CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-786 /S005

Trade Name: Allegra-D

Generic Name: fexofenadine HCl/pseudoephedrine

Sponsor: Aventis Pharmaceuticals

Approval Date: December 1, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786 /S005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786 /S005

APPROVAL LETTER

NDA 20-786/S-005

Hoechst Marion Roussel, Inc.
Marion Park Drive
P. O. Box 9627
Kansas City, MO 64134-0627

Attention: J. Michael Nicholas, Ph.D.
Director, US Drug Regulatory Affairs

Dear Dr. Nicholas:

Please refer to your supplemental new drug application dated October 29, 1998, received October 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra-D (fexofenadine HCl/pseudoephedrine HCl) Extended-release Tablets.

Reference is also made to your submissions dated November 10, 1998, and May 7, November 12 and 22, 1999. Your submission of November 22, 1999, constituted a complete response to our November 9, 1999, action letter.

This supplemental new drug application provides for a change in fexofenadine HCl dissolution specifications in the drug product.

We have completed the review of this supplemental application, as amended, and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products,
HFD-570

DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-786
HFD-570/Div. Files
HFD-570/G.Trout
HFD-570/Rogers
HFD-570/Choi
HFD-570/Poochikian
HFD-570/Uppoor
HFD-095/DDMS-IMT
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: GST/November 29, 1999
Initialed by: Barnes/11-30-99
Rogers/11-30-99
Poochikian/11-30-99
Chiu/11-30-99
final: Trout/12-1-99
filename: n:\staff\troutg\20786ap

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786 /S005

APPROVABLE LETTER

NDA 20-786/S-005

Hoechst Marion Roussel
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134

Attention: J. Michael Nicholas, Ph.D.
Director, US Drug Regulatory Affairs

Dear Dr. Nicholas:

Please refer to your supplemental new drug application dated October 29, 1998, received October 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra-D (fexofenadine HCl/pseudoephedrine HCl) Extended Release Tablets.

We acknowledge receipt of your submissions dated November 10, 1998 and May 7, 1999. Your submission of May 7, 1999, constituted a complete response to our December 11, 1998, action letter.

This supplement proposes [redacted] for fexofenadine HCl dissolution, and a change in fexofenadine HCl dissolution specifications for the drug product.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to adopt the following dissolution specification and conditions for fexofenadine HCl dissolution: Q = [redacted]% at [redacted] minutes and Q = [redacted]% at [redacted] minutes with USP II Apparatus, 37^{0}C, 900 mL of 0.001 N HCl.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-786
HFD-570/Div. Files
HFD-570/G.Trout
HFD-570/Rogers
HFD-570/Poochikian
HFD-570/Choi
HFD-570/Uppoor
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: GST/November 9, 1999
Initialed by: Barnes/11-9-99
Choi/11-9-99
Uppoor/11-9-99
Rogers/11-9-99
final: GTrout/11-9-99
filename: n:\staff\troutg\20786s005

APPROVABLE (AE)

NDA 20-786/S-005

DEC 11 1998

Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-5000

Attention: Dhiren N. Shah, Ph.D.
Director-CMC, US Drug Regulatory Affairs

Dear Dr. Shah:

Please refer to your supplemental new drug application dated October 29, 1998, received October 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra-D Tablets (fexofenadine HCl/pseudoephedrine HCl) Extended-release Tablets.

We acknowledge receipt of your submission dated November 10, 1998.

This supplement proposes a change in the fexofenadine HCl dissolution specifications for the drug product, and requests allowing the [redacted] of drug product [redacted] for fexofenadine HCl dissolution.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). We have the following comments and requests for information.

1. [redacted]

   Duplicates of all letters sent in response to this comment should be sent to both the FDA Kansas City District Office and this Division.

