CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20786

CHEMISTRY REVIEW(S)

AUG 7 1997

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

NDA #: 20-786 **CHEM. REVIEW #** 2 **REVIEW DATE:** 7/31/97

RECOMMEND ACTION: NOT APPROVABLE

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/20/96	12/20/96	1/3/97
Amendment	2/5/97	2/6/97	2/12/97
Amendment	2/12/97	2/13/97	2/20/97
Amendment	3/10/97	3/11/97	3/11/97
Amendment	3/14/97	3/18/97	3/18/97
Amendment	6/26/97	6/30/97	7/2/97

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel, Inc.
PO Box 9627
Kansas City, MO 64134-0627

DRUG PRODUCT NAME

Proprietary: Allegra-D™ Extended-release Tablets

Nonproprietary/USAN: Fexofenadine HCl 60 mg/Pseudoephedrine HCl 120 mg Extended-release Tablets

Code Name/#: MDL 173

Chem. Type/Ther. Class: 4S

PHARMACOL. CATEGORY/INDICATION: Histamine H_1-receptor antagonist/decongestant for treatment of symptoms associated with seasonal allergic rhinitis

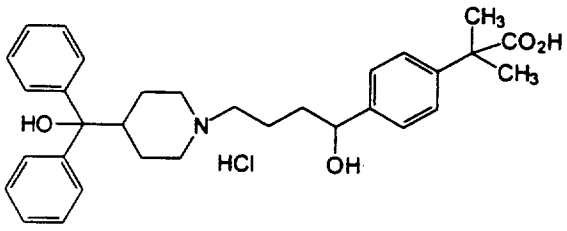
DOSAGE FORM: Extended-release tablet

STRENGTHS: 60 mg Fexofenadine HCl/120 mg Pseudoephedrine HCl per tablet

ROUTE OF ADMINISTRATION: Oral

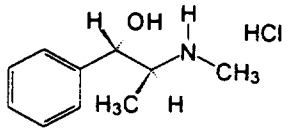
DISPENSED: _X_ Rx ___ OTC

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



Fexofenadine HCl

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



Pseudoephedrine HCl

[S-(R*,R*)]-α-[1-(Methylamino)ethyl]-benzenemethanol HCl

Molecular Formula: $C_{32}H_{39}NO_4 \cdot HCl$ $C_{10}H_{15}NO \cdot HCl$

Molecular Weight: 538.13 201.70

Redacted 1

page(s) of trade secret and/or confidential commercial information

RELATED DOCUMENTS:

Type Number Owner Subject

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	1/16/97 and 1/24/97	Satisfactory	Recommendation dated 7/8/97
Microbiology, HFD-160	Not applicable		
Biometrics, HFD-710	To be requested once specifications are finalized and additional stability data are submitted.		
Environmental Assessment			Chemist and pharmacologist will jointly prepare EA.
Methods Validation	Not requested: pending method issues resolution by applicant		
Labeling & Nomenclature Committee	Not applicable		All portions of the trade name have been previously approved.
Biopharmaceutics	7/28/97	Incomplete	Biopharm review is necessary to assess applicant's response to comment 3.a.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not approvable from the standpoint of chemistry, manufacturing, and controls.

cc:
Orig. NDA 20-786
HFD-570/Division File
HFD-570/BRogers/7/31/97
HFD-570/GStrange
HFD-570/GPoochikian
HFD-570/AWorobec
R/D Init by: QB 8/7/97
filename: 20786.002

Brian D. Rogers, Ph.D. Review Chemist

APR 15 1997

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

NDA #: 20-786 **CHEM. REVIEW #** 1 **REVIEW DATE:** 4/14/97

RECOMMEND ACTION: NOT APPROVABLE

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/20/96	12/20/96	1/3/97
Amendment	2/5/97	2/6/97	2/12/97
Amendment	2/12/97	2/13/97	2/20/97
Amendment	3/10/97	3/11/97	3/11/97
Amendment	3/14/97	3/18/97	3/18/97

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel, Inc.
PO Box 9627
Kansas City, MO 64134-0627

