Manufacturing

Clarinex Tablets are light blue, round, filmcoated tablets containing 5 mg desloratadine (DL), and the following excipients: dibasic calcium phosphate dihydrate, microcrystalline cellulose, corn starch, tacl, carnauba wax, white wax, coating material consisting of lactose monohydrate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and FD&C Blue #2 Aluminum Lake. The formulation is already approved for marketing. There are no new or outstanding CMC issues.

### **Pharmacology and Toxicology**

The applicant has referenced all preclinical pharmacology and toxicology data to NDA 21-165 submission). This is acceptable. There are no outstanding pharmacology and toxicology issues.

### **Clinical Program:**

Schering has submitted results from five clinical pharmacology studies, two studies in patients with perennial allergic rhinitis (PAR), four studies in patients with seasonal allergic rhinitis (SAR), and two studies in patients with SAR and concurrent asthma (Table 1). The studies relevant to this application are briefly reviewed in the subsequent sections. Detailed reviews of the studies can be found in the primary reviews of Dr. Suarez and Dr. Nicklas.

**Table 1. Overview of the clinical program**

Study No.	Objective	Design	Treatment	Number	Age in years
<b>Clinical pharmacology studies:</b>					
P01380	Influence of grapefruit juice on oral bioavailability of DL and fexofenadine	Randomized, single dose, 4-way crossover	DL 5mg Tablet Allegra 60mg Capsule	24	19-44
P01378	Evaluation of PK and ECG of DL administered with Prozac	Randomized, single and repeat dose, placebo controlled, parallel group	DL 5mg Tablet Prozac 20mg Pulvules DL placebo	54	22-49
P01381	Evaluation of PK and ECG of DL administered with Azithromycin	Randomized, repeat dose, placebo controlled, parallel group	DL 5mg Tablet Allegra 60mg Capsule Zithromax 250mg Cap DL placebo	90	19-46
P01430	Evaluation of PK and ECG of DL administered with Cimetidine	Randomized, repeat dose, parallel group	DL 5mg Tablet Cimetidine 300mg Tab	37	18-45
P1868	Evaluation of PK and ECG of DL administered with Cimetidine	Randomized, repeat dose, parallel group	DL 5mg Tablet Cimetidine 300mg Tab	36	22-45
P1430	Evaluation of PK and ECG of DL administered with Cimetidine	Randomized, repeat dose, parallel group	DL 5mg Tablet Cimetidine 300mg Tab	37 (study canceled for AE)	18-45
<b>PAR studies:</b>					
C00-218	4-wk efficacy and safety study	Multi dose, double blind, randomized, parallel group	DL 5mg QD Placebo	676	11-79
C00-219	4-wk efficacy and safety study	Multi dose, double blind, randomized, parallel group	DL 5mg QD Placebo	698	12-80
<b>SAR studies:</b>					
C98-001	2-wk dose-ranging efficacy and safety study	Multi dose, double blind, randomized, parallel group	DL 2.5mg, 5mg, 7.5mg, 10mg, 20mg QD Placebo	1036	12-75

Study No.	Objective	Design	Treatment	Number	Age in years
C98-223	2-wk efficacy and safety study	Multi dose, double blind, randomized, parallel group	DL 5mg, 7.5mg QD Placebo	496	12-72
C98-224	2-wk efficacy and safety study	Multi dose, double blind, randomized, parallel group	DL 5mg, 7.5mg QD Placebo	492	12-73
C98-225	4-wk efficacy and safety study	Multi dose, double blind, randomized, parallel group	DL 5mg, 7.5mg QD Placebo	475	12-75
<b>SAR and Asthma studies:</b>					
C00-214	4-wk efficacy and safety study	Multi dose, double blind, randomized, parallel group	DL 5mg QD Montelukast 10mg QD Placebo	501	15-75
C00-215	4-wk efficacy and safety study	Multi dose, double blind, randomized, parallel group	DL 5mg QD Montelukast 10mg QD Placebo	423	15-68
<b>PAR studies:</b>					
Source: Section 6.A.1, page 8-10; Section 8.B., page 5-6; Section 8.D, page 4-9					

#### **Clinical pharmacology studies:**

The applicant has previously reported in NDA 21-165 the results of the concomitant administration of DL with ketoconazole and erythromycin (inhibitors of CYP3A4). Neither ketoconazole nor erythromycin resulted in clinically relevant alterations of the safety profile of DL. To further characterize the DL's interaction potential, the applicant has conducted further PK studies with DL and submitted with this application (Table 1). These studies evaluated the co-administration of fluoxetine, cimetidine, azithromycin, or grapefruit juice with Clarinex Tablets. These studies are discussed in detail in Dr. Suarez's excellent review and briefly commented on below.

The clinical pharmacology program identified some drug interactions of minor or modest degree. Co-administration of fluoxetine and DL increased in mean DL C<sub>max</sub> by 18% and mean 3-OH DL C<sub>max</sub> by 18% and mean 3-OH DL AUC by 14%. Co-administration of fluoxetine and DL reduced Prozac C<sub>max</sub> by 13% and Prozac AUC by 17%, and increased norfluoxetine C<sub>max</sub> by 22% and norfluoxetine by 18%. Co-administration of azithromycin and DL increased in mean DL C<sub>max</sub> by 15% and mean 3-OH DL C<sub>max</sub> by 15% and mean 3-OH DL AUC by 5%. Co-administration of Prozac and DL increased in mean DL C<sub>max</sub> by 18% and mean 3-OH DL C<sub>max</sub> by 18% and mean 3-OH DL AUC by 14%. Co-administration of Prozac and DL reduced Prozac C<sub>max</sub> by 13% and Prozac AUC by 17%, and increased norfluoxetine C<sub>max</sub> by 22% and forfluoxetine by 18%. None of these PK findings are clinically meaningful and therefore they do not need extensive mention in the Clarinex label.

There were no clinically meaningful changes in ECG parameters, including QTc changes, when DL was given alone or in combination with other drugs. There were also no clinically meaningful changes in vital signs, or in clinical laboratory tests. In the clinical pharmacology program there were two subjects who were poor metabolizers of DL (subjects

4 and 22 in study P1380). These subjects had a ratio of parent drug (AUC of DL) to metabolite (AUC of 3-OH DL) ratio of 10%. This definition of slow metabolizers was used previously in other DL studies to identify slow metabolizers. These subjects did not appear to have any problem in metabolizing fexofenadine. This further confirms the observation of the existence of a subset of the healthy population who metabolize DL poorly. The currently approved DL label addressed this issue. This will be further discussed under a separate heading towards the end of this review.

