CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-300

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Patent Information Pursuant to 21 CFR§314.59

RE: CLARINEX™ (Brand of Desloratadine) Syrup for relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis and for use in the treatment of symptoms of chronic idiopathic urticaria in subjects 2 years of age and older.

Trade Name: CLARINEX(tm)

Active Ingredient: Desloratadine

Strength: 0.5 mg/1 mL.

Dosage Form: Syrup

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 syrup, 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 syrup product used for the indications 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-piperidyidene]-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 syrup and a method of treating allergy mammals by use of the active metabolite of desloratadine in the desloratadine syrup product used for the indications 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, while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, by using desloratadine, the active ingredient in the desloratadine syrup product used for the indication for which approval is sought.
	Patent Owner:	Sepracor Inc.
1E	**U.S. Patent No.**	**6,100,274**
	Expiration Date:	July 7, 2019
	Type of Patent:	Pharmaceutical compositions suitable for oral administration covering, among other things, an anti-allergic effective amount of desloratadine in a pharmaceutically acceptable carrier medium wherein the compositions contain less than about 1% by weight of N-formyldesloratadine.
	Patent Owner:	Schering Corporation

The undersigned declares (a) that U.S. Patent No. 4,659,716 covers desloratadine, as the compound per se, pharmaceutical compositions containing it and a method of treating allergic reactions, e.g., seasonal allergic rhinitis, and chronic idiopathic urticaria, in a mammal using it, (b) that U.S. Patent No. 4,863,931 covers the desloratadine syrup product used for treating allergic reactions, (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, (d) that U.S. Patent No. 6,100,274 covers the pharmaceutical composition containing desloratadine used for the treatment of allergic reactions, e.g., seasonal allergic rhinitis, and chronic idiopathic urticaria, and (e) the U.S. Patent No. 5,595,997 covers a method of treating of seasonal allergic rhinitis in a human using desloratadine; and (g) that desloratadine is the active ingredient in the desloratadine syrup product used for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria, and (f) that the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria are the indications for which approval is being sought.

The undersigned further declares that (a) approval of desloratadine syrup 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; 5,595,997; and 6,100,274 could reasonably be asserted if a person not licensed by the owner of each of the above-listed U.S. Patents engaged in the commercial manufacture, importation, use, sale or offer for sale of desloratadine for the treatment of seasonal allergic rhinitis, and/or chronic idiopathic urticaria in subjects 2 years of age and older.

In accordance with Section 306 (k) of the Food, Drug and Cosmetic Act, Schering Corporation certifies that, with respect to this application, it did not and will not knowingly use the services of any persons that have been debarred under the provisions of Section 306 (a) or (b) of the Act.

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

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

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 Investigators		
	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	TITLE
Heribert W. Staudinger, MD	Vice-President Clinical Research Allergy/Respiratory Diseases/Clinical Immunology
FIRM/ORGANIZATION	
Schering-Plough Research Institute	
SIGNATURE	DATE
[signature]	5-18-00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attn: Joseph F. Lamendola, Ph.D.

2. TELEPHONE NUMBER (*Include Area Code*)
(908) 740-2628

3. PRODUCT NAME
CLARINEX™ (desloratadine) Syrup

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO ____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER
4000

6. LICENSE NUMBER / NDA NUMBER
NO21300

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
/for Dr. Lamendola	Vice President U.S. Regulatory Affairs	12/8/2000

FORM FDA 3397 (5/98)

REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

IND/NDA/BLA number (as applicable) NDA 21-300

Sponsor: Schering Corporation

Indication(s): Seasonal Allergic Rhinitis and Chronic Idiopathic Urticaria

(NOTE: If more than one indication address the following for each indication.)

(a) Is the indication for a life-threatening condition that occurs in the pediatric population? Yes_____ No X

(b) If yes, are there approved therapies labeled for use in the pediatric population? Yes_____ No_____

(c) If yes, list the approved therapies and labeled pediatric age group(s) of approval.

1. What ages are included in your deferral request? 6 months to less than 2 years.

Reason for not including the entire pediatric population in the studies or in the deferral request:

(a) Adequate pediatric labeling
(b) Studies Completed in Ages 2 years to less than 2 years and 12 years to adult.
(c) Requesting a waiver
(d) Other
(e) Currently conducting pediatric studies that will be submitted with application. 6 months to less than 2 years data will be submitted not later than December 2002.

