CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20872

CHEMISTRY REVIEW(S)

Cobbs

APR 5 1999

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-872 **CHEM. REVIEW #** 1 **REVIEW DATE:**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	July 17, 1998	July 17, 1998	August 4, 1998
AMENDMENT	July 30, 1998	August 3, 1998	August 15, 1998
	November 20, 1998	November 23, 1998	November 24, 1998
	November 23, 1998	November 24, 1998	November 24, 1998
	December 10, 1998	December 11, 1998	December 11, 1998
	December 16, 1998	December 16, 1998	December 16, 1998
CORRESPONDENCE	November 4, 1998	November 5, 1998	November 6, 1998
	November 9, 1998	November 10, 1998	November 10, 1998
	December 16, 1998	December 18, 1998	December 19, 1998

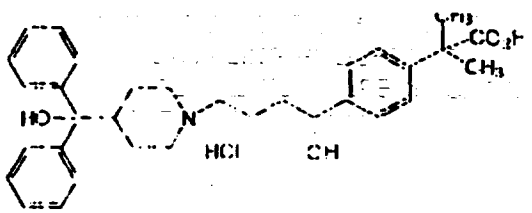
NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel, Inc.
P.O.Box 9627
Kansas City, MO 641344-0627

DRUG PRODUCT NAME

Proprietary:	Allegra Tablet®
Nonproprietary/USAN:	Fexofenadine HCl
Code Name/#:	MDL 16,455A
Chem.Type/Ther.Class:	1S

PHARMACOL. CATEGORY/INDICATION: Histamine H_1-receptor antagonist
DOSAGE FORM: Film coated tablets
STRENGTHS: 30, 60, and 180 mg tablets
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethylbenzeneacetic acid hydrochloride (MDL 16,455A)

Molecular Formula: $C_{32}H_{39}NO_4 \cdot HCl$
Molecular Weight 538.13

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed
		HDPE Bottles:	Adequate	C. Bertha (5/2/96)
		HDPE Bottles:	Adequate	C. Bertha (3/15/96)
		HDPE Bottles	Adequate	H. Khorshidi (3/3/99)
		Closure	Adequate	S. Kim (12/5/95)
		Closure	Adequate	C. Bertha (3/13/96)
		HDPE Resin	Inadequate	H. Khorshidi (3/3/99)
		Resin	Adequate	C. Bertha (7/2/97) Linda Ng (11/18/92)
		(Foil Blister)	Adequate	H. Khorshidi (3/3/99)
		HDPE bottles	Adequate	S. Zimmerman (9/3/98)
		Push through foil (foil blister)	Adequate	S. Zimmerman (7/17/98)
		Pigment Blends	Adequate	H. Khorshidi (3/3/99)
		I closure of HDPE bottles	Adequate	C. Bertha (3/17/96)

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND			MDL 16,455A
IND			
IND			
NDA	20-625	HMR	Allegra Capsules (approval date: 7/25/96)
NDA	20-786	HMR	Allegra-D tablets (approval date: 12/24/97)

CONSULTS:

Consult	Date forwarded	Status	Comments
EER	10/5/98	Acceptable (All sites)	Result reported to be acceptable by the Office of Compliance on 12/21/1998.
Pharmacology, HFD-570	1/21/99	Acceptable 3/12/99	Qualification of impurities; MDL 120,038, MDL 46,619 and MDL 46,016 at specified level of NMT % (in drug substance) was requested.
Bio-pharm HFD-570	1/21/99	Pending	Clarification is requested on acceptance and appropriateness of 0.001M HCl as dissolution media.
Statistical analysis, HFD-570	2/17/99	Pending	Upon receipt of updated stability data, a statistical analysis for estimation of shelf-life will be requested.

REMARKS/COMMENTS

1. Establishment evaluation requests (EER) has been forwarded on 10/5/98. Results reported to be acceptable for all proposed sites by the Office of Compliance on 12/21/98.

2. The Agency's laboratories will be validating the methods once all method related issues are resolved.

3. DMF # is inadequate in support of NDA 20-872. Review of this DMF will be done once we receive an updated LOA from the DMF holder.

