

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-313

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ATTACHMENT 1

Pursuant to the requirements of 21 C.F.R. §314.50(i)(1)(ii), we are hereby submitting the following patent statement for Schering Corporation's CLARINEX-D® 12 Hour Extended Release Tablets' NDA No. 21-313. An explanation of the basis for this statement is set forth in Attachment 2 of this submission.

In the opinion and to the best knowledge of Schering Corporation, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.


Henry Madad
Staff Vice President-Patent Law
Schering Corporation



ATTACHMENT 2

Consistent with the provisions of 21 C.F.R. §314.50(i)(1)(ii), the NDA submission for CLARINEX-D® 12 Hour Extended Release Tablets does not rely on investigations or other data of any reference listed drug for which we do not have a right of reference. Therefore, as set forth in that regulatory provision, there are no relevant patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs. Schering Corporation's determination in this regard is based on the following:

1. CLARINEX-D® 12 Hour Extended Release Tablets NDA 21-313 does not refer to investigations or other data provided by a Reference Listed Drug ("RLD") for which we do not have a right of reference.
2. CLARINEX-D® 12 Hour Extended Release Tablets NDA 21-313 contains data to support the clinical safety and efficacy of the combination desloratadine/pseudoephedrine sulfate product. Schering Corporation is the owner of data for desloratadine and makes reference to the CLARINEX® NDA (21-165).
3. The pseudoephedrine comparator to which the combination was compared in the clinical program was a pseudoephedrine sustained release tablet. This pseudoephedrine sustained release tablet was developed and is owned by Schering Corporation.
4. In the clinical pharmacokinetic program, pseudoephedrine from the CLARINEX-D® 12 Hour Extended Release Tablets was found to be bioequivalent to that of the marketed pseudoephedrine product or the Drixoral Nasal Decongestant. As the pharmacokinetic profile of pseudoephedrine was established following administration of both CLARINEX-D® 12 Hour Extended Release Tablets and the pseudoephedrine sustained release tablet or the Drixoral Nasal Decongestant product NDA (18-191), the CLARINEX-D® 12 Hour Extended Release Tablets NDA (21-313) refers to data contained within the CLARITIN-D® 12 NDA (19-670) and Claritin-D® 24 Hour Tablet NDA (20-470) (e.g., see Section 5.B Toxicology Technical Summary, Section 8.J, Benefit and Risk Information). Schering Corporation owns all of the data in these NDAs.
5. The two clinical safety and efficacy studies provided in the CLARINEX-D® 12 Hour Extended Release Tablets NDA demonstrate the clinical superiority of the combination desloratadine/pseudoephedrine sulfate product (CLARINEX-D® 12 Hour Extended Release Tablets) to that of the individual components (i.e., desloratadine 5 mg tablet and pseudoephedrine 120 mg. sustained release tablet). Schering Corporation is the owner of these clinical data.



6. To further support the safety of pseudoephedrine sulfate, reference is also made to the information set forth in the published Final Monographs for OTC Nasal Decongestant Products (21 C.F.R. 341) for the limited purposes of referencing the publicly available pre-clinical data therein supporting the safety of pseudoephedrine.
7. Since Schering's NDA submission for CLARINEX-D® 12 Hour Extended Release Tablets does not rely on data of any reference listed drug for which we do not have a right of reference, a certification of "no relevant patents" is appropriate under the applicable regulations and the statutory provisions they implement.

55223_1

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

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

/s/

Anthony Zeccola
1/12/2006 08:16:22 AM
CSO

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0043 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
		NDA NUMBER 21-313	
		NAME OF APPLICANT / NDA HOLDER Schering Corporation	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) CLARINEX-D® 12 HOUR Extended Release Tablets			
ACTIVE INGREDIENT(S) Desloratadine Pseudoephedrine Sulfate, USP		STRENGTH(S) 2.5 mg. Desloratadine 120 mg. Pseudoephedrine Sulfate, USP	
DOSAGE FORM Tablets			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(e)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 6,100,274		b. Issue Date of Patent August 3, 2000	c. Expiration Date of Patent July 07, 2019
d. Name of Patent Owner Schering Corporation		Address (of Patent Owner) 2000 Gallopig Hill Road	
		City/State Kenilworth, New Jersey	
		ZIP Code 07033-0530	FAX Number (if available) (908) 298-5388
		Telephone Number 908-298-2959	E-Mail Address (if available) james.nelson@spcorp.com
e. Name of agent or representative who resides or maintains a place of business within the United States, authorized to receive notice of patent certification under section 505(b)(3) and (i)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.53 and 314.96 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Schering Corporation, the applicant, has a place of business in the U.S.		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	



For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? See Attachment 1. Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes



6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 806 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.63. I attest that I am familiar with 21 CFR 314.63 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

James R. Nelson

Date Signed
7/20/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.63(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
James R. Nelson

Address Schering Corporation, Patent Department, K-6-1, Mailstop 1990 2000 Gallatin Hill Road	City/State Kenilworth, New Jersey
ZIP Code 07033-0530	Telephone Number 908-298-2906
FAX Number (if available) 908-298-5388	E-Mail Address (if available) james.nelson@spcorp.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and reviewing 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.



Page 4 of 4

Form FDA 3542a
Clarinox D® 12 Hour Extended Release Tablets
USPN 6,100,274

ATTACHMENT 1

Item 2.2:

Because U.S. Patent No. 6,100,274 claims the drug product for which approval is sought, it qualifies for listing on that basis and thus, Question 3.1 is answered in the affirmative. Because U.S. Patent No. 6,100,274 does not claim the drug substance in the drug product for which approval is sought *per se*, Question 2.1 is answered in the negative. Accordingly, we do not address Questions 2.2, 2.3 or 2.4 on the Form concerning other forms of the drug substance.