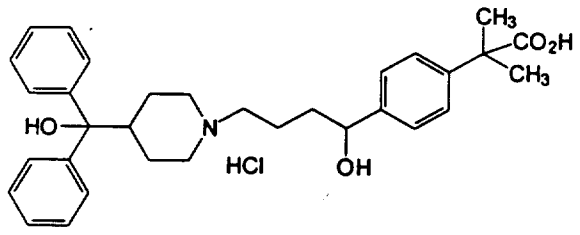
DRUG PRODUCT NAME
Proprietary: Allegra-D™ Extended-release Tablets
Nonproprietary/USAN: Fexofenadine HCl 60 mg/Pseudoephedrine HCl 120 mg Extended-release Tablets
Code Name/#: MDL 173
Chem. Type/Ther. Class: 4S

PHARMACOL. CATEGORY/INDICATION: Histamine H_1-receptor antagonist/decongestant for treatment of symptoms associated with seasonal allergic rhinitis

DOSAGE FORM: Extended-release tablet
STRENGTHS: 60 mg Fexofenadine HCl/120 mg Pseudoephedrine HCl per tablet

ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ Rx ___ OTC

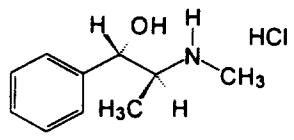
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Fexofenadine HCl

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

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



Pseudoephedrine HCl

[S-(R*,R*)]-α-[1-(Methylamino)ethyl]-benzenemethanol HCl

$C_{10}H_{15}NO \cdot HCl$
201.70

Redacted 1

page(s) of trade secret and/or confidential commercial information

RELATED DOCUMENTS:

Type Number Owner Subject

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	1/16/97 and 1/24/97	Incomplete	E-Mail from OC (4/15/97) states will not be ready for inspection for at least 4 months
Microbiology, HFD-160	Not applicable		
Biometrics, HFD-710	To be requested once specifications are finalized and additional stability data are submitted.		
Environmental Assessment			Chemist and pharmacologist will jointly prepare EA.
Methods Validation	Not requested: pending method issues resolution by applicant		
Labeling & Nomenclature Committee	Not applicable		All portions of the trade name have been previously approved.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not approvable from the standpoint of chemistry, manufacturing, and controls.

cc:
Orig. NDA 20-786
HFD-570/Division File
HFD-570/BRogers/4/14/97
HFD-570/GStrange
HFD-570/GPoochikian
HFD-570/AWorobec
R/D Init by: 4/15/97
filename: 20786.001

Brian D. Rogers, Ph.D. Review Chemist

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20786

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Allegra-D™

(fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg)

NDA 20-786

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF PULMONARY DRUG PRODUCTS
(HFD-570)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-786

Allegra-D™

(fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg)

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. FDA's review focuses on the relevant environmental issues relating to use and disposal from use of FDA-regulated articles.

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-D™**, **Hoechst Marion Roussel** has conducted a number of environmental studies and prepared an environmental assessment (attached) in accordance with 21 CFR Part which evaluates the potential environmental impacts of the use of the product.

Allegra-D™ is an oral tablet product containing fexofenadine hydrochloride (60 mg) and pseudoephedrine hydrochloride (120 mg) which is used to relieve the symptoms of seasonal allergic rhinitis and for the temporary relief of nasal congestion. The finished drug product will be used predominantly by patients in their homes. Because of the quantity of fexofenadine expected to be used in Allegra 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. Pseudoephedrine hydrochloride has been used in approved prescription and over-the-counter drugs for many years with no reported environmental impacts.

Chemical and physical test results indicate that fexofenadine will most likely be restricted to the aquatic environment and will not undergo significant 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 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 be used and disposed of without any expected adverse environmental effects.