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not approvable from standpoint of chemistry, manufacturing, and controls. Deficiencies are detailed in the accompanying review notes and summarized in the attached chemistry lists of deficiencies and comments letter. These deficiencies should be forwarded to the applicant by the CSO.

cc:
Org. NDA 20-872
HFD-570/Division File
HFD-570/HKhorshidi
HFD-570/GPoochikian
HFD-570/LCobbs

/S/ 3/26/99
Hossein S. Khorshidi, Ph.D. Review Chemist

R/D Init by: 4/7/99

filename: N20-872/Chemistry/99-03-26. Rev

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manufacturing and Controls

Chem Review #1

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

JUL 15 1999

NDA #: 20-872 **CHEM. REVIEW #** 2 **REVIEW DATE:** July 14, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	July 17, 1998	July 17, 1998	August 4, 1998
AMENDMENT	July 30, 1998	August 3, 1998	August 15, 1998
	November 20, 1998	November 23, 1998	November 24, 1998
	November 23, 1998	November 24, 1998	November 24, 1998
	December 10, 1998	December 11, 1998	December 11, 1998
	December 16, 1998	December 16, 1998	December 16, 1998
	***May 6, 1999**	**May 7, 1999**	**May 7, 1999**
	***May 13, 1999**	**May 14, 1999**	**May 14, 1999**
	***May 21, 1999**	**May 24, 1999**	**May 24, 1999**
	***May 26, 1999**	**May 27, 1999**	**May 28, 1999**
	***June 11, 1999**	**June 14, 1999**	**June 15, 1999**
CORRESPONDENCE	November 4, 1998	November 5, 1998	November 6, 1998
	November 9, 1998	November 10, 1998	November 10, 1998
	December 16, 1998	December 18, 1998	December 19, 1998

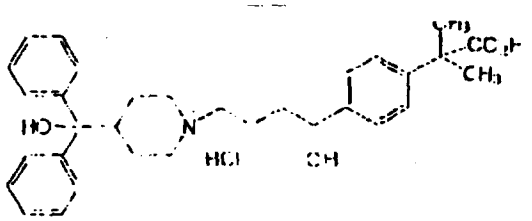
*** Subject of this review**

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel, Inc.
P.O.Box 9627
Kansas City, MO 641344-0627

DRUG PRODUCT NAME

Proprietary:	Allegra Tablet®
Nonproprietary/USAN:	Fexofenadine HCl
Code Name/#:	MDL 16,455A
Chem.Type/Ther.Class:	1S
PHARMACOL. CATEGORY/INDICATION:	Histamine H_1-receptor antagonist
DOSAGE FORM:	Film coated tablets
STRENGTHS:	30, 60, and 180 mg tablets
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	**_X_ Rx ___ OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethylbenzeneacetic acid hydrochloride (MDL 16,455A)

Molecular Formula: $C_{32}H_{39}NO_4 \cdot HCl$
Molecular Weight 538.13

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed
		HDPE Bottles:	Adequate	C. Bertha (5/2/96)
		HDPE Bottles:	Adequate	C. Bertha (3/15/96)
		HDPE Bottles	Adequate	H. Khorshidi (3/3/99)
		Closure	Adequate	S. Kim (12/5/95)
		Closure	Adequate	C. Bertha (3/13/96)
		HDPE Resins	Adequate	H. Khorshidi (6/30/99)
		Resin	Adequate	C. Bertha (7/2/97) Linda Ng (11/18/92)
		(Foil Blister)	Adequate	H. Khorshidi (3/3/99)
		HDPE bottles	Adequate	S. Zimmerman (9/3/98)
		Push through foil (foil blister)	Adequate	S. Zimmerman (7/17/98)
		Pigment Blends	Adequate	H. Khorshidi (3/3/99)
		closure of HDPE bottles	Adequate	C. Bertha (3/17/96)

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND			MDL 16,455A
IND			
IND			
NDA	20-625	HMR	Allegra Capsules (approval date: 7/25/96)
NDA	20-786	HMR	Allegra-D tablets (approval date: 12/24/97)

CONSULTS:

Consult	Date forwarded	Status	Comments
EER	10/5/98	Acceptable (All sites)	Result reported to be acceptable by the Office of Compliance on 12/21/1998.
Pharmacology, HFD-570	1/21/99	Acceptable 3/12/99	Qualification of impurities; MDL 120,038, MDL 46,619 and MDL 46,016 at specified level of NMT .% (in drug substance) was requested.
Bio-pharm HFD-570	1/21/99	Acceptable 6/25/99	Clarification is requested on acceptance and appropriateness of 0.001M HCl as dissolution media.
Statistical analysis, HFD-570	6/25/99	Acceptable 7/12/99	Statistical analysis for acceptance of the proposed shelf-life (18 months for 30 mg tablets and 30 months for 60 mg, 180 mg tablets) was requested.