SCHERING-PLOUGH RESEARCH INSTITUTE

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use		NDA NUMBER 21-313	
		NAME OF APPLICANT / NDA HOLDER Schering Corporation	
The following is provided in accordance with Section 305(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME) CLARINEX-D® 12 HOUR Extended Release Tablets			
ACTIVE INGREDIENT(S) Desloratadine Pseudoephedrine Sulfate, USP		STRENGTH(S) 2.5 mg. Desloratadine 120 mg. Pseudoephedrine Sulfate, USP	
DOSAGE FORM Tablets			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 4,659,716		b. Issue Date of Patent April 21, 1987	c. Expiration Date of Patent April 21, 2006 (by Pat. Term. Ext.)
d. Name of Patent Owner Schering Corporation		Address (of Patent Owner)	
		2000 Gallopig Hill Road	
		City/State Kenilworth, New Jersey	
		ZIP Code 07033-0530	FAX Number (if available) (908) 298-5388
Telephone Number 908-298-2959	E-Mail Address (if available) james.wilson@spcorp.com		
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 305(b)(3) and (c)(2)(ii) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.82 and 314.85 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Schering Corporation, the applicant, has a place of business in the U.S.		Address (of agent or representative named in 1.a.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
1. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
2. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	



For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? See Attachment 1. Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? See Attachment 2. Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

14 and 15

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
See Attachment 3.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes



Page 4 of 6

Form FDA 3542a
Clarinet-D® 12 Hour Extended Release Tablets
USPN 4,659,716

ATTACHMENT 1

Item 2.1:

On August 1, 2003, the U.S. Court of Appeals for the Federal Circuit in *Schering Corp. v. Geneva Pharmaceuticals Inc., et al*, 339 F. 3rd 1373 (Fed. Cir. 2003), affirmed the Opinion and Order of the U.S. District Court for the District of New Jersey, that invalidated claims 1 and 3 of U.S. Patent No. 4,659,716 as anticipated by U.S. Patent No. 4,282,233, and also stated that claims 5-13 covering pharmaceutical compositions and claims 14-16 covering methods of treating allergic reactions were not anticipated by U.S. Patent No. 4,282,233.

At least claims 5, 7, 9, 14 and 15 of U.S. Patent No. 4,659,716 read on Clarinet-D® 12 Hour Extended Release (desloratadine and Pseudoephedrine, USP) Tablets or on the indication for which approval is sought, namely, for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis, including nasal congestion, in patients 12 years of age and older. Clarinet-D® 12 Hour Extended Release Tablets can be administered when the antihistaminic properties of desloratadine and the nasal decongestant properties of pseudoephedrine are desired.

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

5. Declaration Certification	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)</p> <p><i>James R. Nelson</i></p>	<p>Date Signed</p> <p>7/26/05</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>James R. Nelson</p>	
<p>Address</p> <p>Schering Corporation, Patent Department, K-6-1, Mailstop 1990 2000 Galloping Hill Road</p>	<p>City/State</p> <p>Kennilworth, New Jersey</p>
<p>ZIP Code</p> <p>07033-0530</p>	<p>Telephone Number</p> <p>908-298-2906</p>
<p>FAX Number (if available)</p> <p>908-298-5388</p>	<p>E-Mail Address (if available)</p> <p>james.nelson@spcorp.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 9 hours 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:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-407) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>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.</i></p>	



Page 5 of 6

Form FDA 3542a
Clarinet D® 12 Hour Extended Release Tablets
USPN 4,659,716

ATTACHMENT 2

Item 2.2:

Because U.S. Patent No. 4,659,716 claims the drug product for which approval is sought, it qualifies for listing on that basis and thus Question 3.1 is answered in the affirmative. Because listing of U.S. Patent No. 4,659,716 is not based on its claiming the drug substance, Question 2.1 is answered in the negative. Accordingly, we do not address Questions 2.2, 2.3 or 2.4 on the Form concerning other forms of the drug substance.

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

Page 6 of 6

Form FDA 3542a
Clarinet D® 12 Hour Extended Release Tablets
USPN 4,859,716

ATTACHMENT 3

Item 4.2a:

INDICATIONS AND USAGE:

CLARINEX-D® 12 Hour Extended Release Tablets is indicated for the relief of of symptoms of seasonal allergic rhinitis including nasal congestion, in adults and children 12 years of age and older. CLARINEX-D® 12 Hour Extended Release Tablets can be administered when the antihistaminic properties of desloratadine and the nasal decongestant properties of pseudoephedrine are desired.

DOSAGE AND ADMINISTRATION:

Adults and children 12 years of age and over: The recommended dose of CLARINEX-D® 12 Hour Extended Release Tablets is one tablet twice a day, administered with or without a meal. A dose of one tablet once a day is recommended in patients with renal impairment. CLARINEX-D® 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic impairment.

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

Claim for Exclusivity

1. Pursuant to the provisions of Sections 505(c)(3)(D)(iii) and 505 (j)(4)(D)(iii) of the Food, Drug and Cosmetic Act (FDCA) and 21 CFR 314.108 (b)(4)(iv), the applicant claims three (3) years of exclusivity for its CLARINEX™-D 12 Brand of Desloratadine/Pseudoephedrine Sulfate) Extended Release Tablets, for use in the treatment of symptoms of seasonal allergic rhinitis in patients 12 years of age and older.
2. The applicant certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).
3. A list of all published studies or publicly available reports of clinical investigations known to the applicant through a computer-assisted literature search that are relevant to the conditions for which the applicant is seeking approval is provided as Attachment 1.
4. The applicant certifies that it has thoroughly searched the scientific literature through a computer-assisted search of the Scholar database, and Dialog database encompassing the following subfiles: CHEMSEARCH, covering the period from to 1957 to 10/2000; MEDLINE covering the period from to 1966 to 10/2000; Toxline covering the period from to 1965 to 10/2000; BIOSIS Previews covering the period from to 1969 to 10/2000; and EMBASE covering the period from to 1974 to 10/2000 for English and non-English literature relating to tablets in humans.
5. To the best of the applicant's knowledge, the list of scientific literature pertaining to desloratadine/pseudoephedrine sulfate extended release tablets is complete



and accurate, and in the opinion of the applicant, such published studies or publicly available information do not provide a sufficient basis for the approval of the use of desloratadine extended release tablets for the treatment of symptoms of seasonal allergic rhinitis without reference to the new information contained in the clinical trials in the application. The applicant's opinion that the studies or reports are insufficient is based on the following:

- The literature does not contain adequate characterization of the efficacy and safety profile of desloratadine/pseudoephedrine sulfate extended release tablets in the treatment of symptoms of seasonal allergic rhinitis which is established by the data from the new clinical studies conducted by the applicant under IND 58,506, and included in this application.

The applicant was the sponsor named in the Form FDA-1571 for IND under which the new clinical investigations were conducted.

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

Attachment 1

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

DATABASES SEARCHED:

File 398:CHEMSEARCH(TM) 1957-2000/Oct
(c) 2000 Amer.Chem.Soc.

SYSTEM:OS - DIALOG OneSearch

File 155:MEDLINE(R) 1966-2000/Dec W4

(c) format only 2000 Dialog Corporation

*File 155: For changes to the file and check tags information
please see Help News155.

File 156:Toxline(R) 1965-2000/Oct

(c) format only 2000 The Dialog Corporation

*File 156: This file will not be reloaded this year.

For changes to the file please see Help News156.

File 5:Biosis Previews(R) 1969-2000/Nov W2

(c) 2000 BIOSIS

File 73:EMBASE 1974-2000/Oct W3

(c) 2000 Elsevier Science B.V.

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

SEARCH STRATEGY:

Set	Items	Description
S1	171	DESCARBOETHOXYLORATADINE + DESLORATADINE + SCH()34117 + RN- =100643-71-8
S2	1529	D() ISOEPHEDRINE () SULFATE + PSEUDOEPHEDRINE () SULFATE + RN=7- 460-12-0 + RN=7681-21-2 + RN=93778-69-9
S3	0	CLARINEX
S4	14	S1 AND S2
S5	6	RD (unique items)
S6	6	Sort S5/ALL/PY,D

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

REFERENCES DISCUSSING DESLORATADINE + PSEUDOEPHEDRINE SULFATE

6/7/1 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2000 Elsevier Science B.V. All rts. reserv.

10737566 EMBASE No: 2000217587
Allergic rhinitis: Treating the adult
Corren J.
Dr. J. Corren, Allergy Research Foundation, Inc., 11620 Wilshire Blvd,
Los Angeles, CA 90025 United States
Journal of Allergy and Clinical Immunology (J. ALLERGY CLIN. IMMUNOL.)
(United States) 2000, 105/6 II (S610-S615)
CODEN: JACIB ISSN: 0091-6749
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 45

Allergic rhinitis is now recognized as a chronic medical condition that markedly affects patient quality of life and is a cause of substantial medical care expenditures. Effective treatment of adults with allergic rhinitis usually requires an integrated regimen that combines allergen avoidance measures, pharmacotherapy, and possible specific-allergen immunotherapy. This approach can control bothersome symptoms with minimal adverse effects in most patients. New medications, such as anti-immunoglobulin E therapy and cytokine antagonists, may provide relief to patients who are refractory to or do not tolerate currently available treatments.

6/7/2 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2000 Elsevier Science B.V. All rts. reserv.

10681476 EMBASE No: 2000164381
Desloratadine Sepracor
Norman P.
P. Norman, Norman Consulting, 18 Pink Lane, Burnham, Bucks SL1 8JW
United Kingdom
AUTHOR EMAIL: Peter.Norman@nationwideisp.net
Current Opinion in Anti-inflammatory and Immunomodulatory
Investigational
Drugs (CURR. OPIN. ANTI-INFLAMMATORY IMMUNOMODULATORY INVEST. DRUGS)
(United Kingdom) 2000, 2/2 (117-126)
CODEN: COAIF ISSN: 1464-8474
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 90

The use of the loratadine metabolite, decarboethoxyloratadine (DCL), for the treatment of both allergic rhinitis and diabetic retinopathy is claimed. DCL is claimed to display fewer cardiovascular and tumor promoting side effects than loratadine. DCL was disclosed in US-04659716.



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

6/7/3 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2000 Elsevier Science B.V. All rts. reserv.

10648088 EMBASE No: 2000113028
Fexofenadine: A review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria
Simpson K.; Jarvis B.
K. Simpson, Adis International Limited, 41 Centorian Drive, Mairangi Bay, Auckland 10 New Zealand
AUTHOR EMAIL: demail@adis.co.nz
Drugs (DRUGS) (New Zealand) 2000, 59/2 (301-321)
CODEN: DRUGA ISSN: 0012-6667
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 78