Study P1430, a desloratadine and cimetidine interaction study, was stopped on day 6 of the planned 15 days because of excessive adverse event reports. All subjects had PK samples drawn on day 6 (day 4 of concomitant dosing of DL 5mg QD and cimetidine 600mg BID) and all subjects except 4 who were lost to follow-up, had a return visit two weeks after discontinuing from the study. On the limited PK sampling, plasma levels of DL and 3-OH DL were not higher than expected. In this study all patients except 1 was of Hispanic race. The adverse events were reported evenly among the groups. Ten of 18 subjects receiving DL alone reported adverse events. Sixteen of 19 subjects receiving DL plus cimetidine reported adverse events. Six subjects in the DL plus cimetidine group had cardiovascular complaints, such as palpitation, and chest pain. None of these complaints were corroborated on physical examination and ECG.

The applicant performed study P01868 as a replacement for study P1430. The study was completed uneventfully. The study was conducted on 36 subjects. All subjects except 2 were of Caucasian race.

#### **Controlled clinical studies:**

The controlled clinical studies submitted with this NDA are listed in Table 1. The four SAR studies were also submitted to NDA 21-165 and were reviewed with that NDA. The four SAR studies are not reviewed further in this document. The reader is referred to the Medical Team Leader Memorandum dated September 29, 2000, to NDA 21-165 for review of the four SAR studies. The new studies submitted are the two studies conducted in PAR patients, and the two studies conducted in patients with SAR and concomitant asthma. The two pairs of studies were conducted under identical protocols. The four studies are briefly reviewed below. Detailed review of these studies can be found in Dr. Nicklas's primary medical review.

#### **Study P00218: Four-week PAR efficacy and safety study**

This was a two-arm, 1:1 randomized, multi-center, double-blind, placebo-controlled, parallel-group study. The primary objective of the study was to assess the efficacy of DL 5mg in patients with PAR. The secondary objective was to evaluate the safety profile of DL. The study was conducted in 33 centers in US, Canada, and Germany during the Fall of 1999 (between August 1999 and January 2000). There were 21 US sites and 12 international sites. The study patients were required to be 12 years of age and older, of either gender or any race, free of any medical problems other than PAR, symptomatic at the time of study entry with at least 2-year history of PAR. Patients were required to have IgE-mediated response to appropriate perennial allergen as documented by either a positive skin prick test (wheal

diameter at least 3mm larger than diluent control) or a positive skin intradermal test (wheal diameter at least 7mm larger than diluent control). The study had a 4-14 day screening period followed by 4 weeks of double-blind treatment period. Study patients received DL 5mg administered orally once daily in the morning after arising or a matching placebo. Clinic visits occurred at screening, and on days 1 (baseline), 8, 15, and 29.

Efficacy assessment was based on patients' scoring of five nasal symptoms (rhinorrhea, postnasal drip, congestion, itching, and sneezing) and three non-nasal symptoms (itchy or burning eyes, tearing, 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 in the evening. Scoring was instantaneous (status at the time of recording), and reflective (status over previous 12 hours). Scoring for both rhinorrhea and postnasal drip is unusual because this in essence scores the same symptom twice. Nonetheless, it is a fair approach because some patient may complain of rhinorrhea and not of postnasal drip and vice versa. In order to qualify at screening, the patients were to have a total reflective score of at least 10, and a nasal congestion score of at least 2. In order to qualify for randomization, the patients were required to have a minimum of 3 complete days of scoring prior to baseline, and for these 3 days the 6 twice-daily total reflective score had to total at least 60, and score for congestion had to total at least 12. The primary efficacy variable was the mean change from baseline in the patient assessed AM plus PM total instantaneous symptom score excluding nasal congestion (four nasal plus three non-nasal symptoms described above, except nasal congestion) averaged over the 4 weeks of treatment period. The baseline score was the average of the last 3 days of diary data prior to the baseline day and the AM evaluation on the baseline day before the first dose of study drug was given. Secondary efficacy variables included reflective and instantaneous total symptom, total nasal symptom with and without congestion, total non-nasal symptom, individual symptom, overall condition of PAR, and response to therapy. Safety assessment included recording of adverse events, vital signs, physical examination, clinical laboratory tests, and ECGs.

The study was originally designed to randomize 300 patients or 150 per treatment group in order to detect 1.6 units or more difference in the mean change from baseline in the primary efficacy variable with 90% power and 5% significance level, assuming a pooled standard deviation of 4.25. The original primary efficacy variable was the reflective symptom score. Based on FDA's recommendation, on October 8, 1999, the protocol was amended to change the primary efficacy variable from reflective symptom score to instantaneous symptom score. The applicant assumed that with instantaneous symptom score as the primary, the estimate of standard deviation would be greater (about 5), which would require a corresponding increase for the sample size. The sample size requirement in the amended protocol was 600 patients or 300 per treatment group. In order to meet the new sample size requirement, prior to database lock, study centers from another identical study (P00217) were distributed on an alternating basis into this and another identical study (P00218). The applicant and the FDA had discussed this method and the FDA found it acceptable.

A total of 676 patients (199 males, 477 females; age 11-79 years, mean age 34.8 years) were randomized to the two treatment groups; 337 received DL, and 339 received placebo. All patients received at least one dose of the study drug. A total of 42 (6.2%) patients (20 from

DL group and 22 from placebo group) failed to complete the study as planned. A total of 18 (2.7%) patients discontinued due to adverse event, 11 (3.3%) from DL group, and 7 (2.1%) from placebo group. Two data sets were used for analysis in this study. The ITT population included all patients who were assigned a randomization number. Safety data were analyzed on the ITT population. The efficacy-evaluable population included the ITT who met the key eligibility and evaluability criteria. These criteria were established prior to unblinding the treatment assignment and were based on inclusion and exclusion criteria, compliance, and concomitant medication use. The applicant has not defined these criteria further in the submission. In general, these criteria seem reasonable. The efficacy evaluable population included 296 patients in the DL group, and 298 patients in the placebo group. A total of 41 patients each from the two groups were excluded from the efficacy evaluable subset. Data from all randomized patients are presented in this review.

Results of change from baseline in the patient assessed AM plus PM total instantaneous symptoms scores excluding nasal congestion are shown in Table 2. The primary time point was the average over the 4 weeks of treatment (Days 1-29). Results of other analyses such as total instantaneous symptom score including nasal congestion, total instantaneous symptom score for the efficacy evaluable population with and without nasal congestion, and the same for the reflective symptom scores were similar to those observed the randomized subjects (data not shown in this review). Results of change from baseline in the individual instantaneous symptom scores are shown in Table 3. The results support efficacy of DL 5mg QD for the symptomatic treatment of PAR. The effect size was quite modest and was primarily driven by nasal symptoms. Total symptom score data from an unusually large number of patients are missing on day 1, but not on subsequent days or baseline. The applicant was not able to give a reasonable explanation as to why patients failed to comply with symptom scoring in the evening of day 1, but not on other days surrounding the day 1. Although this does not change the overall conclusion, but raises question on any conclusion specific to day 1.