REMARKS/COMMENTS

1. Establishment evaluation requests (EER) has been forwarded on 10/5/98. Results reported to be acceptable for all proposed sites by the Office of Compliance on 12/21/98.

2. The Agency's laboratories will be validating the methods once all method related issues are resolved.

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not approvable from standpoint of chemistry, manufacturing, and controls. Deficiencies are detailed in the accompanying review notes and summarized in the attached chemistry lists of deficiencies and comments letter. These deficiencies should be forwarded to the applicant by the CSO.

cc:
Org. NDA 20-872
HFD-570/Division File
HFD-570/HKhorshidi
HFD-570/GPoochikian
HFD-570/LCobbs

/S/ 7/14/99

Hossein S. Khorshidi, Ph.D. Review Chemist

R/D Init by: 7/15/99

filename: N20-872/Chemistry/99-07-14. Rev

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Manufacturing and Controls

Chem Review #2

Coobs
OCT 7 1999

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-872 **CHEM. REVIEW #** 3 **REVIEW DATE:** Sept 22, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	July 17, 1998	July 17, 1998	August 4, 1998
AMENDMENT	July 30, 1998	August 3, 1998	August 15, 1998
	November 20, 1998	November 23, 1998	November 24, 1998
	November 23, 1998	November 24, 1998	November 24, 1998
	December 10, 1998	December 11, 1998	December 11, 1998
	December 16, 1998	December 16, 1998	December 16, 1998
	May 6, 1999	May 7, 1999	May 7, 1999
	May 13, 1999	May 14, 1999	May 14, 1999
	May 21, 1999	May 24, 1999	May 24, 1999
	May 26, 1999	May 27, 1999	May 28, 1999
	June 11, 1999	June 14, 1999	June 15, 1999
	***August 26, 1999**	**August 27, 1999**	**August 30, 1999**
CORRESPONDENCE	November 4, 1998	November 5, 1998	November 6, 1998
	November 9, 1998	November 10, 1998	November 10, 1998
	December 16, 1998	December 18, 1998	December 19, 1998

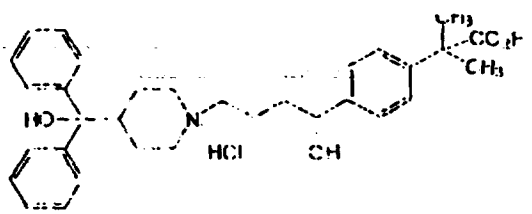
* Subject of this review

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel, Inc.
P.O.Box 9627
Kansas City, MO 641344-0627

DRUG PRODUCT NAME

Proprietary:	Allegra Tablet®
Nonproprietary/USAN:	Fexofenadine HCl
Code Name/#:	MDL 16,455A
Chem.Type/Ther.Class:	1S
PHARMACOL. CATEGORY/INDICATION:	Histamine H_1-receptor antagonist
DOSAGE FORM:	Film coated tablets
STRENGTHS:	30, 60, and 180 mg tablets
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-4-[1-Hydroxy-4-[4 (hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethylbenzeneacetic acid hydrochloride (MDL 16,455A)

Molecular Formula: $C_{32}H_{39}NO_3 \cdot HCl$
Molecular Weight 538.13

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed
		HDPE Bottles:	Adequate	C. Bertha (5/2/96)
		HDPE Bottles:	Adequate	C. Bertha (3/15/96)
		HDPE Bottles	Adequate	H. Khorshidi (3/3/99)
		Closure	Adequate	S. Kim (12/5/95)
		Closure	Adequate	C. Bertha (3/13/96)
		HDPE Resins	Adequate	H. Khorshidi (6/30/99)
		Resin	Adequate	C. Bertha (7/2/97) Linda Ng (11/18/92)
		(Foil Blister)	Adequate	H. Khorshidi (3/3/99)
		HDPE bottles	Adequate	S. Zimmerman (9/3/98)
		Push through foil (foil blister)	Adequate	S. Zimmerman (7/17/98)
		Pigment Blends	Adequate	H. Khorshidi (3/3/99)
		HDPE bottles	Adequate	C. Bertha (3/17/96)