12/6/97 Nancy B. Sager
DATE PREPARED BY
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

12-8-97 Eric B. Sheinin
DATE CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

c.c. original NDA 20-786/through GTrout/HFD-570
HFD-357/FONSI File NDA #20-786
HFD-357/Docket File
HFD-205/FOI COPY

NDA 20-786
Div File
HFD-570/Rogers

Exhibit 14. Allegra-D Environmental Assessment FOI (Nonconfidential) Copy

E. Environmental Assessment

Introduction and Summary

This Environmental Assessment (EA) follows the content and format described in 21 CFR § 25. 30, specifically, Format 1 as described in 21 CFR §25.31a., and the Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements, Center for Drug Evaluation and Research, November 1995. The document which follows this introduction and summary is a nonconfidential copy. Based on the information provided herein the applicant concludes it has submitted sufficient information to provide a basis for the agency's determination to prepare a Finding of No Significant Impact (FONSI).

Allegra-D labeling is indicated for use in the relief of symptoms of seasonal allergic rhinitis and temporary relief of nasal congestion. Allegra-D is a combination formulation of fexofenadine hydrochloride (MDL 16,455A) (60 mg) and pseudoephedrine hydrochloride (120 mg). Fexofenadine hydrochloride has previously been approved for use in the United States under the trade name Allegra™. Fexofenadine hydrochloride is a metabolite and hydrochloride salt of terfenadine, a nonsedating H_1 antihistamine which has been 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. Pseudoephedrine hydrochloride has been approved in the United States (Final Monograph for OTC Nasal Decongestant Drug Products) for the temporary relief of nasal congestion due to the common cold, hay fever or other upper respiratory allergies, and nasal congestion associated with sinusitis.

Fexofenadine hydrochloride drug substance is manufactured by HMRI at their facilities located within The Dow Chemical Company, Midland, Michigan. Pseudoephedrine hydrochloride drug substance is manufactured and delivered to the applicant by Ganes Chemicals, Inc., Carlstadt, New Jersey. Allegra-D tablets will be manufactured and packaged by Hoechst Marion Roussel Inc., (HMRI) Kansas City, Missouri. Rejected, expired, or returned goods will be returned to HMRI, Kansas City, Missouri for evaluation, and materials identified for disposal will be shipped to ENSCO Inc., El Dorado, Arkansas for incineration. The manufacture of drug substance or drug product at the Midland and Kansas City sites will be conducted with sufficient controls to maintain compliance with applicable emissions requirements and will not impact compliance with emissions requirements at each site. There will be no significant impact on use of resources or energy at these sites. The proposed action is not expected to have adverse effects on endangered or threatened species or historical sites near the Midland or Kansas City manufacturing sites.

Pseudoephedrine hydrochloride is a drug substance that is included in long-standing OTC monographs (Final Monograph for OTC Nasal Decongestant Drug Products [*NDA 20-786, S8–V1.33–P8*]; Tentative Final Monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Combination Drug Products [*NDA 20-786, S8–V1.33–P81*]). The compound is well known and it has been on the market for many years with no known adverse environmental

impacts. In addition, the EIC for pseudoephedrine hydrochloride in the aquatic environment from patient use of Allegra-D is less than 1 ppb; therefore, information regarding Items 6 through 11 is not included further in this document.

The expected introduction concentration (EIC) from patient use of fexofenadine hydrochloride is based on total fifth year production estimates for all dosage forms and strengths of fexofenadine hydrochloride in this application and in the previously approved Allegra™ application. Total fifth year production is estimated to [confidential]. Therefore, this EA does not qualify for the Tier 0 approach.

Metabolism of fexofenadine hydrochloride and pseudoephedrine hydrochloride is minimal and primarily parent substance is expected to enter the environment from patient use. In addition, based on physical/chemical properties of fexofenadine hydrochloride, no structurally related substances are expected to exist in the environment. Therefore environmental fate and effects are considered only for the parent substance, fexofenadine hydrochloride.

Fexofenadine hydrochloride is slightly soluble in water, is not expected to hydrolyze or photodegrade, and has a low partition coefficient and vapor pressure. Based on these physical/chemical properties, there appears to be no environmental depletion mechanism for fexofenadine hydrochloride, and it will most likely amass predominantly in the aquatic environment. A biodegradation in water study indicated biodegradation in water is insignificant (< 4%) therefore fexofenadine hydrochloride is not expected to be depleted in the aquatic environment. In a microbial growth inhibition study, the minimum inhibitory concentrations for the microorganisms tested were ≥ 400 mg/L fexofenadine hydrochloride.