2. Reason(s) for deferring pediatric studies:

(a) Adult studies completed and ready for approval Yes

(b) Additional postmatketing safety data needed

(c) Technological problems with development of a pediatric formulation (provide documentation)

(d) Difficulty in enrolling pediatric patients (provide documentation)

(e) Other (specify) Studies being conducted in accordance with official pediatric Written Request

3. Have pediatric drug development planned been submitted to the Agency?

Yes X No_____

If yes, date submitted June 6, 2000 as amended October 19, 2000 and December 5, 2000

If no, projected date pediatric plan is to be submitted

4. Suggested deferred date for submission of studies. No later than December 2002

RECORD OF TELEPHONE CONVERSATION

Date:	**September 5, 2001**
Project Manager:	Hilfiker
Subject:	Pharmacokinetic Outliers in Pediatric Database
NDA:	21-300
Sponsor:	Schering Corporation
Product Name:	Clarinex Syrup

NDA 21-300 was submitted for the marketing of Clarinex (desloratadine) Syrup for signs and symptoms of seasonal allergic rhinitis and chronic idiopathic urticaria in adults and children 2 years of age and above. Other currently pending NDAs include Clarinex Tablets, Clarinex Reditabs (orally dissolving tablets), and Clarinex-D 12 Hour and Clarinex-D 24 Hour Tablets (pseudoephedrine combination products).

During the review of the pediatric studies submitted in support of Clarinex Syrup (Studies 116, 225, 1125, and 270), FDA noted that greater than 10% of the study population consistently across each of the 4 studies had pharmacokinetic profiles that were far outside the mean and the median. Two subsets of patients of concern emerged in the data and were not explained by the applicant: patients who had AUC levels up to eight times the median AUC with no apparent metabolite detected, and patients who had increased C_{max} levels without a notable increase in AUC. Patients with high AUC of parent drug and low AUC of the metabolite (i.e., the slow metabolizers) are of primary concern from a safety perspective.

FDA requested a teleconference to discuss these findings and possible explanations with the applicant.

Teleconference Participants

FDA	Division of Pulmonary and Allergy Drug Products	
	Badrul Chowdhury	Clinical Team Leader
	Emmanuel Fadiran	Team Leader, Office of Clinical Pharmacology and Biopharmaceutics
	David Hilfiker	Regulatory Project Manager
	Marianne Mann	Deputy Division Director
	Robert J. Meyer	Division Director
	Richard Nicklas	Clinical Reviewer
	Sandra Suarez	Reviewer, Office of Clinical Pharmacology and Biopharmaceutics
Schering	M. Affrime	Clinical Research
	H. Amkraut	Statistics
	C. Banfield	Clinical Research Fellow

M. Bloom	Clinical Research
C. Chung	Biostatistics
M. Dunn	Biostatistics
S. Gupta	Pharmacokinetics
S. Khalilieh	Clinical Pharmacology
J. Lamendola	Regulatory Affairs
D. McHugh	Regulatory Affairs
L. Reyderman	Pharmacokinetics
P. Rohane	Clinical Research
L. Shneyer	Biostatistics

Teleconference Summary

FDA noted that there was a consistent subpopulation of patients in these studies who exhibited abnormally high AUC values for desloratadine and practically no measurable metabolite in the pharmacokinetic profiles. Schering acknowledged this finding and stated that AUC variability was most likely due to an inability or a reduced capacity to metabolize desloratadine. [redacted]

FDA also noted a subset of patients, although the finding was less consistent, that incurred abnormally high C_{max} values without an increase in AUC or a decrease in metabolite concentration. Schering had not considered these findings as a consistent finding requiring further follow-up, and FDA agreed that this finding is less of a concern than the metabolic variability as displayed by AUC values.

Schering stated that the patients who had higher AUC values had no apparent differences in safety profile. FDA agreed, but pointed out that these were limited numbers of patients who were exposed to only a single dose of desloratadine. Additionally, Schering pointed out that studies in adults who were identified to have metabolic differences with desloratadine and high AUC exposures did not reveal any heightened concerns for safety. FDA maintained that the safety profile in children who may be poor metabolizers and who may be exposed to very high AUC levels of desloratadine remains unknown. Schering stated that 72% of the pediatric patients enrolled in the safety studies submitted to this NDA (302 and 303) were African-American, who were believed to be more predisposed to have high AUC levels with desloratadine (25% of all African Americans as opposed to 2% of Caucasian), but that pharmacokinetic profiles were not collected in these patients.

FDA was not willing to make the assumption without definitive PK data that a significant subset of the patients in the pediatric safety study were poor metabolizers, and thus had high AUC

levels. FDA also commented that although reduced or inactive metabolism is the suspected deficiency, given the pharmacokinetic profiles, Schering should investigate other explanations such as altered absorption or excretion.

FDA stated that the elevated AUCs observed with single-dose administration in the subset of the pediatric patient population may be even more exaggerated with multiple-dosing. Schering stated that adults who were given high doses repetitively did not incur any unexpected safety signals. In terms of pharmacokinetics, pediatric patients have not been studied in a multiple-dose fashion, but in adults, the results were six- to eight-fold the median AUC levels. FDA stated that the adult patients had different pharmacokinetic profiles (e.g., they had reduced, but measurable metabolite) than the subset of pediatric patients of concern, so the data generated in adults may not be reassuring of pediatric safety.