Fexofenadine, the active metabolite of terfenadine, is a selective histamine H₁ receptor antagonist that does not cross the blood brain barrier and appears to display some anti-inflammatory properties. Fexofenadine is rapidly absorbed (onset of relief <=2 hours) and has a long duration of action, making it suitable for once daily administration. Clinical trials (<=2 weeks' duration) have shown fexofenadine 60mg twice daily and 120mg once daily to be as effective as loratadine 10mg once daily, and fexofenadine 120mg once daily to be as effective as cetirizine 10mg once daily in the overall reduction of symptoms of seasonal allergic rhinitis. When given in combination, fexofenadine and extended release pseudoephedrine had complementary activity. Fexofenadine was effective in relieving the symptoms of sneezing, rhinorrhoea, itchy nose palate or throat, and itchy, watery, red eyes in patients with seasonal allergic rhinitis. There were often small improvements in nasal congestion that were further improved by pseudoephedrine. Fexofenadine produced greater improvements in quality of life than loratadine to an extent considered to be clinically meaningful, and enhanced patients' quality of life when added to pseudoephedrine treatment. Although no comparative data with other H₁ antagonists exist, fexofenadine 180mg once daily was effective in reducing the symptoms of chronic idiopathic urticaria for up to 6 weeks. Fexofenadine was well tolerated in clinical trials in adults and adolescents and the adverse event profile was similar to placebo in all studies. The most frequently reported adverse event during fexofenadine treatment was headache, which occurred with a similar



incidence to that seen in placebo recipients. Fexofenadine does not inhibit cardiac K⁺ channels and is not associated with prolongation of the corrected QT interval. When given alone or in combination with erythromycin or ketoconazole, it was not associated with any adverse cardiac events in clinical trials. As it does not cross the blood brain barrier, fexofenadine is free of the sedative effects associated with first generation antihistamines, even at dosages of up to 240 mg/day. Conclusions: fexofenadine is clinically effective in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria for which it is a suitable option for first-line therapy. Comparative data suggest that fexofenadine is as effective as loratadine or cetirizine in the treatment of seasonal allergic rhinitis. In those with excessive nasal congestion the combination of fexofenadine plus pseudoephedrine may be useful. In clinical trials fexofenadine is not associated with adverse cardiac or cognitive/psychomotor effects.

6/7/4 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2000 Elsevier Science B.V. All rts. reserv.

10533590 EMBASE No: 1999418376
Allergic rhinitis: Basic pathophysiology and therapeutic strategies
Segura T.; Casale T.B.
Dr. T. Segura, Nebraska Medical Research Institute, 401 East Gold Coast
Road, Papillion, NE 68046-4796 United States
Canadian Journal of Allergy and Clinical Immunology (CAN. J. ALLERGY
CLIN. IMMUNOL.) (Canada) 1999, 4/7 (318-330)
CODEN: CJAIF ISSN: 1203-844X
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 122

A quarter of the population is affected by allergic rhinitis, an inflammatory disorder of the nasal mucosa, with considerable economic impact and adverse effects on quality of life. Most patients experience typical nasal and ocular symptoms, but many individuals present with fatigue, headaches, psychosocial problems, or associated diseases (otitis media, sinusitis, asthma). This article reviews the pathophysiology of allergic rhinitis, the principles of diagnosis, and the pharmacological rationale for existing and emerging therapies. Also discussed are important safety issues regarding specific medications and allergen immunotherapy.

6/7/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

09341344 98046597
Pharmacokinetics of loratadine and pseudoephedrine following single and multiple doses of once- versus twice-daily combination tablet formulations in healthy adult males.
Kosoglou T; Radwanski E; Batra VK; Lim JM; Christopher D; Affrime MB
Clinical Pharmacology Department, Schering-Plough Research
Institute, Kenilworth, New Jersey, USA.



SCHERING-PLOUGH RESEARCH INSTITUTE

Clinical therapeutics (UNITED STATES) Sep-Oct 1997, 19 (5) p1002-12,
ISSN 0149-2918 Journal Code: CPE

Languages: ENGLISH

Document type: CLINICAL TRIAL; JOURNAL ARTICLE; RANDOMIZED
CONTROLLED TRIAL

The pharmacokinetic profiles of single and multiple doses of loratadine, ***descarboethoxyloratadine*** (DCL) (the major active metabolite of loratadine), and pseudoephedrine were determined in a randomized, open-label, two-way crossover study in 24 healthy men. Subjects received a single dose (day 1) and multiple doses (days 3 to 10) of a once-daily (QD) formulation of loratadine 10 mg in an immediate-release coating and ***pseudoephedrine*** ***sulfate*** 240 mg in an extended-release core (CLAR-ITIN-D 24 HOUR tablets), and a twice-daily (BID) formulation of loratadine 5 mg in an immediate-release coating and ***pseudoephedrine*** ***sulfate*** 120 mg, with 60 mg in an immediate-release coating and 60 mg in the barrier-protected core (CLARITIN-D 12 HOUR tablets) in study sessions, each separated by a 10-day washout period. Both regimens were safe and well tolerated. On day 1, plasma loratadine, DCL, and pseudoephedrine concentrations were higher following the QD formulation than following the BID formulation, as expected. On day 10, loratadine and DCL maximum plasma concentration (C_{max}) values were, on average, 87% and 35% higher, respectively, for the QD formulation than for the BID formulation; however, the values of the area under the plasma concentration-time curve from 0 to 24 hours (AUC₀₋₂₄) for loratadine and DCL were equivalent (90% confidence interval [CI]: 83% to 110% for loratadine; 90% to 107% for DCL). On day 10, pseudoephedrine C_{max} and AUC₀₋₂₄ values were equivalent (90% CI for C_{max}: 94% to 109%; for AUC: 91% to 106%) for the two formulations, and lower pseudoephedrine concentrations were observed from 16 to 24 hours with the QD formulation. Both loratadine/pseudoephedrine formulations produced equivalent loratadine and DCL AUC₀₋₂₄ values and equivalent pseudoephedrine C_{max} and AUC₀₋₂₄ values following multiple dosing. The lower pseudoephedrine concentrations in the evening with the QD formulation may minimize the potential for insomnia in patients when compared with the BID formulation.

6/7/6 (Item 6 from file: 155)
DIALOG(R) File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

08951860 97084436

Influence of food on the oral bioavailability of loratadine and pseudoephedrine from extended-release tablets in healthy volunteers.