2. [redacted]

3. Since there is an [redacted], additional batches of [redacted] stability testing. This request is based upon the existence of both the proposed and implemented changes in your manufacturing process. [redacted]

state of the Allegra-D manufacturing process. The extent of additional testing needed will be reevaluated based on the data obtained in response to comment 2. above.

4. [redacted] should be thoroughly investigated and reports submitted to the NDA.

5. If and when your supplement dated June 19, 1998 (S-002 which supports changes in pseudoephedrine HCl raw material specifications and test methods) is approved, submit complete dissolution profiles [redacted] approval. These profiles should be compared to [redacted] dissolution profiles. The fexofenadine dissolution specifications [redacted] The dissolution data in your October 29 and November 10, 1998 submissions were not evaluated to support a [redacted] since you have not provided sufficient data at your [redacted]

6. If the dissolution profiles in the submission requested above are different than those of the [redacted] once the product manufacturing has been finalized, a [redacted] may be necessary to [redacted] fexofenadine dissolution specifications (as discussed previously in the teleconference dated April 24, 1998).

7. In the future, we request that you provide dissolution data on [redacted] in addition to the maximum and minimum values. This will enable evaluation of the number [redacted] that are at or near the minimum dissolution specification.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, contact Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products (HFD-570)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-786
HFD-570/Div. Files
HFD-570/G.Trout
HFD-570/Rogers
HFD-570/Poochikian
HFD-870/Uppoor
HFD-95/DDMS
HFD-820/DNDC Division Director
DISTRICT OFFICE
HFR-SW300/Kansas District Office/AMehl

GST 12/10/98
CVR 12/11/98

Drafted by: GST/December 8, 1998

Initialed by: Schumaker/12-8-98
Rogers/12-9-98
Poochikian (with revisions)/12-9-98

Final: LGrimshaw/12-10-98
filename: n:\staff\troutg\20786let

NOT APPROVABLE (NA)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786 /S005

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

	1. ORGANIZATION HFD-570 DPDP	2. NDA NUMBER 20-786
3. NAME AND ADDRESS OF APPLICANT (City and State) Hoechst Marion Roussel, Inc. PO Box 9627 Kansas City, MO 64134-0627	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER: SCS-005 DATE: 10/29/98
6. NAME OF DRUG Allegra-D™ Extended-release Tablets	7. NONPROPRIETARY NAME fexofenadine hydrochloride and pseudoephedrine hydrochloride extended-release tablets	
8. SUPPLEMENT PROVIDES FOR: Support a change in fexofenadine HCl dissolution specifications in the drug product.		9. AMENDMENT(S), REPORT(S), ETC. SCS-005 BC 11/10/98 SCS-005 BC 5/7/99 SCS-005 BC* 11/12/99 SCS-005 AC* 11/22/99 *Subject of this review
10. PHARMACOLOGICAL CATEGORY Histamine H_1-receptor antagonist/decongestant for treatment of symptoms associated with seasonal allergic rhinitis	11. HOW DISPENSED RX X OTC __	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) Extended-release Tablet	14. POTENCY 60 mg immediate-release fexofenadine HCl and 120 mg extended-release pseudoephedrine HCl	
15. CHEMICAL NAME AND STRUCTURE (±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-dimethylbenzeneacetic acid HCl and [S-(R*,R*)]-α-[1-(Methylamino)ethyl]-benzenemethanol HCl (for structures see USAN)		16. RECORDS AND REPORTS CURRENT REVIEWED YES_ NO_

17. COMMENTS: See attached

cc:
Orig. NDA #20-786
HFD-570/div. File
HFD-570/BRogers/11/26/99
HFD-570/GPoochikian
HFD-570/GTrout
HFD-870/RUppoor
R/D Init. by:_____
F/T by: B. Rogers11/26/99
doc # 20786.B05.DOC

18. CONCLUSIONS AND RECOMMENDATIONS: The supplement is APPROVED

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Brian D. Rogers, Ph.D.		11/26/99