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND			MDL 16,455A
IND			
IND			
NDA	20-625	HMR	Allegra Capsules (approval date: 7/25/96)
NDA	20-786	HMR	Allegra-D tablets (approval date: 12/24/97)

CONSULTS:

Consult	Date forwarded	Status	Comments
EER	10/5/98	Acceptable (All sites)	Result reported to be acceptable by the Office of Compliance on 12/21/1998.
Pharmacology, HFD-570	1/21/99	Acceptable 3/12/99	Qualification of impurities; MDL 120,038, MDL 46,619 and MDL 46,016 at specified level of NMT .% (in drug substance) was requested.
Bio-pharm HFD-570	1/21/99	Acceptable 6/25/99	Clarification is requested on acceptance and appropriateness of 0.001M HCl as dissolution media.
Statistical analysis, HFD-570	6/25/99	Acceptable 7/12/99	Statistical analysis for acceptance of the proposed shelf-life (18 months for 30 mg tablets and 30 months for 60 mg, 180 mg tablets) was requested.

REMARKS/COMMENTS

1. Chemistry review #2 (dated July 15, 1999) found NDA 20-872 not approvable. An AE letter was forwarded to the applicant on July 16, 1999.

2. The current amendment is in full response to the Agency's letter dated July 16, 1999.

3. The original establishment evaluation requests (EER) have been forwarded on 10/5/98. Results reported to be acceptable for all proposed sites by the Office of Compliance on 12/21/98. To update the status of the request, an additional EER was sent on 9/24/99, result pending.

4. The Agency's laboratories will be validating the methods validation packages once all method related issues of this NDA application is resolved.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not approvable from standpoint of chemistry, manufacturing, and controls. Deficiencies are detailed in the accompanying review notes and summarized in the attached chemistry lists of deficiencies and comments letter. These deficiencies should be forwarded to the applicant by the CSO.

cc:
Org. NDA 20-872
HFD-570/Division File
HFD-570/HKhorshidi
HFD-570/GPoochikian
HFD-570/LCobbs

/S/ 9/24/99
Hossein S. Khorshidi, Ph.D. Review Chemist

R/D Init by: 10/7/99

filename: N20-872/Chemistry/99-09-23. Rev

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Manufacturing and Controls
Chem Review #3

Cobbs

DEC 13 1999

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-872 **CHEM. REVIEW #** 4 **REVIEW DATE:** December 10, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	July 17, 1998	July 17, 1998	August 4, 1998
AMENDMENT	July 30, 1998	August 3, 1998	August 15, 1998
	November 20, 1998	November 23, 1998	November 24, 1998
	November 23, 1998	November 24, 1998	November 24, 1998
	December 10, 1998	December 11, 1998	December 11, 1998
	December 16, 1998	December 16, 1998	December 16, 1998
	May 6, 1999	May 7, 1999	May 7, 1999
	May 13, 1999	May 14, 1999	May 14, 1999
	May 21, 1999	May 24, 1999	May 24, 1999
	May 26, 1999	May 27, 1999	May 28, 1999
	June 11, 1999	June 14, 1999	June 15, 1999
	August 26, 1999	August 27, 1999	August 30, 1999
	***October 15, 1999**	**October 18, 1999**	**October 20, 1999**
	***December 6, 1999**	**December 7, 1999**	**December 7, 1999**
CORRESPONDENCE	November 4, 1998	November 5, 1998	November 6, 1998
	November 9, 1998	November 10, 1998	November 10, 1998
	December 16, 1998	December 18, 1998	December 19, 1998

*** Subject of this review**

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel, Inc.
P.O.Box 9627
Kansas City, MO 641344-0627

DRUG PRODUCT NAME

Proprietary: Allegra Tablet®
Nonproprietary/USAN: Fexofenadine HCl
Code Name/#: MDL 16,455A
Chem.Type/Ther.Class: 1S

PHARMACOL. CATEGORY/INDICATION: Histamine H_1-receptor antagonist

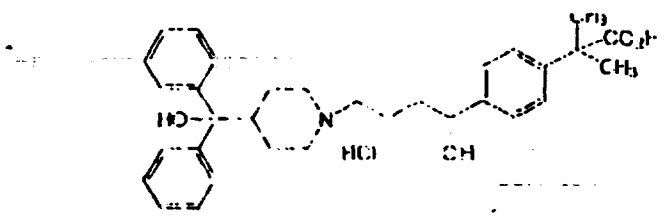
DOSAGE FORM: Film coated tablets

STRENGTHS: 30, 60, and 180 mg tablets

ROUTE OF ADMINISTRATION: Oral

DISPENSED: X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethylbenzeneacetic acid hydrochloride (MDL 16,455A)