DL was well tolerated in the study. The most frequently reported adverse events in both treatment groups were headache and viral infection, which occurred in 7.4% and 3.3% of patients in the DL 5mg group, and in 7.1% and 5.3%, respectively, in patients in the placebo group. More patients in the DL group compared to placebo group reported dry mouth and somnolence as adverse events. Dry mouth was reported by 8 (2.4%) and 6 (1.8%) of DL and placebo treated patients, respectively. Somnolence was reported by 4 (1.2) and 3 (0.9%) of DL and placebo treated patients, respectively. A total of 18 patients discontinued from the study because of adverse events, 11 (3.3%) from the DL group, and 7 (2.1%) from the placebo group. There were no death, or serious adverse event attributable to DL in the study. Physical examination, clinical laboratory test, and ECG did not reveal any safety signals.

**Table 2. Total instantaneous symptoms score (excluding nasal congestion), all randomized subjects**

	DL 5mg QD			Placebo QD			Analysis	
	n	LS mean	Mean % change	n	LS mean	Mean % change	Pooled SD	p-value
Baseline	337	10.70		337	10.64		3.11	0.789
Change from baseline:								

	DL 5mg QD			Placebo QD			Analysis	
	n	LS mean	Mean % change	n	LS mean	Mean % change	Pooled SD	p-value
Day 1	325	-2.58	-22.0	324	-2.02	-18.0	3.72	0.057
Day 2	335	-3.07	-25.2	331	-2.16	-17.7	3.58	0.001
Day 3	335	-3.30	-28.2	334	-2.40	-20.3	3.73	0.002
Day 4	334	-3.40	-30.8	333	-2.32	-20.7	3.78	<0.001
Days 1-8	336	-3.26	-29.1	336	-2.41	-21.3	3.34	<0.001
Days 9-15	327	-3.73	-35.0	332	-2.94	-28.0	3.75	0.008
Days 16-22	323	-4.14	-39.1	324	-3.31	-31.3	4.04	0.010
Days 23-29	319	-4.23	-39.8	319	-3.58	-32.9	4.18	0.050
Days 1-29	337	-3.73	-35.0	337	-2.95	-27.4	3.55	0.005

Source: Item 8, Study P00218, Section 11.4.1.1, page 61

**Table 3. Change from baseline in individual instantaneous scores, all randomized subjects, days 2-29**

	DL 5mg QD			Placebo QD			Analysis	
	n	LS mean	Mean % change	n	LS mean	Mean % change	Pooled SD	p-value
Rhinorrhea	337	-0.50	-23.1	337	-0.37	-15.8	0.68	0.014
PN drip	337	-0.49	-23.2	337	-0.39	-17.7	0.68	0.053
Congestion	337	-0.30	-15.7	337	-0.30	-14.9	0.59	0.878
Nasal itch	337	-0.53	-34.4	337	-0.42	-23.5	0.65	0.024
Sneezing	337	-0.56	-37.9	337	-0.42	-21.5	0.68	0.006
Itchy eyes	337	-0.49	-32.9	337	-0.44	-28.3	0.65	0.320
Tearing	337	-0.45	-36.0	337	-0.39	-30.8	0.65	0.252
Ear itch	337	-0.43	-34.2	337	-0.39	-28.3	0.67	0.465

Source: Item 8, Study P00218, Section 14, pages 241-248

#### **Study P00219: Four-week PAR efficacy and safety study**

The design and conduct of the study was identical to the PAR study P00218 except the study centers. This study was conducted in 30 centers in US, Canada, Colombia, Guatemala, Peru, Mexico, and Venezuela during the Fall of 1999 (between July 1999 and January 2000). There were 22 US sites and 8 international sites. Unlike study P00218, this study had some Latin American centers and no European centers. As in study P00218, some centers from another identical study (P00217) were distributed on an alternating basis into this study.

A total of 698 patients (232 males, 466 females; age 12-80 years, mean age 35 years) were randomized to the two treatment groups; 348 received DL, and 350 received placebo. All patients received at least one dose of the study drug. A total of 38 (10.9%) patients from the DL group and 22 (6.3%) from placebo group were excluded from the efficacy-evaluable population because of the following reasons: failure to meet protocol specified entrance criteria, use of prohibited concomitant medication, no valid visits, and insufficient medications. A total of 18 (2.6%) patients discontinued due to adverse event, 6 (1.7%) from DL group, and 12 (3.4%) from placebo group. As in study P00218, in this study two data sets were used analysis. These were the ITT population and the efficacy-evaluable population. The efficacy evaluable population included 310 patients in the DL group, and 328 patients in the placebo group. A total of 38 patients from the DL group and 22 patients

from the placebo group were excluded from the efficacy evaluable subset. Data from all randomized patients are presented in this review.

Results of change from baseline in the patient assessed AM plus PM total instantaneous symptoms scores excluding nasal congestion are shown in Table 2. The primary time point was the average over the 4 weeks of treatment (Days 1-29). Curiously the mean baseline score for the primary efficacy variable was significantly different between the two treatment groups. Results of other analyses such as total instantaneous symptom score including nasal congestion, total instantaneous symptom score for the efficacy evaluable population with and without nasal congestion, and the same for the reflective symptom scores were similar to those observed the randomized subjects (data not shown in this review). Results of change from baseline in the individual instantaneous symptom scores are shown in Table 3. The results show that DL 5mg was not superior to placebo for the symptomatic treatment of PAR.

DL was well tolerated in the study. The most frequently reported adverse events in both treatment groups were headache and viral infection, which occurred in 9.8% and 6.0% of patients in the DL 5mg group, and in 11.7% and 5.4%, respectively, in patients in the placebo group. More patients in the DL group compared to placebo group reported somnolence and dry mouth as adverse events. Somnolence was reported by 12 (3.45) and 7 (2.0%) of DL and placebo treated patients, respectively. Dry mouth was reported by 14 (4.0%) and 7 (2.0%) of DL and placebo treated patients, respectively. A total of 18 patients discontinued from the study because of adverse events, 6 (1.7%) from the DL group, and 12 (3.4%) from the placebo group. There were no death, or serious adverse event attributable to DL in the study. Physical examination, clinical laboratory test, and ECG did not reveal any safety signals.