Tier 1 testing included acute toxicity studies with fexofenadine hydrochloride in *Daphnia magna* and bluegill fish. In *Daphnia*, the 48-hour no-observed effect concentration (NOEC) was 330 mg/L and in bluegill fish the 96-hour NOEC was 570 mg/L.

The maximum expected environmental concentration (MEEC) of fexofenadine hydrochloride is calculated assuming no metabolism, environmental depletion mechanism or dilution. Therefore the MEEC = EIC = [confidential]. For *Daphnia* and bluegill fish, the NOEC divided by the MEEC is greater than the Tier 1 assessment factor of 1000 for both species, so no further testing was conducted. Introduction of fexofenadine hydrochloride into the environment from patient use is not expected to have adverse effects in the environment.

The alternative to the proposed action is nonapproval and the prevention of Allegra-D from being available for use in the relief of symptoms of seasonal allergic rhinitis and nasal congestion. Since the proposed action is not expected to have adverse effects in the environment, no alternatives are proposed.

NDA 20-786 REVISED December 3, 1997

ALLEGRA-D™
(combination fexofenadine hydrochloride 60 mg and pseudoephedrine hydrochloride 120 mg tablets)

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment (Nonconfidential)

1. Date

November 26, 1996
Revised November 5, 1997 and December 3, 1997

2. Name of Applicant

Hoechst Marion Roussel, Inc. (HMRI)

3. Address

10236 Marion Park Drive
Kansas City, Missouri
64137-1405

4. Description of the Proposed Action

a. Description of Requested Approval/Need for the Proposed Action

The Applicant requests approval of a New Drug Application for Allegra-D tablets for oral use in the relief of symptoms of seasonal allergic rhinitis and temporary relief of nasal congestion. Allegra-D is a combination formulation of fexofenadine hydrochloride (MDL 16,455A) (60 mg) and pseudoephedrine hydrochloride (120 mg) in a bi-layered tablet and will be packaged in HDPE bottles and unit dose blister packages. The recommended dose is 60/120 mg BID. Fexofenadine hydrochloride has previously been approved for use in the United States under the trade name Allegra™. Fexofenadine hydrochloride is the hydrochloride salt of terfenadine, a nonsedating H_1 antihistamine which has been 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. Pseudoephedrine hydrochloride has been approved in the United States (Final Monograph for OTC Nasal Decongestant Drug Products) for the temporary relief of nasal congestion due to the common cold, hay fever or other upper respiratory allergies, and nasal congestion associated with sinusitis. Pseudoephedrine hydrochloride is a drug substance that is included in long-standing OTC monographs (Final Monograph for OTC Nasal Decongestant Drug Products [*NDA 20-786, S8–V1.33–P8*]; Tentative Final Monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Combination Drug Products [*NDA 20-786, S8–V1.33–P81*]). The compound is well known and it has been on the market for many years with no known adverse environmental impacts. In addition, the EIC for pseudoephedrine hydrochloride in the aquatic environment from patient use of Allegra-D is less than 1 ppb; therefore, information regarding Items 6 through 11 is not included further in this document.

This Environmental Assessment (EA) follows the content and format described in 21 CFR § 25. 30, specifically, Format 1 as described in 21 CFR §25.31a., and the Guidance for

Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements, Center for Drug Evaluation and Research, November 1995. This document is a nonconfidential copy.

b. Location Where Product Will Be Produced

i. Drug Substance

Fexofenadine hydrochloride drug substance and proprietary intermediates are manufactured by HMRI at their facilities located within The Dow Chemical Company, Midland, Michigan 48667. The Michigan Division of The Dow Chemical Company is situated on approximately 1900 acres in the Saginaw Valley of mid-Michigan. The Tittabawasee River runs through the Michigan Division site. The manufacturing site is adjacent to Midland, Michigan which has a population of approximately 35,000 people. Wastes from the manufacture of fexofenadine hydrochloride drug substance will be treated at the Michigan Division site of The Dow Chemical Company in Midland, Michigan.