Molecular Formula: $C_{32}H_{39}NO_3 \cdot HCl$
Molecular Weight 538.13

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed
		HDPE Bottles:	Adequate	C. Bertha (5/2/96)
		HDPE Bottles:	Adequate	C. Bertha (3/15/96)
		HDPE Bottles	Adequate	H. Khorshidi (3/3/99)
		/ Closure	Adequate	S. Kim (12/5/95)
		Closure	Adequate	C. Bertha (3/13/96)
		HDPE Resins	Adequate	H. Khorshidi (6/30/99)
		Resin	Adequate	C. Bertha (7/2/97) Linda Ng (11/18/92)
		(Foil Blister)	Adequate	H. Khorshidi (3/3/99)
		'HDPE bottles	Adequate	S. Zimmerman (9/3/98)
		Push through foil (foil blister)	Adequate	S. Zimmerman (7/17/98)
		Pigment Blends	Adequate	H. Khorshidi (3/3/99)
		HDPE bottles	Adequate	C. Bertha (3/17/96)

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND			MDL 16,455A
IND			
IND			
NDA	20-625	HMR	Allegra Capsules (approval date: 7/25/96)
NDA	20-786	HMR	Allegra-D tablets (approval date: 12/24/97)

CONSULTS:

Consult	Date forwarded	Status	Comments
EER	10/26/99	Acceptable (All sites)	Result reported to be acceptable by the Office of Compliance on 11/19/1999.
Pharmacology, HFD-570	1/21/99	Acceptable 3/12/99	Qualification of impurities; MDL 120,038, MDL 46,619 and MDL 46,016 at specified level of NMT .% (in drug substance) was requested.
Bio-pharm HFD-570	1/21/99	Acceptable 6/25/99	Clarification is requested on acceptance and appropriateness of 0.001M HCl as dissolution media.
Statistical analysis, HFD-570	6/25/99	Acceptable 7/12/99	Statistical analysis for acceptance of the proposed shelf-life (18 months for 30 mg tablets and 30 months for 60 mg, 180 mg tablets) was requested.

REMARKS/COMMENTS

1. The amendment dated 10/15/99 is in response to the Agency's IR letter dated September 24, 1999 and also includes the response to the question asked by the FDA during the teleconference held on Oct 6, 1999.
2. Amendment dated December 6, 1999 is in response to the Agency's telecon dated November 29, 1999.

CONCLUSIONS & RECOMMENDATIONS:

From CMC standpoint, this NDA application is approved. The comment listed in draft deficiencies letter of this review should be forwarded to the applicant with the approval letter.

cc:
Org. NDA 20-872
HFD-570/Division File
HFD-570/HKhorshidi
HFD-570/GPoochikian
HFD-570/LCobbs

/S/ 12/10/99

Hossein S. Khorshidi, Ph.D. Review Chemist

R/D Init by 12/13/99

filename: N20-872/Chemistry/99-12-10. Rev

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Manufacturing and Controls
Chem Review #4

Coobs

FEB 10 2000

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-872 **CHEM. REVIEW #** 5 **REVIEW DATE:** February 8, 2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	July 17, 1998	July 17, 1998	August 4, 1998
AMENDMENT	July 30, 1998	August 3, 1998	August 15, 1998
	November 20, 1998	November 23, 1998	November 24, 1998
	November 23, 1998	November 24, 1998	November 24, 1998
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	May 6, 1999	May 7, 1999	May 7, 1999
	May 13, 1999	May 14, 1999	May 14, 1999
	May 21, 1999	May 24, 1999	May 24, 1999
	May 26, 1999	May 27, 1999	May 28, 1999
	June 11, 1999	June 14, 1999	June 15, 1999
	August 26, 1999	August 27, 1999	August 30, 1999
	***October 15, 1999**	**October 18, 1999**	**October 20, 1999**
	*December 6; 1999	December 7, 1999	December 7, 1999
CORRESPONDENCE	November 4, 1998	November 5, 1998	November 6, 1998
	November 9, 1998	November 10, 1998	November 10, 1998
	December 16, 1998	December 18, 1998	December 19, 1998