**Table 4. Total instantaneous symptoms score (excluding nasal congestion), all randomized subjects**

	DL 5mg QD			Placebo QD			Analysis	
	n	LS mean	Mean % change	n	LS mean	Mean % change	Pooled SD	p-value
Baseline	346	10.28		349	11.00		3.01	0.002
Change from baseline:								
Day 1	333	-2.09	-20.2	332	-1.71	-15.6	3.50	0.153
Day 2	345	-2.26	-22.0	347	-1.86	-16.4	3.28	0.109
Day 3	346	-2.75	-25.2	347	-2.42	-20.8	3.56	0.235
Day 4	345	-2.78	-26.0	348	-2.50	-21.6	3.57	0.303
Days 1-8	346	-2.73	-25.6	349	-2.52	-22.2	3.11	0.383
Days 9-15	340	-3.45	-32.0	343	-3.55	-31.0	3.52	0.701
Days 16-22	333	-3.75	-35.2	338	-4.02	-35.5	3.80	0.353
Days 23-29	329	-3.90	-36.5	328	-4.20	-38.1	3.92	0.319
Days 1-29	346	-3.32	-31.1	349	-3.49	-30.9	3.31	0.493

Source: Item 8, Study P00219, Section 11.4.1.1, page 61

**Table 5. Change from baseline in individual instantaneous scores, all randomized subjects, days 2-29**

	DL 5mg QD			Placebo QD			Analysis	
	n	LS mean	Mean % change	n	LS mean	Mean % change	Pooled SD	p-value
Rhinorrhea	346	-0.43	-19.4	349	-0.48	-21.5	0.65	0.273

	DL 5mg QD			Placebo QD			Analysis	
	n	LS mean	Mean % change	n	LS mean	Mean % change	Pooled SD	p-value
PN drip	346	-0.49	-23.2	349	-0.39	-17.7	0.68	0.053
Congestion	346	-0.27	-13.7	349	-0.35	-19.4	0.57	0.079
Nasal itch	346	-0.57	-32.4	349	-0.55	-27.0	0.63	0.622
Sneezing	346	-0.47	-26.9	349	-0.50	-30.2	0.64	0.610
Itchy eyes	346	-0.46	-29.4	349	-0.49	-28.4	0.62	0.414
Tearing	346	-0.38	-22.7	349	-0.45	-26.8	0.61	0.119
Ear itch	346	-0.41	-19.2	349	-0.47	-23.1	0.62	0.162

Source: Item 8, Study P00218, Section 14, pages 242-248

#### Study P00214: Four-week SAR with concurrent asthma efficacy and safety study

This was a three-arm, 1:1:1 randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel-group study. The primary objective of the study was to assess the safety and efficacy of DL 5mg compared to placebo for relieving the symptoms of SAR and for improving forced expiratory volume in one second (FEV1) in patients with concurrent SAR and asthma. The secondary objective were to assess the efficacy of DL for improving pulmonary function (other than FEV1), decreasing in use of asthma rescue medication, reducing asthma symptoms, improving health-related quality of life (HQOL), and to assess safety of DL. The study was conducted in 37 centers in US during the Fall of 1999 (between August 1999 and March 2000). The study patients were required to be 15 years of age and older, of either gender or any race, free of any medical problems other than SAR and asthma, symptomatic at the time of study entry with at least 2-year history of SAR and worsening asthma during the fall and winter allergy season. Patients were required to have IgE-mediated response to appropriate perennial allergen as documented by either a positive skin prick test (wheal diameter at least 3mm larger than diluent control) or a positive skin intradermal test (wheal diameter at least 7mm larger than diluent control). Patients were also required have an FEV1 of  $\geq 70\%$  of the predicted at screening. The study had a 3-14 day screening period followed by 4 weeks of double-blind treatment period. Study patients received DL 5mg, or montelukast 10mg, or a matching placebo, all administered orally once daily in the morning after arising. To maintain blinding of the study drug, a double-dummy design was used. Montelukast was used as an active comparator for the asthma endpoints. Clinic visits occurred at screening, and on days 1 (baseline), 8, 15, 22, and 29.

Efficacy assessment for SAR was based on patients scoring of four nasal symptoms (rhinorrhea that included nasal discharge or postnasal drip, 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 in the evening. Scoring was instantaneous (status at the time of recording), and reflective (status over previous 12 hours). In order to qualify at screening, the patients were to have a rhinorrhea (anterior or posterior) score of at least 2; with a total reflective nasal score of at least 6 and a total non-nasal score of at least 5. In order to qualify for randomization, the patients were required to have a minimum of 3 complete days of scoring prior to baseline, and the reflective score for these 3 days plus the AM score on the day of randomization were to be a minimum of 42 for the total nasal score and a minimum of 35 for the non-nasal score. The primary efficacy variable was the mean

change from baseline in the patient assessed AM plus PM total reflective symptom score (four nasal symptoms described above) averaged over days 1-15 of treatment. The baseline score was the average of the last 3 days of diary data prior to the baseline day and the AM evaluation on the baseline day before the first dose of study drug was given. Secondary efficacy variables included instantaneous total symptom, total nasal symptom, total non-nasal symptom, individual symptom, overall condition of SAR, response to therapy, and Juniper Rhinoconjunctivitis Quality of Life Questionnaire (allergy specific) administered by the subject.

The primary efficacy assessment for asthma was change from baseline in FEV1 averaged over visits at days 8, 15, 22, and 29. Spirometry was done using appropriate techniques with age and race specific corrections. Secondary efficacy measures included other spirometry measures, PEFr recordings, patient rated asthma symptoms (cough, wheezing, and difficulty in breathing) scored on a 4-point scale (0 = none, 1 = less than weekly or on exercise only or both, 2 = greater than weekly but not daily, 3 = daily symptoms or awakening due to symptoms once per week, 4 = daily symptoms or awakening due to symptoms more than once per week or both), frequency on bronchodilator use on a 4-point scale (0 = none, 1 = less than weekly or prior to exercise only or both, 2 = greater than weekly but not daily, 3 = daily 1 to 4 inhalations, 4 = daily 5 or more inhalations), and asthma-specific health-related quality-of-life containing the domains of breathlessness, mood, asthma concerns, psychosocial impact, and physical symptom scales.

Safety assessment included recording of adverse events, vital signs, physical examination, clinical laboratory tests, and ECGs.

The study was originally designed to enroll at least 480 patients or 160 per treatment group in order to detect 1.6 units or more difference in the mean change from baseline in the daily SAR total symptom score with 92% power and 5% significance level, assuming a pooled standard deviation of 4.25; and to detect a difference of 0.12 liters between treatment means in the change from baseline in FEV1, with 98% power and 5% significance level, assuming a standard deviation of 0.26 liters. The original clinical program had 3 identical studies (P00214, P00215, and P00216). With generally low enrollment the 3 studies were later combined into 2. Centers from study P00216 were distributed on an alternating basis into this and another identical study P00215. This method is similar to what the applicant had used to fold the 3 PAR studies into 2 as discussed above.