Pseudoephedrine hydrochloride drug substance is manufactured and delivered to the applicant by Ganes Chemicals, Inc., 630 Broad Street, Carlstadt, New Jersey, 07072.

ii. Drug Product

Allegra-D tablets will be produced and packaged at HMRI facilities located at 10236 Marion Park Drive, Kansas City, Missouri 64137. The plant site is located in the southern portion of Kansas City, Missouri which has a population of 1.6 million people. The site is approximately adjacent to Grandview, Missouri. The metropolitan area has a population of approximately 25,000. The facility is about 14 miles from downtown Kansas City and three to five miles from the business district of Grandview. The facility is located on 180 acres in a mixed use area comprising light industry, retail and wholesale establishments, and residential areas. Roughly half the site has been developed. Manufacturing facilities comprise approximately one-quarter of the developed area with the remainder comprised of Research and Development and general office facilities.

The Kansas City site is in rolling terrain with little undisturbed land remaining in this area. The site is located within one-quarter mile of the confluence of three major highways, US 71, Interstate 470 and Interstate 435, located to the west and south of the site.

HMRI, Kansas City does only minor chemical synthesis at this facility; the majority of the manufacturing operations are comprised of blending, formulation, compounding, and tablet production.

c. Locations of Product Use and Disposal of Rejected/Returned Goods

Allegra-D will be used by patients with seasonal allergic rhinitis and nasal congestion throughout the United States.

i. Drug Substance

Rejected, returned or expired fexofenadine hydrochloride drug substance (if not reprocessed) at the Midland, Michigan manufacturing site will be incinerated at The Dow Chemical Incineration Complex:

The Dow Chemical Company, Midland, Michigan 48667
EPA ID No.: MID 000724724
Permitted by: State of Michigan Department of Natural Resources
Air Use Permit Nos.: 93-73, 471-79, 403-78, 403-78A, 678-83, 887-89, 441-88, 336-81A (no expiration)
Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)
Incinerator emission limits are given in an exhibit in the confidential EA.

Rejected, returned or expired drug substance (if not reprocessed) at the Kansas City, Missouri manufacturing site will be incinerated at:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730
EPA ID No.: ARD069748192
Permitted by Arkansas Department of Pollution Control and Ecology
Hazardous Waste Management Permit: 10-H, CSN 70-0098 (expiration June 26, 1998)
Construction and Operations Permit: 1009A (until terminated or modified)
NPDES Permit: AR0037800 (expiration October 31, 1995; permit remains in effect due to submission of a complete reapplication in accordance with the appropriate regulations and administrative policies)
Incinerator emission limits are given in an exhibit in the confidential EA.

ii. Drug Product

Rejected, expired or returned drug product (if not reprocessed) will be returned to HMRI, 10236 Marion Park Drive, Kansas City, Missouri 64137 for evaluation and disposal. Materials identified for disposal will be shipped to the following facility for incineration:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730
EPA ID No.: ARD069748192
Permitted by Arkansas Department of Pollution Control and Ecology
Hazardous Waste Management Permit: 10-H, CSN 70-0098 (expiration June 26, 1998)
Construction and Operations Permit: 1009A (until terminated or modified)

NPDES Permit: AR0037800 (expiration October 31, 1995; permit remains in effect due to submission of a complete reapplication in accordance with the appropriate regulations and administrative policies)
Incinerator emission limits are given in an exhibit in the confidential EA.

At US hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures and in the home, 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, although minimal quantities of unused drug may be disposed of in the sewer system.

5. Identification of Chemical Substances That Are the Subject of the Proposed Action

a. Drug Substance

Chemical Names:

Fexofenadine hydrochloride
Benzeneacetic acid,
4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethyl-, hydrochloride,
(±)2-(4-{1-Hydroxy-4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyl}-phenyl)-2-methyl-propionic acid, hydrochloride salt

Pseudoephedrine hydrochloride
[S-(R*,R*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrochloride
(+)-pseudoephedrine hydrochloride

Generic Names:

Fexofenadine hydrochloride
fexofenadine hydrochloride

Pseudoephedrine hydrochloride
pseudoephedrine hydrochloride (USP, USAN)

CAS Registry Nos.:

Fexofenadine hydrochloride
138452-21-8

Pseudoephedrine hydrochloride
345-78-8

Code Numbers:

Fexofenadine hydrochloride
MDL 16,455A
MDL 16,455

(Note: MDL 16,455 represents the fexofenadine free base and MDL 16,455A represents the fexofenadine hydrochloride salt.)