*** Subject of this review**

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel, Inc.
P.O.Box 9627
Kansas City, MO 641344-0627

DRUG PRODUCT NAME

Proprietary:	Allegra Tablet®
Nonproprietary/USAN:	Fexofenadine HCl
Code Name/#:	MDL 16,455A
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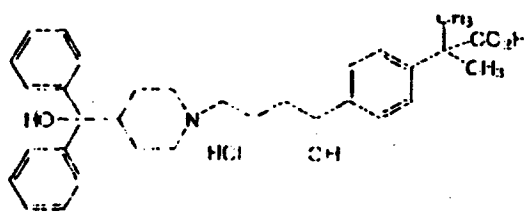
PHARMACOL. CATEGORY/INDICATION:	Histamine H_1-receptor antagonist
DOSAGE FORM:	Film coated tablets
STRENGTHS:	30, 60, and 180 mg tablets
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	**_X_ Rx __ OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



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Molecular Formula $C_{32}H_{39}NO_3 \cdot HCl$
Molecular Weight 538.13

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed
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		HDPE Bottles:	Adequate	C. Bertha (3/15/96)
		HDPE Bottles	Adequate	H. Khorshidi (3/3/99)
		Closure	Adequate	S. Kim (12/5/95)
		CR Closure	Adequate	C. Bertha (3/13/96)
		HDPE Resins	Adequate	H. Khorshidi (6/30/99)
		Resin	Adequate	C. Bertha (7/2/97) Linda Ng (11/18/92)
		(Foil Blister)	Adequate	H. Khorshidi (3/3/99)
		HDPE bottles	Adequate	S. Zimmerman (9/3/98)
		Push through foil (foil blister)	Adequate	S. Zimmerman (7/17/98)
		Pigment Blends	Adequate	H. Khorshidi (3/3/99)
		HDPE bottles	Adequate	C. Bertha (3/17/96)

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND			MDL 16,455A
IND			
IND			
NDA	20-625	HMR	Allegra Capsules (approval date: 7/25/96)
NDA	20-786	HMR	Allegra-D tablets (approval date: 12/24/97)

CONSULTS:

Consult	Date forwarded	Status	Comments
EER	10/26/99	Acceptable (All sites)	Result reported to be acceptable by the Office of Compliance on 11/19/1999.
Pharmacology, HFD-570	1/21/99	Acceptable 3/12/99	Qualification of impurities; MDL 120,038, MDL 46,619 and MDL 46,016 at specified level of NMT % (in drug substance) was requested.
Bio-pharm HFD-570	1/21/99	Acceptable 6/25/99	Clarification is requested on acceptance and appropriateness of 0.001M HCl as dissolution media.
Statistical analysis, HFD-570	6/25/99	Acceptable 7/12/99	Statistical analysis for acceptance of the proposed shelf-life (18 months for 30 mg tablets and 30 months for 60 mg, 180 mg tablets) was requested.

CONCLUSIONS & RECOMMENDATIONS:

From CMC standpoint, this NDA application is approved. The comment listed in draft deficiencies letter of this review should be forwarded to the applicant with the approval letter.

cc:
Org. NDA 20-872
HFD-570/Division File
HFD-570/HKhorshidi
HFD-570/GPoochikian
HFD-570/LCobbs

/S/ 2/08/00

Hossein S. Khorshidi, Ph.D. Review Chemist

R/D Init by: 2/10/00

filename: N20-872/Chemistry/2000-02-08. Rev

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

manufacturing and controls

#5

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

ALLEGRA®

(fexofenadine hydrochloride)

Tablets

NDA 20-872

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary Drug Products (HFD-570)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-872

ALLEGRA®

(fexofenadine hydrochloride)

Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process. The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of their new drug application for ALLEGRA® (fexofenadine hydrochloride) Tablets, Hoechst Marion Roussel, Inc. has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal of the product. Fexofenadine hydrochloride is a chemically synthesized drug which is currently approved for use in treating seasonal allergic rhinitis. This new drug application provides for a new use of the drug in the treatment of chronic idiopathic urticaria and for pediatric use. The finished drug product will be used predominantly by patients in their homes. Because of the quantity of fexofenadine expected to be used in Hoechst Marion Roussel fexofenadine products in the United States, the relevant environmental issue relating to this action is whether fexofenadine entering the environment from consumer use and disposal will adversely affect environmental organisms.