A total of 501 patients (171 males, 330 females; age 15-75 years, overall mean age 33 years) were randomized to the three treatment groups; 168 received DL, 170 received montelukast, and 163 received placebo. All patients received at least one dose of the study drug. The ITT population included all patients who were randomized into the study and who received at least 1 dose of the study drug. A total of 63 (12.6%) patients failed to complete the study, 15 (9%) from the DL group, 16 (9%) from the montelukast group, and 32 (20%) from the placebo group. A total of 11 patients discontinued due to adverse event, 3 (2%) from DL group, 3 (2%) from montelukast group, and 6 (4%) from placebo group. Two data sets were used for analysis in this study, all randomized subjects (ITT), and efficacy-evaluable subjects. Data from all randomized subjects are presented in this review.

Results of change from baseline in the patient assessed AM plus PM total reflective SAR symptom scores are shown in Table 6. The primary time point was the average over the 15-days of treatment (Days 1-15), and the primary comparison was DL versus placebo. Results of change from baseline in the individual reflective symptom scores are shown in Table 7. The results support efficacy of DL 5mg QD for the symptomatic treatment of PAR. DL was statistically superior to placebo for all time points for the primary variable. Secondary efficacy variables were also supportive of DL. Montelukast was also found to be superior to placebo for the primary efficacy variable. No statistically significant difference was observed between DL and montelukast any time during the treatment period.

Results of the change from baseline in FEV1 averaged over visits on days 8, 15, 22, and 29 (primary efficacy variable for asthma) and for the individual days are shown in Table 8. The primary comparison was DL versus placebo. No significant differences in the FEV1 results were observed between DL and placebo treated subjects, and montelukast and placebo treated subjects. For the secondary asthma efficacy variables, montelukast was consistently numerically superior to placebo and to DL, and DL was superior to placebo for some variable. Average (day 1-29) change from baseline for total asthma symptom scores was -1.54 for DL, -1.84 for montelukast, -1.18 for placebo. Average (day 1-29) change from baseline in beta-agonist inhaler use was -0.59 for DL, -0.85 for montelukast, and -0.26 for placebo. Average change from baseline in overall condition of asthma as evaluated jointly by the investigator and patients was -0.44 for DL, -0.60 for montelukast, and -0.34 for placebo. Average change from baseline in therapeutic response as evaluated jointly by investigator and patients was also 3.56 for DL, 3.29 for montelukast, and 3.75 for placebo. For the asthma-specific domains in HQOL, the greatest improvement was observed in the montelukast group. Change from baseline was -1.7 for DL, -1.9 for montelukast, and -1.3 for placebo. Although these findings do not support the use of DL for treatment of asthma, but supports the safety of DL in patient with concurrent SAR and asthma.

DL was well tolerated in the study. The most frequently reported adverse events in all treatment groups were headache, which occurred in 10.1%, 11.2%, and 8.0% of patients in the DL group, montelukast group, and placebo group, respectively. Somnolence was reported by 1 patient in each of the treatment groups. No death or life-threatening adverse events were reported during the study. A total of 12 patients discontinued from the study because of adverse events, 3 (1.8%) from the DL group, 3 (1.8%) from montelukast group, and 6 (3.7%) from the placebo group. Physical examination, clinical laboratory test, and ECG did not reveal any safety signals.

**Table 6. Total reflective symptoms SAR score, all randomized subjects**

	DL 5mg QD			Monteluk. 10mg QD			Placebo QD			p-value	
	n	LS mean	Mean % change	n	LS mean	Mean % change	n	LS mean	Mean % change	DL vs Pbo	Mont vs Pbo
Baseline	166	15.45		168	15.37		160	15.43			
Change from baseline:											
Day 1	161	-3.13	-20.6	163	-2.52	-17.2	156	-1.06	-7.2	<0.001	0.003
Day 2	164	-3.72	-24.7	166	-3.21	-22.9	160	-1.51	-10.8	<0.001	<0.001

	DL 5mg QD			Monteluk. 10mg QD			Placebo QD			p-value	
	n	LS mean	Mean % change	n	LS mean	Mean % change	n	LS mean	Mean % change	DL vs Pbo	Mont vs Pbo
Day 3	164	-4.12	-27.1	166	-3.83	-26.8	159	-1.93	-13.1	<0.001	<0.001
Day 4	164	-4.59	-30.0	166	-4.17	-29.0	158	-2.13	-14.2	<0.001	<0.001
Days 1-15	166	-4.90	-31.3	168	-4.62	-30.9	160	-2.98	-20.1	<0.001	<0.001
Days 1-29	166	-5.47	-34.9	168	-5.37	-35.7	160	-3.73	-25.0	<0.001	<0.001

Source: Item 8, Study P00214, Section 11.4.1.1, page 71

Table 7. Change from baseline in individual reflective SAR scores, all randomized subjects, days 1-15

	DL 5mg QD			Monteluk. 10mg QD			Placebo QD			p-value	
	n	LS mean	Mean % change	n	LS mean	Mean % change	n	LS mean	Mean % change	DL vs Pbo	Mont vs Pbo
Rhinorrhea	166	-0.55	-24.4	168	-0.58	-25.3	160	-0.35	-15.5	0.003	<0.001
Congestion	166	-0.56	-23.5	168	-0.55	-24.1	160	-0.38	-16.2	0.006	0.007
Nasal itch	166	-0.61	-30.2	168	-0.56	-27.9	160	-0.36	-17.0	<0.001	0.003
Sneezing	166	-0.59	-26.9	168	-0.59	-32.8	160	-0.35	-16.4	<0.001	<0.001
Itchy eyes	166	-0.69	-33.7	168	-0.61	-31.9	160	-0.42	-21.4	<0.001	0.008
Red eyes	166	-0.64	-34.0	168	-0.57	-32.8	160	-0.35	-21.3	<0.001	0.002
Ear itch	166	-0.58	-33.7	168	-0.57	-29.8	160	-0.37	-20.9	0.004	0.008
Tearing	166	-0.66	-36.0	168	-0.59	-33.3	160	-0.41	-20.2	<0.001	0.009

Source: Item 8, Study P00214, page 316-331

Table 8. FEV1 (liters), all randomized subjects

	DL 5mg QD			Monteluk. 10mg QD			Placebo QD			p-value	
	n	LS mean	Mean % change	n	LS mean	Mean % change	n	LS mean	Mean % change	DL vs Pbo	Mont vs Pbo
Baseline	165	3.15		168	3.04		158	2.99			
Change from baseline:											
Day 8	159	0.07	1.6	165	0.08	1.7	156	0.08	1.5	0.707	0.890
Day 15	154	0.00	1.0	163	0.05	2.8	141	-0.03	-0.7	0.502	0.050
Day 22	151	-0.01	0.9	155	0.04	2.9	135	0.03	1.6	0.308	0.766
Day 29	143	0.02	1.0	151	0.05	2.8	129	0.00	0.3	0.662	0.241
Average	165	0.02	1.2	168	0.04	2.2	158	0.02	0.6	0.908	0.388

Source: Item 8, Study P00214, Section 11.4.1.2, page 74

#### Study P00215: Four-week SAR with concurrent asthma efficacy and safety study

This design and conduct of the study was identical to the previous study P00214 except the study centers. The study was conducted in 32 centers in US during the fall of 1999 (between August 1999 and March 2000). As in study P00214, some centers from another identical study (P00216) were distributed on an alternating basis into this study.