Nomeir AA; Mojaverian P; Kosoglou T; Affrime MB; Nezamis J; Rodwanski E; Lin CC; Cayen MN Department of Drug Metabolism, Schering-Plough Research Institute, Kenilworth, NJ 07033, USA.

Journal of clinical pharmacology (UNITED STATES) Oct 1996, 36 (10)
p923-30, ISSN 0091-2700 Journal Code: HT9

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The effect of a high-fat breakfast on the bioavailability of the components of an extended-release tablet containing 10 mg loratadine in the immediate-release coating and 240 mg ***pseudoephedrine*** ***sulfate*** in the extended-release core was studied in 24 healthy



SCHERING-PLOUGH RESEARCH INSTITUTE

male volunteers in a single-dose, two-way crossover study. The drug was administered after a 10-hour overnight fast or within 5 minutes of consuming a standardized high-fat breakfast. Serial blood samples were collected over a 48-hour period, and plasma was analyzed for loratadine and its active metabolite ***descarboethoxyloratadine*** (DCL), and pseudoephedrine. For pseudoephedrine, maximum concentration (C_{max}) and area under the concentration-time curve extrapolated to infinity (AUC_{zero-infinity}) were similar after both treatments, indicating no relevant food effect on the bioavailability of pseudoephedrine. Also, the absorption profiles of pseudoephedrine (from Wagner-Nelson analysis) were similar for the fed and fasted treatments, indicating no apparent differences in absorption. Plasma concentration-time profiles and values for C_{max} and AUC_{zero-infinity} of DCL were similar for the two treatments, indicating no relevant food effect on the pharmacokinetics of DCL. In contrast, for loratadine, administration with food resulted in a significantly increased mean C_{max} (53%) and AUC from time zero to the final quantifiable sample (AUC_{if}) (76%). However, the resultant C_{max} and AUC of loratadine under fed conditions were well below those previously obtained at steady-state after multiple-dose administration of loratadine (40 mg/day) that were shown to be safe and well-tolerated in several clinical studies. The effect of food on the bioavailability and pharmacokinetic profiles of the components of a combination loratadine/pseudoephedrine extended-release tablet is not likely to be clinically significant.

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

SCHOLAR
DESLORATADINE + PSEUDOEPHEDRINE: CLINICAL STUDIES
2000/11/13

*Doc ID: 93200013B

Drug Name/ Number: DESLORATADINE (DESCARBOETHOXYLORATA034117

LORATADINE. A REVIEW OF RECENT FINDINGS IN PHARMACOLOGY, PHARMACOKINETICS, EFFICACY, AND SAFETY, WITH A LOOK AT ITS USE IN COMBINATION WITH PSEUDOEPHEDRINE.

CLINICAL REVIEW IN ALLERGY
11,89-110, 1993

ROMAN IJ
DANZIG MR

Study Type: clinical

experimental

in vitro

Abstract/Comment:

AUTHORS REVIEWED THE PRECLINICAL PHARMACOLOGY OF THE ANTIHISTAMINE, LORATADINE (LD), AND ITS PHARMACOKINETICS, CLINICAL PHARMACOLOGY, AND CLINICAL EFFICACY AND SAFETY IN TREATMENT OF SEASONAL AND PERENNIAL ALLERGIC RHINITIS, CHRONIC URTICARIA, SENILE PRURITUS, AND OTHER PRURITIC DERMATOSES. ALSO REVIEWED WAS THE CLINICAL USE OF A COMBINATION OF LD WITH THE DECONGESTANT, PSEUDOEPHEDRINE (PSEPH), IN ALLERGIC RHINITIS. ORAL LD WAS DESCRIBED AS A WELL ABSORBED AGENT WITH AN ELIMINATION HALF LIFE OF ABOUT 9 HRS; IT PRODUCED AN ACTIVE METABOLITE, DESCARBOETHOXY-LD (SCH 34117) (SCH), WITH A HALF LIFE OF 18 HRS, PERMITTING ONCE DAILY LD DOSING. SCH, IN TURN, WAS CONVERTED TO AN INACTIVE METABOLITE AND EXCRETED PRIMARILY IN THE URINE. TOPICAL LD PROVED SIMILAR TO ORAL LD IN INHIBITING ALLERGIC REACTIONS IN THE UPPER AIRWAYS. FROM THE STUDIES CITED, IT WAS CONCLUDED THAT LD WAS COMPARABLE IN EFFICACY TO OTHER 2ND-GENERATION HISTAMINE H1 RECEPTOR ANTAGONISTS, INCLUDING ASTEMIZOLE, AND ALSO THAT LD HAD ADVANTAGES IN BEING EFFECTIVE IN LOW DOSAGE, GIVEN ONCE DAILY, AND IN BEING LESS SEDATING THAN OTHER ANTIHISTAMINES, EG, CLEMASTINE AND CETIRIZINE. DATA FROM 9 EUROPEAN COUNTRIES SHOWED THAT THE INCIDENCE OF SPONTANEOUSLY REPORTED ADVERSE REACTIONS TO LD WAS VERY LOW, ABOUT 5.9/10,000 PT-YRS; THE MOST FREQUENTLY OCCURRING ADVERSE EFFECTS OF LD INCLUDED HEADACHE, FATIGUE, DIZZINESS, AND NAUSEA. LD DID NOT AFFECT ABILITY TO DRIVE AN AUTOMOBILE OR PILOT AN AIRPLANE, AND DID NOT IMPAIR LEARNING ABILITY IN CHILDREN. NO INTERACTION OF LD WITH ALCOHOL WAS NOTED, AND LD, LIKE OTHER 2ND-GENERATION ANTIHISTAMINES, DID NOT SHOW THE TENDENCY TO TACHYPHYLAXIS, WHICH HAD BEEN NOTED WITH 1ST-GENERATION ANTIHISTAMINES. THE COMBINATION OF LD + PSEPH WAS REPORTED TO BE MORE EFFECTIVE THAN LD ALONE IN SEASONAL ALLERGIC RHINITIS, WITH A LOWER INCIDENCE OF SIDE EFFECTS, NAMELY, DRY MOUTH (ATTRIBUTED TO PSEPH), FATIGUE, AND SEDATION, THAN THOSE CAUSED BY CHLORPHENIRAMINE + PSEPH. 61 REFERENCES

*Doc ID: 89163019C



SCHERING-PLOUGH RESEARCH INSTITUTE

Drug Name/ Number: DESLORATADINE (DESCARBOETHOXYLORATA034117
LORATADINE.