Chemical and physical test results indicate that fexofenadine will most likely be restricted to the aquatic environment and will not undergo rapid hydrolysis, photolysis or biodegradation. As fexofenadine is expected to persist in the environment for some time, the toxicity of the material to organisms was characterized. Studies were conducted to assess (1) the acute toxicity to water fleas *(Daphnia magna)* and bluegill fish (*Lepomis macrochrus*) and (2) the inhibitory effect on microbial growth. These studies indicate that there are no expected adverse environmental effects at the expected environmental concentrations. The estimated concentration of the active moiety, fexofenadine entering the aquatic environment is more than 3 orders of magnitude lower than the toxicity test results.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

10/14/98 /S/

DATE PREPARED BY
Nancy B. Sager
Environmental Officer
Center for Drug Evaluation and Research

10-14-98 /S/

DATE CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

cc: Original to NDA 20-872 through PM: LCobbs/HFD-570
HFD-357/EA File
HFD-357/Docket File
HFD-205/FOI copy

3.E Environmental assessment

3.E.1 Date

July 17, 1998

3.E.2 Name of applicant/petitioner

Hoechst Marion Roussel, Inc.

3.E.3 Address

10236 Marion Park Drive
Kansas City, Missouri
64137-1405

3.E.4 Description of proposed action

3.E.4.1 Requested approval

Hoechst Marion Roussel, Inc. has filed a New Drug Application No. 20-872 pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine hydrochloride) 30 mg. 60 mg, 120 mg and 180 mg tablets. Allegra tablets will be packaged in 30ct., 60ct., 100ct., 500ct., and 3000ct. high density polyethyiene bottles and in unit dose blister packages. Fexofenadine hydrochloride has previously been approved for use in the United States under the trade names Allegra capsules (NDA 20-625, 1996) and Allegra-D (fexofenadine hydrochloride/pseudoephedrine hydrochloride, NDA 20-786, 1996), for use in the relief of seasonal allergic rhinitis, and full Environmental Assessments (EAs) were included in those submissions. An EA is submitted for Allegra tablets pursuant to 21 CFR part 25, and follows the content and format of the Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements, Center for Drug Evaluation and Research, November 1997. Where applicable, this EA references the Allegra-D EA, for which a *Finding of No Significant Impact was issued* December 8, 1997. There are no significant differences regarding environmental or other issues associated with the Allegra tablet EA. This document serves as the confidential as well as non-confidential EA. Confidential information is included in *Section 3.E.11.1 Confidential Appendix, S3–V1.11–P339.*

3.E.4.2 Need for action

Fexofenadine hydrochloride is approved for use in the relief of symptoms of seasonal allergic rhinitis at a dose of 60 mg bid. This application includes treatment for seasonal allergic rhinitis at doses of 60 mg bid and 120-180 mg qd; chronic idiopathic urticaria at a dose of 60 mg bid; and pediatric use at a dose of 30-60 mg bid. Fexofenadine hydrochloride is a metabolite and the hydrochloride salt of terfenadine, a non-sedating H_1 antihistamine which was approved for use in the United States under the trade name Seldane®. The antihistaminic activity of Seldane is associated with the presence of fexofenadine hydrochloride in the plasma.

3.E.4.3 Locations of use

Refer to *NDA 20-786, Section 3.E.4.c. Locations of Product Use and Disposal of Rejected/Returned Goods, S3-V1.9-P8.*

3.E.4.4 Disposal sites

Refer to *NDA 20-786, Section 3.E.4.c. Locations of Product Use and Disposal of Rejected/Returned Goods, S3-V1.9-P8.*

3.E.5 Identification of chemical substances that are the subject of the proposed action

Refer to *NDA 20-786, Section 3.E.5. Identification of Chemical Substances that are the Subject of the Proposed Action, S3-V1.9-P9.*

3.E.6 Environmental issues

The Environmental Introduction Concentration (EIC) of fexofenadine hydrochloride from patient use is not less than 1 ppb, therefore fexofenadine hydrochloride applications do not qualify for an EA exclusion. This application includes indications other than the original indication of seasonal allergic rhinitis and approval will result in increased use.