A total of 423 patients (166 males, 257 females; age 15-68 years, overall mean age 32 years) were randomized to the three treatment groups; 143 received DL, 141 received montelukast, and 139 received placebo. All patients received at least one dose of the study drug. The ITT population included all patients who were randomized into the study and who received at

least 1 dose of the study drug. A total of 43 (10.2%) patients failed to complete the study, 12 (8%) from the DL group, 7 (5%) from the montelukast group, and 24 (17%) from the placebo group. A total of 11 patients discontinued due to adverse event, 5 (3%) from DL group, 3 (2%) from montelukast group, and 5 (4%) from placebo group. As in the previous identical study, two data sets were used for analysis in this study, all randomized subjects (ITT), and efficacy-evaluable subjects. Data from all randomized subjects are presented in this review.

Results of change from baseline in the patient assessed AM plus PM total reflective SAR symptom scores are shown in Table 9. The primary time point was the average over the 15-days of treatment (Days 1-15), and the primary comparison was DL versus placebo. Results of change from baseline in the individual reflective symptom scores are shown in Table 10. The results support efficacy of DL 5mg QD for the symptomatic treatment of PAR. DL was statistically superior to placebo for all time points for the primary variable. Secondary efficacy variables were also supportive of DL. In contrast to the previous study, montelukast was not different from placebo in this study

Results of the change from baseline in FEV1 averaged over visits on days 8, 15, 22, and 29 (primary efficacy variable for asthma) and for the individual days are shown in Table 11. The primary comparison was DL versus placebo. No significant differences in the FEV1 results were observed between DL and placebo treated subjects. In contrast to the previous study, montelukast was superior to placebo in this study. For the secondary asthma efficacy variables, montelukast was consistently numerically superior to placebo and to DL, and DL was superior to placebo for some variable. Average (day 1-29) change from baseline for total asthma symptom scores was -1.38 for DL, -1.23 for montelukast, and -1.00 for placebo. Average (day 1-29) change from baseline in beta-agonist inhaler use was -0.63 for DL, -0.80 for montelukast, -0.03 for placebo. Average change from baseline in overall condition of asthma as evaluated jointly by the investigator and patients was -0.52 for DL, -0.54 for montelukast, and -0.29 for placebo. Average change from baseline in therapeutic response as evaluated jointly by investigator and patients was also 3.40 for DL, 3.41 for montelukast, and 3.71 for placebo. For the asthma-specific domains in HQOL, the greatest improvement was observed in the montelukast group. Change from baseline was -1.7 for DL, -2.0 for montelukast, and -1.9 for placebo. Although these findings do not support the use of DL for treatment of asthma, but they do support the safety of DL in patient with concurrent SAR and asthma.

DL was well tolerated in the study. The most frequently reported adverse events in all treatment groups were headache, which occurred in 9.1%, 13.5%, and 7.9% of patients in the DL group, montelukast group, and placebo group, respectively. Somnolence was reported by 0 (0.0%), 1 (0.7%), and 1 (0.0%) of DL, montelukast, and placebo treated patients, respectively. No death or life-threatening adverse events were reported during the study. A total of 13 patients discontinued from the study because of adverse events, 5 (3.5%) from the DL group, 3 (2.1%) from montelukast group, and 5 (3.6%) from the placebo group. Physical examination, clinical laboratory test, and ECG did not reveal any safety signals.

**Table 9. Total reflective symptoms SAR score, all randomized subjects**

	DL 5mg QD	Monteluk. 10mg QD	Placebo QD	p-value
--	-----------	-------------------	------------	---------

	n	LS mean	Mean % change	n	LS mean	Mean % change	n	LS mean	Mean % change	DL vs Pbo	Mont vs Pbo
Baseline	140	16.13		141	16.03		138	16.09			
Change from baseline:											
Day 1	137	-2.16	-12.8	140	-1.66	-9.3	131	-0.99	-6.9	0.036	0.221
Day 2	140	-3.20	-20.6	141	-2.47	-16.4	138	-1.98	-13.6	0.017	0.334
Day 3	140	-3.85	-23.8	139	-2.82	-17.5	137	-2.85	-17.7	0.067	0.960
Day 4	139	-3.96	-23.1	139	-3.04	-17.9	137	-2.94	-17.2	0.070	0.849
Days 1-15	140	-4.33	-26.5	141	-3.69	-22.4	138	-3.22	-19.7	0.021	0.322
Days 1-29	140	-4.97	-30.4	141	-4.58	-28.1	138	-4.03	-24.7	0.058	0.267

Source: Item 8, Study P00215, Section 11.4.1.1, page 72

**Table 10. Change from baseline in individual reflective SAR scores, all randomized subjects, days 1-15**

	DL 5mg QD			Monteluk. 10mg QD			Placebo QD			p-value	
	n	LS mean	Mean % change	n	LS mean	Mean % change	n	LS mean	Mean % change	DL vs Pbo	Mont vs Pbo
Rhinorrhea	140	-0.53	-20.8	141	-0.41	-15.0	138	-0.36	-13.5	0.018	0.517
Congestion	140	-0.52	-19.3	141	-0.50	-18.0	138	-0.37	-12.5	0.025	0.057
Nasal itch	140	-0.60	-26.0	141	-0.45	-17.6	138	-0.38	-13.9	0.004	0.318
Sneezing	140	-0.53	-27.2	141	-0.49	-19.7	138	-0.36	-14.2	0.021	0.076
Itchy eyes	140	-0.54	-26.0	141	-0.43	-15.8	138	-0.43	-18.0	0.157	0.997
Red eyes	140	-0.40	-24.4	141	-0.37	-10.3	138	-0.30	-15.9	0.167	0.311
Ear itch	140	-0.62	-27.3	141	-0.37	-14.1	138	-0.38	-17.5	<0.001	0.850
Tearing	140	-0.48	-24.9	141	-0.45	-16.0	138	-0.41	-15.8	0.394	0.590