Because multiple-dose pharmacokinetics in this pediatric subpopulation have not been determined and because it remains unknown how children who are potentially poor metabolizers will tolerate multiple doses of desloratadine, FDA recommended that Schering conduct a study to determine the pharmacokinetics of multiple-dosing in a population of pediatric patients who are predetermined to be poor metabolizers. Schering should subsequently justify the safety of the exposure level to desloratadine that they identify from the multiple-dose pharmacokinetic study. FDA added that Schering should determine if metabolism is indeed the problem, and if so, by what mechanism.

Additionally, FDA stated that once an upper limit to the AUC variability is identified with multiple-dosing in children, Schering should investigate potential drug interactions and have safety data to support AUC levels achieved at the upper limits of variability in children that are slow metabolizers. If there are unknown drug interactions that might cause similarly elevated levels of desloratadine, the post-marketing safety of this product becomes a more widespread concern.

Schering asked to be able to perform this study as a Phase 4 commitment, but FDA did not agree to this approach. FDA stated that additional data in poor metablizers would be needed to support the safety and tolerability of desloratadine in children prior to approval. Schering offered to submit a letter with supporting desloratadine and loratadine data outlining the reasons why this study should not be required prior to approval. FDA agreed that Schering could do so, but also reminded Schering that this NDA is due on October 8, 2001, and there may not be time to review this submission prior to an action.

Draft by: HFD-570/Hilfiker/9-13-01
Revised by: HFD-570/Sullivan/9-14-01
HFD-570/Nicklas/9-18-01
HFD-570/Chowdhury/9-21-01
HFD-570/Mann/9-14-01
HFD-570/Meyer/9-26-01
HFD-570/Suarez
HFD-570/Fadiran

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Food & Drug Administration

Memorandum

Date : June 8, 2001

From: Kevin Swiss, Ph.D., HFD-570

Subject: Withdrawal of Schering-Plough Ltd. Singapore Branch as a Desloratadine Drug Substance Manufacturing Site.

Memo to Files: NDAs N21-165, N21-297, N21-300, N21-363

Schering Plough has informed the division in an amendment dated May 22, 2001, to the above NDAs, that the Schering Plough Singapore desloratadine drug substance manufacturing site has been withdrawn from the Clarinex 5 mg Tablets NDAs N21-165, N21-297, N21-363 and the Clarinex Syrup N21-300. The appropriate NDA EES's have been changed to include the withdrawal of the Singapore site.

In the future after these NDAs are approved, Schering needs an approved "prior-approval supplement" for commercial manufacture of desloratadine at Singapore.

Org. NDAs 21-165, 21-297, 21-300, 21-363
HFD-570/Division File
HFD-570/KSwiss/6/8/01
HFD-570/COstroff
HFD-570/GPoochikian
HFD-570/GTrout
HFD-800/CHoiberg
R/D Init by: GPoochikian
filename: N21165.memo.doc

Kevin A. Swiss, Ph.D.
Review Chemist (Drug Product)

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

/s/

Kevin Swiss
6/8/01 05:55:56 PM
CHEMIST

Guiragos Poochikian
6/8/01 05:58:52 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-300

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President
US Regulatory Affairs

Dear Dr. Lamendola:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Clarinex (desloratadine) Syrup

Review Priority Classification: Standard (S)

Date of Application: December 8, 2000

Date of Receipt: December 8, 2000

Our Reference Number: NDA 21-300

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 6, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 8, 2001 and the secondary user fee goal date will be December 8, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-1058.

Sincerely yours,

Gretchen Trout
Project Manager
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Gretchen Trout
1/2/01 10:50:25 AM

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE:

December 8, 2000

Robert Meyer, M.D., Director
Division of Pulmonary & Allergy Drug Products
Center for Drug Evaluation and Research
HFD-570, Room 10B03
5600 Fishers Lane
Rockville, MD 20857

NDA 21-300
CLARINEX™ (desloratadine)
SYRUP

SUBJECT: ORIGINAL NEW DRUG APPLICATION

Dear Dr. Meyer,

Enclosed for your review is a New Drug Application (NDA) pursuant to 21 CFR PART 314 for the use of CLARINEX Syrup in adults and children aged 2 years and above. CLARINEX Tablets is currently the subject of two pending NDAs, for use in adults and adolescents in seasonal allergic rhinitis, NDA 21-165, and chronic idiopathic urticaria, NDA 21-297.