6 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-786
5005

DEC 10 1998

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPDP	20-786

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER	DATE
Hoechst Marion Roussel, Inc. PO Box 9627 Kansas City, MO 64134-0627		SCS-005	10/29/98

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Allegra-D™ Extended-release Tablets	fexofenadine hydrochloride and pseudoephedrine hydrochloride extended-release tablets

8. SUPPLEMENT PROVIDES FOR:	9. AMENDMENT(S), REPORT(S), ETC.
1. Allow [redacted] fexofenadine HCl dissolution. 2. Support a change in fexofenadine HCl dissolution specifications in the drug product.	SCS-005 BC 11/10/98

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
Histamine H_1-receptor antagonist/decongestant for treatment of symptoms associated with seasonal allergic rhinitis	RX X OTC _	

13. DOSAGE FORM(S)	14. POTENCY
Extended-release Tablet	60 mg immediate-release fexofenadine HCl and 120 mg extended-release pseudoephedrine HCl

15. CHEMICAL NAME AND STRUCTURE	16. RECORDS AND REPORTS
(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-dimethylbenzeneacetic acid HCl and [S-(R*,R*)]- -[1-(Methylamino)ethyl]-benzenemethanol HCl (for structures see USAN)	CURRENT YES_ NO_ REVIEWED YES_ NO_

17. COMMENTS: See attached

cc:
Orig. NDA #20-786
HFD-570/div. File
HFD-570/BRogers/11/27/98
HFD-570/GPoochikian/ASchroeder ACS for GP 12/10/98
HFD-570/GTrout
HFR-SW300/KAN-DO/AMehl
HFD-870/RUppoor
R/D Init. by:_____
F/T by: B. Rogers/11/27/98
doc # 20786.S05.DOC

(Note that this supplement has been thoroughly discussed with Dr. Poochikian.)

18. CONCLUSIONS AND RECOMMENDATIONS: The supplement is NOT APPROVED. The PM should include the comments in the *Draft Letter to the Applicant* portion of this review in the NA letter.

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Brian D. Rogers, Ph.D.	Brian D. Rogers	11/27/98

DEC - 7 1998

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPDP	20-786

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER	DATE
Hoechst Marion Roussel, Inc. PO Box 9627 Kansas City, MO 64134-0627		SCS-005	10/29/98

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Allegra-D™ Extended-release Tablets	fexofenadine hydrochloride and pseudoephedrine hydrochloride extended-release tablets

8. SUPPLEMENT PROVIDES FOR:	9. AMENDMENT(S), REPORT(S), ETC.
1. Allow [redacted] for fexofenadine HCl dissolution. 2. Support a change in fexofenadine HCl dissolution specifications in the drug product.	SCS-005 BC 11/10/98

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
Histamine H_1-receptor antagonist/decongestant for treatment of symptoms associated with seasonal allergic rhinitis	RX X OTC __	

13. DOSAGE FORM(S)	14. POTENCY
Extended-release Tablet	60 mg immediate-release fexofenadine HCl and 120 mg extended-release pseudoephedrine HCl

15. CHEMICAL NAME AND STRUCTURE	16. RECORDS AND REPORTS
(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-dimethylbenzeneacetic acid HCl and [S-(R*,R*)]- -[1-(Methylamino)ethyl]-benzenemethanol HCl (for structures see USAN)	CURRENT YES_ NO_ REVIEWED YES_ NO_

17. COMMENTS: See attached

cc:
Orig. NDA #20-786
HFD-570/div. File
HFD-570/BRogers/11/27/98
HFD-570/GPoochikian
HFD-570/GTrout
R/D Init. by: _____
F/T by: B. Rogers/11/27/98
doc # 20786.S05.DOC

HFD-870/RUppoor
HFR-SW300/KAN-DO/AMehl
acs for GP 12/7/98 (Note that this review was previously discussed with Dr. Poochikian.)