Source: Item 8, Study P00215, page 326-342

**Table 11. FEV1 (liters), all randomized subjects**

	DL 5mg QD			Monteluk. 10mg QD			Placebo QD			p-value	
	n	LS mean	Mean % change	n	LS mean	Mean % change	n	LS mean	Mean % change	DL vs Pbo	Mont vs Pbo
Baseline	139	3.05		140	3.11		138	3.11			
Change from baseline:											
Day 8	137	0.03	1.2	136	0.10	4.1	135	-0.03	-1.1	0.115	0.001
Day 15	132	0.00	0.7	136	0.09	4.4	120	-0.03	-0.8	0.573	0.007
Day 22	129	-0.01	0.3	132	0.08	4.4	115	-0.02	-0.1	0.857	0.041
Day 29	126	0.02	1.8	126	0.05	2.3	111	-0.05	-1.3	0.142	0.047
Average	139	0.00	0.6	140	0.07	3.6	138	-0.05	-1.3	0.196	<0.001

Source: Item 8, Study P00215, Section 11.4.1.2, page 74

### **Efficacy assessment**

The clinical program presented in this NDA included 8 controlled clinical trials, 4 trials in patients with SAR (submitted in the original NDA 21-165), 2 trials in patients with PAR, and 2 trials in patients with SAR and concurrent asthma. The applicant had previously demonstrated efficacy of DL 5mg QD for the treatment of SAR symptoms. The two trials in patients with SAR and concurrent asthma further support the efficacy of DL in SAR. In one of the two PAR trials, DL was statistically significantly better than placebo in reducing the

total symptoms of PAR except nasal congestion. In the other PAR study DL was not different than placebo. As in the SAR trials, the effect size of DL for the PAR trial was only modest. Evidence of efficacy for PAR from one clinical trial is adequate because DL is already approved for SAR. The pathophysiology of SAR and PAR are similar and the clinical response to treatment is expected to be similar. Therefore, from a regulatory perspective, the applicant has submitted adequate evidence to support the efficacy of DL 5mg QD for the treatment of PAR symptoms.

#### **Safety assessment**

The data submitted to the NDA support the safety of DL in adults and adolescents down to 12 years of age with PAR. Safety assessment in the controlled clinical studies were based on adverse event reporting, vital signs, physical examination, clinical laboratory tests, and ECGs. None of these assessments raises any new safety concerns for DL. Additionally, for patients suffering from SAR and concurrent asthma, DL improved symptoms of SAR, and did not worsen asthma. No particular new safety concerns were noted in patient subgroups by age, race, or gender.

Safety of DL in slow metabolizers continues to be a problem with this drug substance. Although this is not an approvability issue for this NDA, the overall database from various NDAs relevant to the safety of DL in slow metabolizers are reviewed in the following section.

#### **Safety of desloratadine in slow metabolizers**

During the review of DL 5mg Tablets for SAR (NDA 21-165) it was noted that a small number of patients had an unusually high concentration of DL in the plasma with a corresponding low concentration of its major metabolite 3-OH DL.

Confidential

COMMERCIAL

INFO

The applicant discussed the safety of DL in slow metabolizers in the four-month safety update dated April 6, 2001,

The applicant has summarized data from 38 pharmacology studies and 1 clinical study. The safety of DL in slow metabolizers, in adults, is discussed below.

#### **Clinical Pharmacology Studies**

The DL clinical pharmacology studies are listed in Table 12. There were 1087 subjects enrolled in the studies. Most of the studies were single dose. In all studies, excepting two, the proposed therapeutic dose, or a 2-fold higher dose was used. In study C98-357, 45 mg (9-fold of the proposed dose) was given to 24 subjects. In study C98-013, 20 mg (4-fold of the proposed dose) was given to about 10 subjects.

**Table 12. Desloratadine (DL) clinical pharmacology studies, as of December 1, 2000**

Study	Study description	Study design, DL dosage	Age(yr)	No.(M,F)
<b>DL Tablet</b>				
C98-097	AME	Open-label, single-dose, 10 mg	31-40	6, 0
C98-215	Food effect	Open-label, single-dose, crossover, 7.5 mg	18-43	11, 7
I97-24B	Rising single-dose	Parallel-group, single-dose, 0, 2.5, 5, 10, 20 mg	18-45	48, 0
C98-013	Rising multiple-dose	Parallel-group, multi-dose, 0, 5, 7.5, 10, 20 mg	24-45	49, 0
C98-214	Dose-proportionality	Open-label, single-dose, crossover, 5, 7.5, 10, 20mg	19-45	20, 0
C98-352	ECG w wo keteconaz	Multi-dose, crossover, 7.5 mg w and wo keto	19-50	12, 12
C98-353	ECG w wo erythro	Multi-dose, crossover, 7.5 mg w and wo erhtyro	19-46	12, 12
C98-356	Gender and race	Open-label, multi-dose, 7.5 mg	19-45	24, 24
P0017	PK of DL, 3OH-DL	Open-label, multi-dose, crossover, 5, 7.5 mg	19-41	18, 7
P0025	PK of DL, 3OH-DL	Open-label, multi-dose, 5 mg	18-70	57, 56
P0031	BA polymorphs	Open-label, crossover, 5 mg	19-41	63, 0
C98-357	ECG	Multi-dose, crossover, 0, 45 mg	19-41	12, 12
C98-577	Pediatric PK	Open-label, single-dose, 7.5 mg	6-11	9, 9
C98-354	PK in liver disease	Open-label, single-dose, parallel-group, 7.5 mg	42-65	16, 4
P00272	PK in liver disease	Open-label, multi-dose, parallel-group, 5 mg	40-66	10, 10
C98-355	PK in renal disease	Open-label, single-dose, parallel-group, 7.5 mg	26-70	26, 11
P01196	Wheal and flare	Double-blind, multi-dose, parallel-group, 0, 5 mg	20-44	25, 3
P01228	Adolescent PK	Open-label, single-dose, parallel-group, 5 mg	12-17	12, 12
P01378	ECG Prozac interact	Open-label, parallel-group, multiple-dose, 5 mg	22-49	38, 16
P01379	Food effect with fexo	Open-label, single-dose, crossover, 5 mg	21-45	12, 12
P01430	ECG Cimetidine inter	Open-label, parallel-group, multiple-dose, 5 mg	18-45	18, 19
P01380	Grapefruit, fexo inter	Open-label, single-dose, crossover, 5 mg	19-44	13, 11
P01381	ECG Azithro, fexo	Placebo-control, multi-dose, crossover, 5 mg	19-46	45, 45
P01868	ECG Cimetidine inter	Open-label, multi-dose, parallel-group, 5 mg	22-45	18, 18

Study	Study description	Study design, DL dosage	Age(yr)	No.(M,F)
CONFIDENTIAL COMMERCIAL INFO				
Source: April 6, 2001, submission to _____, Section 1, page 24-26				

Approximately 6% of adults \_\_\_\_\_ were slow metabolizers in the clinical pharmacology studies. A subject was considered to be a slow metabolizer of DL if their AUC ratio of 3-OH DL to DL was less than 10% in all periods evaluated. If 3-OH DL was not analyzed during the study, then a subject with DL half-life value exceeding 50 hours was considered to be a slow metabolizer. AUC values for DL for normal and slow metabolizers are presented in Table 13.