SCRIP'S NEW PROD REV
25, PP. 1,3,5-11,13-9,21-5,27,29-32, AUG. 1988

clinical

experimental

chemical

Study Type: in vitro

Abstract/Comment:

THE EFFICACY AND SAFETY OF LORATADINE (LD) WAS REVIEWED THROUGH THE USE OF CHEMICAL, PHARMACOKINETIC AND CLINICAL STUDIES. AMONG THESE WERE PHARMACOKINETIC STUDIES WHICH IDENTIFIED SCH 34117 AS A MAJOR METABOLITE OF LD AND AS AN ACTIVE ANTIHISTAMINE ITSELF. THIS REVIEW COMPARED LD WITH OTHER H1 RECEPTOR ANTAGONISTS, INCLUDING CHLORPHENIRAMINE (CP), NOTED EFFICACY OF LD IN SUPPRESSION OF WHEAL FORMATION COMPARED TO OTHER DRUGS, INCLUDING CP, LISTED PERIPHERAL AND CENTRAL EFFECTS AND DOSAGES. CLINICAL TRIALS COMPARED LD TO OTHER ANTIHISTAMINES FOR SEASONAL ALLERGIC RHINITIS. COMBINED EFFECTS WITH PSEUDOEPHEDRINE WERE NOTED. ADVERSE EFFECTS WERE FATIGUE, HEADACHE, DRY MOUTH, AND SOMNOLENCE. 48 REFERENCES

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

Debarment Certification

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

APPEARS THIS WAY
ON ORIGINAL



SCHERING-PLOUGH RESEARCH INSTITUTE

Memorandum of Telephone Facsimile Correspondence

Date: January 30, 2006
To: Beth DiDomenico
Fax No.: 908-740-2566
From: Anthony M. Zeccola
Subject: FDA Labeling Comments
Schering Corporation
NDA 21-313 – Clarinex D-12

Number of Pages: 3 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

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

Thank you.

{See appended electronic signature page}

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

We are reviewing your submission to NDA 21-313 dated January 27, 200, and have the following comments regarding the proposed labeling for Clarinex D-12. Please note that the review of this application is ongoing and additional comments may be sent as the review progresses.

The follow comments pertain to the package insert, revise as follows:

1. Line 293 (Precautions, General):

CLARINEX-D[®] 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic impairment and patients with renal impairment.

2. Line 475 (Dosage and Administration):

CLARINEX-D[®] 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic impairment and patients with renal impairment.

.....
Ui jt ljt !blsf qsf t f obypolpgbol f rfduspojdlf dpse!u bux bt !t jhof e!f rfduspojdbnz!boe
u jt !qbhf ljt lu f !n! bojg t ubypo!pgu f !f rfduspojdl!t jhobw/sf /
.....

! 0t 0

.....
Boui poz! [f ddpnb
204103117! 1: ; 53; 3: ! BN
DTP

.....
if rhdte



Labeling Review

DATE: January 30, 2006

TO: Division File System

FROM: Prasad Peri, Ph.D, Pharmaceutical Assessment Lead for Pulmonary and Allergy Products, DPA 1, Branch 2, ONDQA

SUBJECT: **Clarinox D 12 Hour (desloratadine 2.5 mg/pseudoephedrine sulfate 120 mg) (NDA 21-313) Evaluation of revised labels**

Schering Corporation submitted labels for cartons and container in the resubmission of NDA dated July 30, 2005. These labels were consistent with the previously approved labels for Clarinox Syrup. They all possessed a mark in between the letters C and L in the trade name. In addition, the Agency also requested that the applicant make the letters uniform and not as had been proposed.

The Agency asked the applicant to remove the mark because it was distracting to the legibility of the trade name. This was also discussed with DMETS internally (email correspondence between the project manager and DMETS representative) and the Agency came to the conclusion that the was indeed a distraction to the legibility of the trade name in the trade presentations. In a teleconference dated January 25th 2006, the Agency indicated this decision to the applicant.

The applicant agreed to remove the from all trade carton and container labels, and make the trade name text more uniform. Copies of the revised labeling have been provided in an email Amendment dated January 27, 2006. They were evaluated and found acceptable to this reviewer. See label on the next page.

In the same teleconference the Agency also indicated that they reconsidered the comment by the Agency for the applicant to revise the storage statement to indicate excursion permitted between 15-30 C. Hence Schering need not revise the storage statement for the word "to" to in the cartons and containers.