This NDA contains clinical safety data from two, 15 day, phase III studies in children aged 2-11 years and five clinical pharmacology studies. The clinical studies demonstrated that CLARINEX Syrup is safe for use in children between the ages of two and 11. The clinical pharmacology studies demonstrated that a 5 mg dose (0.5 mg/ml) of CLARINEX Syrup is bioequivalent to a 5 mg CLARINEX Tablet in adults and when dosed in an age appropriate manner, the exposure to CLARINEX in children is similar to the exposure seen in adults.

This NDA satisfies, in part, the required pediatric use assessment described in 21 CFR 314.55 for NDAs 21-165 (CLARINEX SAR indication), 21-297(CLARINEX CIU indication), and 21-313 (CLARINEX-D™ 12 HOUR). Safety studies in children between the ages of six months and two years are ongoing and will be submitted as part of an application that will be responsive to the amended formal Written Request issued by the Agency on December 5, 2000. This submission is not intended to be responsive to the formal Written Request. However, the data contained herein will be used when an exclusivity determination is requested. For the purposes of the formal Written Request, P00302 is Study 1 and P00303 is Study 2.

Consistent with 21 CFR 314.55 the Sponsor is requesting a deferred submission of pediatric studies in children aged 6 months to less than 2 years. These studies have been requested as part of the pediatric exclusivity request. The Sponsor hereby certifies that the pediatric studies for children 6 months to less than 2 years are being conducted in accordance with the official pediatric Written Request and subsequent amendments. As specified in the request, the studies in the older children, which is the subject of this application, had to be completed before initiating the younger children. The Sponsor is acting with due diligence to complete and submit the studies in children 6 months to 2 years and requests a deferral to December 2002.

The content and format of this NDA were discussed with the Division of Pulmonary and Allergy Drug Products at a January 18, 2000 pre-NDA meeting. A summary of meetings and communications between the Agency and Sponsor are summarized in section 8.B. This application is being submitted in an electronic format similar to that used for NDAs 21-165 and 21-297, as requested by the Agency.

As requested by the Agency during the January 18, 2000 pre-NDA meeting, the Sponsor has included, in Section 20 of this Application, an integrated discussion of safety for CLARINEX™ from all of the indications studied. It is also located in volumes 25, 26, and 27 of the Clinical section and volumes 34, 35, and 36 of the Statistical section.

Chemistry, Manufacturing and Control issues were discussed at the pre-NDA meeting. Based on that discussion, we have cross-referenced the drug substance information to the tablet NDA 21-165. Included in this NDA are the specification pages for the drug substance. As agreed upon, a consolidated drug substance package has been submitted to the tablet NDA 21-165 on June 29, 2000 and updated on August 2 and September 14, 2000. The influence of the environmental elements on the color of the product is addressed in Section 4.B.6 of this NDA.

In accordance with 21 CFR PART 54, FDA Forms 3454 are included with this submission, which certifies that Schering did not participate in any financial arrangement with any clinical investigator whereby the value of the compensation could be affected by the outcome of the study.

Claim for Exclusivity In accordance with the provisions of Sections 505(c) (3) (D) (iii) and 505 (j) (4) (D) (iii) of the Food, Drug and Cosmetics Act and 21 CFR 314.108 (b) (4), exclusivity is claimed for this product. Information in support of the claim for exclusivity is provided in Section 20 of this application.

Debarment Certification In accordance with Section 306 (k) of the Food, Drug and Cosmetics Act, Schering Corporation certifies that, with respect to this application, it did no and will not knowingly use the services of any persons that have been debarred under the provisions of Section 306 (a) or (b) of the Act.

Field Copy Certification In accordance with 21 CFR 314.50 (d) (1) (v), Schering Corporation certifies that a true copy of Section 4, Chemistry, Manufacturing and Control Information of this original NDA is being sent to FDA's New Jersey District Office.

This submission is being provided in hardcopy and electronic format. We have followed the final guidance, "Providing Regulatory Submissions in Electronic-Format-NDA's" issued January of 1999. The electronic portion of the submission is divided into two sections. The first section contains read only files consisting of reports, summaries, etc., and is presented in portable document format (pdf). The second section consists of the clinical data portion, presented in SAS Transport file format and the Chemistry, Manufacturing and Controls drug product stability data in Excel and SAS Transport file formats.

A check in the amount of $ 285,740.00 was sent to FDA's designated Pittsburgh location on August 18, 2000. This check represented the estimated user fee in the amount for the current fiscal year as provided by FDA. The User Fee Cover Sheet (User Fee ID No. 4000) is included with this submission.

The following sections of the labeling, proposed in NDA 21-297, have been changed:

DESCRIPTION:
CLINICAL PHARMACOLOGY:
    Pharmacokinetics:
    Clinical Trials:
INDICATIONS AND USAGE:
PRECAUTIONS:
    Pediatric Use:
ADVERSE REACTIONS:
DOSAGE AND ADMINISTRATION:
HOW SUPPLIED:

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

DM/sb