**Table 13. Median (range) AUC (ng.hr/mL) of DL in normal and slow metabolizers**

	Single dose	Multiple dose
Normal metabolizer		
Slow metabolizer		
Source: April 6, 2001, submission to _____, Section 13, page 167		

Of the 1087 subjects enrolled in the clinical pharmacology studies, 75 were slow metabolizers. Demographic analyses show that 72% of the slow metabolizers were Black subjects.

The percentages of subjects reporting adverse events were similar in the slow metabolizers (21%) and normal metabolizers (31%). Curiously 54% of placebo treated subjects reported adverse events. Anticholinergic events and CNS adverse events did not differ between the slow and normal metabolizers. Clinical laboratory adverse events and ECGs were also not different between the groups. The lack of safety signal is not totally reassuring because of the small database (n=75) and because most of the subjects were exposed to a single dose of DL.

The applicant states that the phenomenon of greater DL exposure in some patients was also seen in the loratadine program. Since 3-OH-DL was not identified during the loratadine program, such subjects were considered to be "outliers." On retrospective analyses of loratadine studies the applicant identified that approximately 9.2% of subjects were possibly slow metabolizers.

#### **Clinical Study P01434**

Plasma samples from DL treated subjects participating in this study were analyzed for concentrations of DL and 3-OH-DL. In this study blood was collected between 2 and 6 hours after the final morning dose of the study drug. Based on the same definition of slow metabolizer used for the clinical pharmacology studies, 21 subjects were determined to be slow metabolizers and 488 subjects were determined to be normal metabolizers. Status of 101 subjects could not be established either because their plasma levels were too low to be categorized or because plasma samples were not available.

In this study also slow metabolism was more frequent in Blacks. Of the slow metabolizers, 52% were Blacks, and 38% were Caucasian. Of the normal metabolizers, 11% were Blacks, and 79% were Caucasian. As in the clinical pharmacology studies, adverse event reporting, and ECG were not different between the groups. The lack of safety signal is not totally reassuring because of the small database (n=21).

#### **Safety of DL in slow metabolizers**

There are two data sources that are relevant to the evaluation of safety of DL in slow metabolizers – safety data from known slow metabolizers who were exposed to DL at the proposed therapeutic dose (category 1), and safety data from subjects of unknown metabolism status who were exposed to higher than the proposed therapeutic dose of DL (category 2). Under category 1 (known slow metabolizers) a total of 75 subjects were exposed to DL at 1x or 2x of proposed therapeutic dose in various clinical pharmacology studies. Most of the subjects received single dose of DL. Under category 2 (subjects exposed to high DL dose) are 3 studies – C98-357, C98-013, and C98-001. In study C98-357 (cardiac safety clinical pharmacology study) a total of 24 subjects were treated with DL 45mg/day for 10 days. In study C98-013 (rising dose study) a total of 10 subjects were treated with DL 20mg/day for 10 days. In study C98-001 (dose-ranging study submitted to NDA 21-165) a total of 169 subjects were treated with DL 20mg/day for 14 days.

Safety data from category 1 (75 known slow metabolizers) and from study P01434 (21 slow metabolizers) did not show any difference in adverse event reporting, clinical laboratory, and ECG findings between slow metabolizers and normal metabolizers. In the three studies under category 2, no safety signal was seen. Specifically in the cardiac safety study (C98-357) 24 subjects tolerated 45mg of DL for 10 days without any clinically relevant safety signals. The lack of safety signal from these studies do not absolutely rule out the possibility of safety problems in the slow metabolizers, however, the safety data is quite reassuring. Furthermore, the post-marketing safety data of loratadine (Claritin) is also reassuring. The loratadine database is relevant because exposure to DL following dosing with 10mg loratadine is the same as that following dosing with 5mg DL. With these considerations the NDA 21-165 (DL 5mg for SAR) was approved with adequate description of the slow-metabolism phenomenon in the metabolism section of the label. The same reasoning to justify safety of DL 5mg will also apply to this NDA because the target population is the same. The current age of approval is 12 years and above.

The risk-benefit assessment for DL for pediatric patients may potentially be different.

The applicant also does not have any safety data on pediatric subjects who are known slow metabolizers, or any high dose safety data on pediatric subjects to cover for the potential high level of exposure that can occur in slow metabolizers.

**Financial disclosure and data integrity**

The applicant has submitted the financial disclosure form FDA 3454 with the NDA.

A number of investigators did not return financial disclosure after due diligence on the part of Schering.

The design minimize any bias by any individual investigator or patient. Biometrics reviewer analyzed the data for treatment-by-center effect. No such effect was seen. The are unlikely to have affected the results. There was no reason, based on review of the data submitted, to doubt the quality or integrity of the database. Therefore, DSI audit was not request for this NDA.

**Pediatric use**

a second NDA for use of Clarinex Syrup in children down to the age of 6 months will be submitted by December 2002, which be a response to the pediatric Written Request issued on June 6, 200, and all subsequent amendments.

**Recommendation**

This NDA is recommended an APPROVAL action. The applicant has submitted adequate efficacy and safety data to support approval of Clarinex 5mg Tables (desloratadine) for the treatment or symptoms of PAR in adults and adolescents down to the age of 12 years. The applicant has submitted two PAR studies, one of which showed significant benefit for desloratadine compared to placebo. Clarinex 5mg is already approved for treatment of SAR symptoms. The pathophysiology of SAR and PAR are similar and the clinical response to treatment is expected to be similar. Therefore, from a regulatory perspective, demonstration of efficacy from one study is adequate to support the indication of Clarinex 5mg for PAR. The applicant has also submitted adequate data to demonstrate improvement in SAR symptoms in patients with concurrent SAR and asthma without worsening of asthma control.

The applicant has proposed labeling change in the Clinical Trial, Indication and Usage, and Adverse Reactions sections to add information regarding the use of Clarinex in PAR and in patients with SAR and concurrent asthma. In addition, information regarding the drug-drug and drug-food interaction is updated in the Pharmacokinetics and Absorption and Drug Interactions sections. The proposed labeling changes are in general reasonable. Specific language in these sections will need to be modified to increase clarity and to accurately reflect the new data. The applicant is proposing to merge the SAR and PAR trial results in the Clinical Trials section, and is proposing a single "Allergic Rhinitis" Indication with the terms SAR and PAR in mentioned in parenthesis. The two types of allergic rhinitis should be kept separate in order to be consistent among labels for other drug products that has same or similar indications.

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

/s/

-----  
Badrul Chowdhury  
1/30/02 12:02:25 PM  
MEDICAL OFFICER

Marianne Mann  
1/30/02 05:34:48 PM  
MEDICAL OFFICER  
Signing as Acting Director