Refer to *NDA 20-786 , Section 3.E.7. Fate of Emitted Substances in the Environment, S3-V1.9-P26 and NDA 20-786, Section 3.E.8. Environmental Effects of Released Substances, S3-V1.9-P29.* Calculation of the EIC from all dosage forms and strengths and related applications is included in *Section 3.E.11.1 Confidential Appendix, S3–V1.11–P339.*

Summary: The Maximum Expected Environmental Concentration (MEEC) of fexofenadine hydrochloride is calculated assuming no metabolism, environmental depletion mechanisms or dilution, therefore the MEEC = EIC = Expected Environmental Concentration. In the microbial, *Daphnia magna* and bluegill fish toxicity studies, the MIC or NOEC divided by the MEEC is greater than the Tier 1 assessment factor of 1000, so no further testing was conducted. No adverse effects are expected from the introduction of fexofenadine hydrochloride into the environment.

3.E.7 Mitigation measures

Refer to *NDA 20-786, Section 3.E.10. Mitigation Measures, S3-V1.9-P32.*

3.E.8 Alternatives to the proposed action

Refer to *NDA 20-786, Section 3.E.11. Alternatives to the Proposed Action, S3-V1.9-P33.*

3.E.9 List of preparers

Vicki J. Selzer DVM
Scientist
DVM Kansas State University College of Veterinary Medicine, 1985
BS Life Science and Physical Science, Kansas State University, 1980
MPH University of Kansas Medical Center, currently enrolled

Persons and agencies consulted
Nancy B. Sager
Environmental Officer
Center for Drug Evaluation and Research
Food and Drug Administration

3.E.10 References

Refer to *NDA 20-786, Section 3.E.14. References, S3-V1.9-P37.*

3.E.11 Appendices

Refer to *NDA 20-786, Section 3.E.15. Appendices, S3-V1.9-P38.*

3.E.11.1 Confidential Appendix

Refer to Confidential Appendix on the following page.

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-872

ALLEGRA®

(fexofenadine hydrochloride)

Tablets

DIVISION OF PULMONARY DRUG PRODUCTS
(HFD-570)

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: October 14, 1998

SUMMARY

A FONSI is recommended.

FONSIs have previously been signed for this active moiety for the approvals of NDA 20-625 (6/17/96) and NDA 20-786 (12/8/97). This application includes indications other than the original indication of seasonal allergic rhinitis, therefore approval is considered to increase use. An EIC of 3.7 ppb is estimated based on a 5 year market projection of 150,626 kg. The toxicity test results included in 20-786 are reproduced below. A FONSI is indicated for this action because the difference between the EIC and the EC_{50} for daphnids is greater than 1000 and the NOEC is greater than the EIC. There is no indication that extraordinary circumstances exist.

Organism		NOEC
Daphnia magna	= 780 ppm (EC_{50})	= 330 ppm
Bluegill fish *Lepomis macrochirus*	> 940 ppm (LC_{50})	= 570 ppm
Microbial Growth *(Anabaena flos-aquae)* Other 4	= 400 ppm (MIC) > 1000 ppm (MIC)	

ENVIRONMENTAL ASSESSMENT

1. Date:

EA dated: 07/17/1998

CSO: Lindsay Cobbs

2. Name of applicant/petitioner:

Hoechst Marion Roussel, Inc.

3. Address:

10236 Marion Park Drive
Kansas City, Missouri 64137-1405

Note: The applicant has filed an NDA application for Allegra® Tablets (fexofenadine hydrochloride). FONSIs have previously been signed for this active moiety for the approvals of NDA 20-625 (6/17/96) and NDA 20-786 (12/8/97). This application includes indications other than the original indication of seasonal allergic rhinitis, therefore approval is considered to increase use.

Review:

- The EA submitted in support of the NDA 20- 872 references the EA for NDA 20-786.
- In addition to an indication for seasonal allergic rhinitis, indications for chronic idiopathic urticaria and pediatric use are included.
- The environmental issue associated with this action is the potential toxicity of the drug to environmental organisms.
- Updated market projections are provided. An estimate in 150,626 kg is provided. An EIC of 3.7 ppb is calculated based on this estimate.
- A FONSI is indicated for this action because the difference between the EIC and the EC_{50} for daphnids is greater than 1000 and the NOEC is greater than the EIC. There is no indication that extraordinary circumstances exist.

Endorsements:

HFD-357/NBSager /S/ 10/14/98

HFD-800/EBSheinin /S/ 10-14-98

CC: Original to NDA 20-872/through LCobbs/HFD-570

EA File 20-872