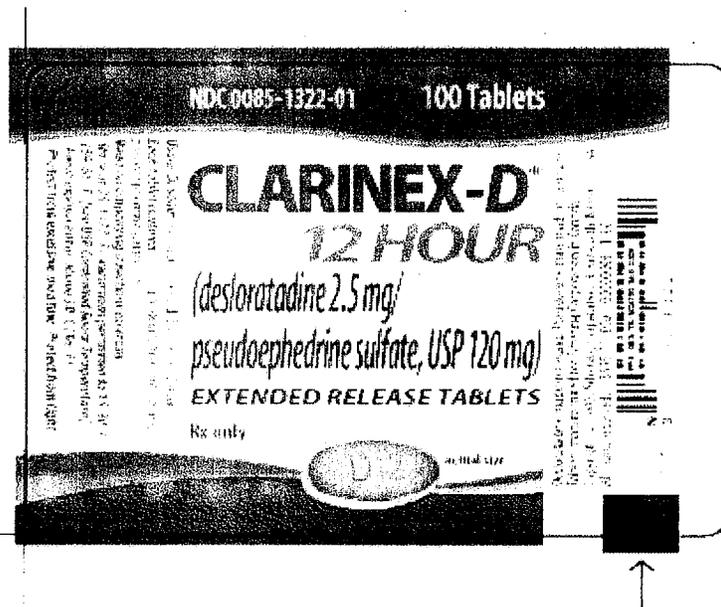
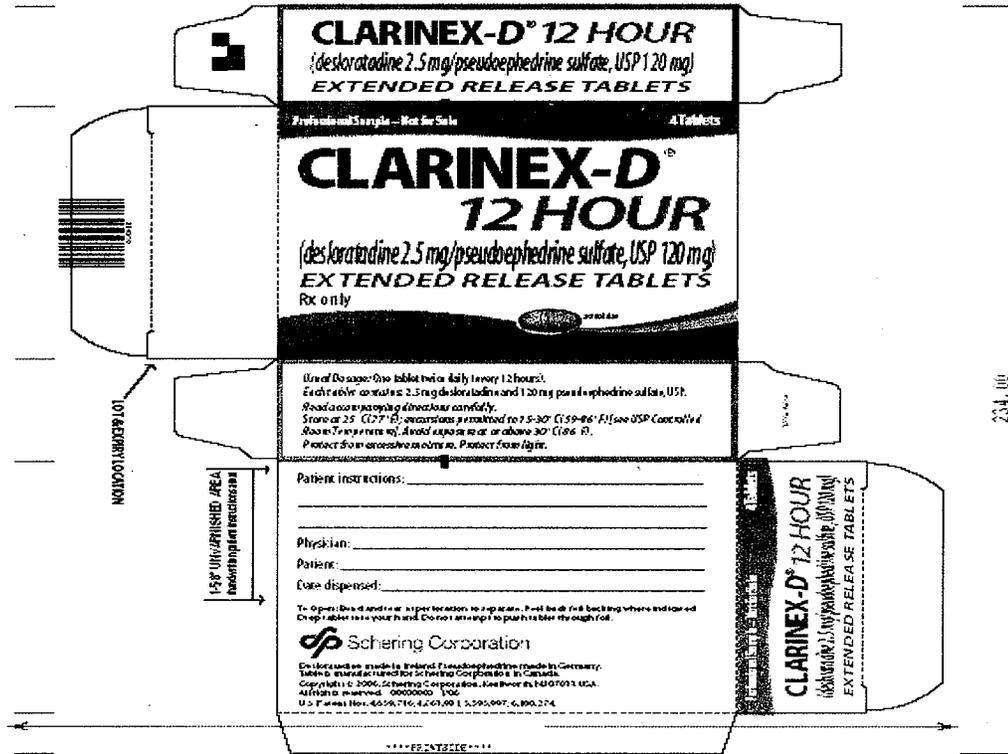
Evaluation: Adequate

Based on the current revised labeling there are no outstanding issues as noted by this reviewer.

The application may be approved from a CMC standpoint.



Labeling Review



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

/s/

Suong Tran
1/30/2006 09:44:34 AM
CHEMIST

for P. Prasad: acceptable labeling

Blair Fraser
1/30/2006 11:55:48 AM
CHEMIST

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: January 25, 2006
TIME: 4:20 AM
LOCATION: White Oak Conference Room 3201
APPLICATION: NDA 21-313 Clarinex D-12

FDA Representatives:

Sayed Al Habet, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Badrul Chowdhury, M.D., Ph.D., Division Director
Tayo Fadiran, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Michelle Safarik, DDMAC Reviewer
Sally Seymour, M.D., Medical Officer
Eugene Sullivan, M.D., Deputy Division Director
Denise Toyer, Deputy Director, DMETS
Anthony M. Zeccola, Regulatory Management Officer

Schering Corporation Representatives:

Beth DiDomenico, Regulatory Affairs
Robert Kowalski, Regulatory Affairs
David De Sousa, Regulatory Affairs
Maryjane Boyle, Labeling
Abbey Abraham, Labeling
Yvette Henderson, Labeling
Robert Mullinnix, Regulatory Affairs /CMC
Valerie Cotler, Regulatory Promotion & Advertising
Karen Yutsus, Media Services
Richard Lorber, Clinical
David Cutler, Clinical Pharmacology

Background

This labeling teleconference was held in response to label comments provided by the Agency via telephone facsimiles dated December 27, 2005 and January 13, 2006. These facsimiles included suggested modifications as discussed below.

Schering agreed to submit the following revisions to the carton and container labeling:

1. Revise the Established name to delete the . Such graphics are distracting to the name. This may apply to all your approved dosage forms.

2. Revise the Established name to delete the ~~text~~ and make it a uniform text.

Schering noted several examples of existing product labels (including other Clarinex products) with similar graphics on their carton and container labeling. Dr. Sullivan stated that the Division is aware of these products and that based on the recommendation of the Division of Medication Errors and Technical Services (DMETS), the Division of Pulmonary and Allergy Products will be requesting that this type of graphic be removed from all carton and container labeling within our area of responsibility. These changes will be requested at "next printing", which will also apply to the other Clarinex products. While DMETS recommended this change to the carton and container labeling on the basis of safety as a means of reducing the likelihood of selection error, they have no objection to this type of graphic in promotional materials. DDMAC agreed with this position.