Pseudoephedrine hydrochloride
MDL 18,712A
MDL 18,712

(Note: MDL 18,712 represents the pseudoephedrine free base and MDL 18,712A represents the pseudoephedrine hydrochloride salt.)

Synonyms:

Fexofenadine HCl/Pseudoephedrine HCl combination product: Fexofenadine-D

TAM-D

Molecular Weights:

Fexofenadine hydrochloride
538.13

Pseudoephedrine hydrochloride
201.70

Molecular Formulas:

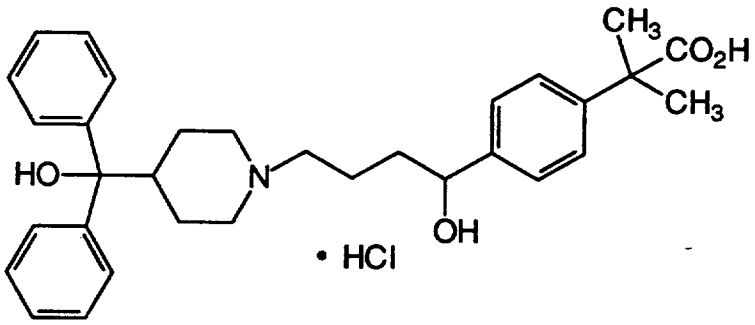
Fexofenadine hydrochloride
$C_{32}H_{39}NO_4 \cdot HCl$

Pseudoephedrine hydrochloride
$C_{10}H_{15}NO \cdot HCl$

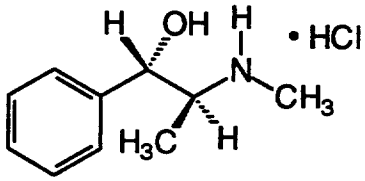
3. Chemistry, Manufacturing and Controls
E. Environmental Assessment (Nonconfidential)

Structures:

Fexofenadine hydrochloride



Pseudoephedrine hydrochloride



Physical Descriptions:

Fexofenadine hydrochloride
White to off-white crystalline powder.

Pseudoephedrine hydrochloride (USP)
Fine, white to off-white crystals or powder, having a faint characteristic odor.

A list of materials used in the preparation of the drug substance is included in the confidential EA.

A list of drug substance impurities and degradation products is given in the confidential EA.

b. Drug Product

Product Name: Allegra-D

A list of dosage form components is given in *Attachment 1. Dosage Form Components of Allegra-D Tablets, S3–V1.10–P272.*

6. Introduction of Substances into the Environment

a. Introduction from Manufacture of Drug Substance

Pseudoephedrine hydrochloride drug substance is manufactured and delivered to the applicant by Ganes Chemicals, Inc., 630 Broad Street, Carlstadt, New Jersey, 07072.

Fexofenadine hydrochloride drug substance is manufacutred by HMRI at their facilities located within The Dow Chemical Company, Midland, Michigan, 48667. The estimated total fifth year production includes all dosage forms and strengths of fexofenadine hydrochloride in this application and in the previously approved Allegra™ application. The confidential EA describes the chemical synthesis of MDL 16,455A and the chemical substances which may be expected to be emitted to the air, aquatic and terrestrial compartments of the environment as a result of the bulk drug substance manufacturing process. The following provides details of the emissions in the air, aquatic, and terrestrial compartments as a result of the manufacture of the drug substance; statement of controls exercised; citation of and statement of compliance with applicable emissions requirements; and effect of approval on compliance with current emissions requirements.

i. Air Emissions

List of components of emitted streams:

Component	CAS #
Confidential	Confidential

Statement of controls exercised:

Process vent gasses are treated with a gas-fueled thermal oxidizer with minimum design efficiency of 99.9% organic destruction efficiency. Acidic process vent gasses are pretreated with a scrubber using 12 to 25 wt. % NaOH scrubbing fluid with a design efficiency of 90%.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Current air emissions are in compliance with the requirements set forth in The Dow Chemical Air Use Permit as granted by the State of Michigan Department of Natural Resources, Air Use Permit Nos. 1371-91. Ash from the vent gas combustion process is disposed of in The Dow Chemical Company Salzburg Landfill, Midland, Michigan 48667.