18. CONCLUSIONS AND RECOMMENDATIONS: The supplement is NOT APPROVED. The PM should include the comments in the *Draft Letter to the Applicant* portion of this review in the NA letter.

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Brian D. Rogers, Ph.D.	Brian D. Rogers	11/27/98

9 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-786
5002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786 /S005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
KANSAS CITY DISTRICT

Memorandum

10/20/98

F99-016

cc: HFD-570
HFD-320

Date 10/19/98

From Alan E. Mehl
Acting NDA Field Alert Monitor.

Subject NDA 20-786 Fexofenadine HCL/Pseudoephedrine Extended Release, 60 mg/120mg.

To

On 10/19/98, I received a telephone call from William (Rick) Lohrey, Manager of Quality Management of Hoechst Marion Roussel (HMR). In addition, Ernie Parente, Director Q.C., and Al Kintrup, were also HMR representatives attending the phone call. Mr. Lohrey wanted to inform failed dissolution test result for the interval of the An investigation performed by HMR has confirmed the Out-of-Specification result. failed the Q value of % dissolved in minutes.

Mr. Lohrey stated this failure was He stated products are normally approved at the normal Q value of % dissolved in minutes, but CDER had imposed the more Those studies are currently ongoing. HMR has requested a meeting with to discuss the stability failure. HMR stated they would notify the proper CDER personnel or reviewing chemist. I stated would contact the FDA review chemist after HMR has completed their proper notifications.

---

time unless otherwise directed. HMR feels a this Time.

Shirley J. Berryman, Investigator,
KAN-DO Drug Team

0: Roger Gregorio HFD-336
cc: MHW
cc:

ORIGINAL NDA SUPP AMEND SCS-005 (BC)

Hoechst Marion Roussel

November 10, 1998

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000
U.S. Web site: www.hmri.com

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary Drug Products
(HFD-570)
5600 Fishers Lane
Rockville, MD 20857

Attention: Mr. L Cobbs, CSO

Sent via Telefax: (301) 827-1271

Re: NDA 20-786/S-005
Allegra-D Tablets
(fexofenadine HCl/pseudoephedrine HCl)

Amendment to Supplement S-005:
Chemistry, Manufacturing, and Controls
Response to FDA's Request and Report
on [redacted] OOS

Dear Mr. Cobbs:

Please refer to our telephone conversation on November 6, 1998 regarding the above-referenced supplement to the New Drug Application which was submitted on October 29, 1998. In that phone conversation you requested the following information on the Out of Specification (OOS) [redacted] Allegra-D tablets:

- History of stability
- [redacted] dissolution data
- All stability time points
- A statement from HMR as how the investigation is going and what is the company doing to address this issue and a proposal to address the issue

The purpose of this submission, in duplicate, is to (a) respond (attachment 1) to the above four requests and (b) to provide information (attachment 2) [redacted] out of specification [redacted] Allegra-D tablets. Please note that [redacted] out of specification is also due to the failure to meet the fexofenadine dissolution specification of Q=[redacted] % at [redacted] minutes.

In conclusion, HMRI requests the agency (a) to allow us to keep [redacted] and (b) the fexofenadine dissolution specification from Q=[redacted] % at [redacted] minutes to Q=[redacted] % at [redacted] minutes and Q=[redacted] % at [redacted] minutes in order to avoid similar occurrences in the future.

Please note that HMRI is available to meet with the agency at any time to discuss this issue, if necessary.

Hoechst

Pursuant to 21 CFR 314.71(b), an exact copy of this submission has been sent to the Kansas City District Office.

A paper copy of this Amendment will be sent to the NDA in the near future.

Should you have any comments or questions, please contact the undersigned at (816) 966-7104.

Sincerely,
Hoechst Marion Roussel, Inc.
Mail Station H3-M2112

FOR DNS

Dhiren N. Shah, Ph.D.
Director - CMC, US Drug Regulatory Affairs