Schering agreed to submit the following revisions to the package insert, revise as follows:

4. Lines 41 – 43: (Clinical Pharmacology section):
... Results of a radiolabeled tissue distribution study in rats and a radioligand H1-receptor binding study in guinea pigs showed ~~that~~ that desloratadine does not readily cross the blood brain barrier.
5. Lines 231-232 (Effect on QTc section):
[New paragraph] Single dose ~~administration~~ administration of desloratadine did not alter the corrected QT interval (QTc) in rats (up to 12 mg/kg, oral), or guinea pigs (25 mg/kg, intravenous).
6. Lines 334 – 336 (Carcinogenesis section):
The estimated desloratadine and ~~metabolite~~ metabolite exposures in mice at these doses were 12 and 27 times, respectively, the AUC in humans at the recommended daily oral dose.
7. Line 153 (Special Populations, Renally Impaired section):
CLARINEX-D® 12 HOUR Extended Release Tablets should generally be avoided in patients with renal impairment: ~~_____~~
8. Line 293 (Precautions, General):
~~_____~~
~~_____~~
~~_____~~
~~_____~~

9. Line 475 (Dosage and Administration):

~~_____~~
~~_____~~
~~_____~~

With regard to items 7, 8 and 9 above, Schering noted that the current labels of other currently marketed antihistamine/pseudoephedrine combination products (including Clarinex D-24) recommend a reduced dose in patients with renal impairment. Dr. Sullivan noted that there are no data available to establish the appropriate dosing interval in patients with renal impairment. In the absence of data establishing the safety and efficacy of a reduced dose/dosing interval for this type of combination product in this population, it is the Division's position that all antihistamine/pseudoephedrine combination product labels should be labeled in a similar and consistent manner.

Addendum to Teleconference Minutes

Schering responded to the teleconference with a submission on January 27, 2006 which contained revised labeling as noted above. Following review of the submission by the Division, it was recommended that the items 7 and 8 above be modified to read "...patients with hepatic impairment and patients with renal impairment..." This recommendation was communicated to Schering via facsimile dated January 30, 2006.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Anthony Zeccola
1/30/2006 12:42:06 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: January 13, 2006
To: Beth DiDomenico
Fax No.: 908-740-2566
From: Anthony M. Zeccola
Subject: FDA Labeling Comments
Schering Corporation
NDA 21-313 – Clarinex D-12

Number of Pages: 3 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

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

Thank you.



Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

We are reviewing your submission to NDA 21-313 dated July 29, 2005, received August 1, 2005, and have the following comments regarding the proposed labeling for Clarinex D-12. Please note that the review of this application is ongoing and additional comments may be sent as the review progresses.

As discussed during telephone conversations which took place on December 27, 2005 and January 10, 2006, the following comments pertain to the labeling associated with the cartons, container, blister and immediate container labeling:

1. Revise the Established name to delete the " ——— ". Such graphics are distracting to the name. This may apply to all your approved dosage forms.
2. Revise the Established name to delete the wavy text and make it a uniform text.
3. Revise the text for the Storage statement on all labels to state "Excursions permitted ~~—————~~ 15-30°C".

The follow comments pertain to the package insert, revise as follows:

4. Lines 41 – 43: (Clinical Pharmacology section):
... Results of a radiolabeled tissue distribution study in rats and a radioligand H1-receptor binding study in guinea pigs showed ~~—————~~ that desloratadine does not readily cross the blood brain barrier.
5. Lines 231-232 (Effect on QTc section):
[New paragraph] Single dose ~~—————~~ administration of desloratadine did not alter the corrected QT interval (QTc) in rats (up to 12 mg/kg, oral), or guinea pigs (25 mg/kg, intravenous).
6. Lines 334 – 336 (Carcinogenesis... section):
The estimated desloratadine and ~~—————~~ metabolite exposures in mice at these doses were 12 and 27 times, respectively, the AUC in humans at the recommended daily oral dose.

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

/s/

Anthony Zeccola
1/13/2006 10:25:45 AM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: January 13, 2006
To: Beth DiDomenico
Fax No.: 908-740-2566
From: Anthony M. Zeccola
Subject: FDA Request for Information
Schering Corporation NDA 21-313 – Clarinex D-12

Number of Pages: 3 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

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

Thank you.

(An appended electronic signature page)

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

We are reviewing your submission to NDA 21-313 dated July 29, 2005, received August 1, 2005, and have the following information request:

Justify your proposed labeling regarding dose adjustment of Clarinex D 12 Hour in patients with renal impairment (one tablet once a day). Submit a summary of pharmacokinetic data for pseudoephedrine or literature references that support your recommendation.

Justify your proposed labeling regarding avoiding use of Clarinex D 12 Hour in patients with hepatic impairment. Submit a summary of pharmacokinetic data for pseudoephedrine or literature references that support your recommendation.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Anthony Zeccola
1/13/2006 01:27:24 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: December 27, 2005

To: Beth DiDomenico Senior Manager and Liaison Global Regulatory Affairs	From: Anthony Zeccola Senior Regulatory Management Officer
Company: Schering Corporation	Division of Pulmonary and Allergy Drug Products
Fax number: 908-740-4131	Fax number: 301-796-1318
Phone number: 973-476-2742	Phone number: 301-796-1219

Subject: NDA 21-313

Total no. of pages including cover: 3

Comments:

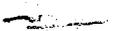
Document to be mailed: YES X NO

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

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-1050. Thank you.

NDA 21-313
Clarinet D-12

We are reviewing your submission dated July 29, 2005, and we have the following comments relating to the container and carton labeling. Please note that the review of this submission is ongoing and that additional container and carton label comments may be sent as the review progresses.

Remove the graphic  above the proprietary name as it obscures and crowds the proprietary name. In addition, by increasing the prominence of the proprietary name, the presence of the  decreases the relative prominence of the established name. See 21 CFR 201.15(a) (6) and 21 CFR 201.10(g) (2).

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Anthony Zeccola
12/27/2005 01:36:22 PM
CSO