Occupational exposures are regulated by Federal Occupational Safety and Health Act Standards (OSHA). Exposures are controlled by engineering design or the use of appropriate personal protective equipment. The facility is in compliance with the applicable regulations. Material Safety Data Sheets are available in (*Attachment 4. MSDS for Fexofenadine Hydrochloride Drug Substance and Allegra-D Drug Product, S3–V1.10–P278*).

A signed statement of compliance for drug substance manufacture at the Midland site is included in *Attachment 2. Statement of Compliance, The Dow Chemical Company, Midland, Michigan, S3–V1.10–P274.*

Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will have no impact on compliance with current emission requirements.

ii. Aquatic Emissions

List of components of emitted streams:

Component	CAS #
Confidential	Confidential

Statement of controls exercised:

The aqueous streams are discharged to The Dow Chemical Company Waste Water Treatment Plant (WWTP). The acids and bases are subsequently neutralized and are discharged as dissolved solids from the WWTP to the Tittabawassee River.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Aqueous discharge from The Dow Chemical Company Waste Water Treatment Plant is in compliance with the requirements set forth in the National Pollutants Discharge Elimination System (NPDES) Permit No. MI 40000868 for the Dow Chemical Waste Water Treatment Plant. Total Dissolved Solids daily maximum limit is 750 mg/L and total maximum monthly average is 500 mg /L.

Occupational exposures are regulated by Federal Occupational Safety and Health Act Standards (OSHA). Exposures are controlled by engineering design or the use of appropriate personal protective equipment. The facility is in compliance with the applicable regulations. Material Safety Data Sheets are available (*Attachment 4. MSDS for Fexofenadine Hydrochloride Drug Substance and Allegra-D Drug Product, S3–V1.10–P278*).

A signed statement of compliance for drug substance manufacture at the Midland site is included in *Attachment 2. Statement of Compliance, The Dow Chemical Company, Midland, Michigan, S3–V1.10–P274.*

Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will have no impact on compliance with current emission requirements.

iii. Terrestrial Emissions

List of components of emitted streams:

Component	CAS #
Confidential	Confidential

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ALLEGRA-D™
(combination fexofenadine hydrochloride 60 mg and pseudoephedrine hydrochloride 120 mg tablets)

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment (Nonconfidential)

Component	CAS #
Confidential	Confidential

Statement of controls exercised:

These streams are incinerated at The Dow Chemical Company Incineration Complex. The thermal oxidizer operates at a minimum efficiency of 99.9%. Ash from the combustion process is disposed of in The Dow Chemical Company Salzburg Landfill, Midland, Michigan 48667.

Citation of and statement of compliance with applicable emission requirements at federal, state and local levels:

The Dow Chemical Thermal Oxidation Unit Permit is operated according to the requirements set forth by the State of Michigan Department of Natural Resources in the Dow Chemical Incineration Complex Air Use Permit Nos. 336-81A, 93-73I, 471-79, 441-88 and State of Michigan Department of Natural Resources Hazardous Waste Facility Operating License EPA ID No. MID 000 724 724. The Dow Chemical Company Salzburg Landfill is operated according to the regulations set forth by the State of Michigan Department of Natural Resources, Hazardous Waste Facility Operating License EPA ID No. MID 890 617 435.

Occupational exposures are regulated by Federal Occupational Safety and Health Act Standards (OSHA). Exposures are controlled by engineering design or the use of appropriate personal protective equipment. The facility is in compliance with the applicable regulations. Material Safety Data Sheets are available in (*Attachment 4. MSDS for Fexofenadine Hydrochloride Drug Substance and Allegra-D Drug Product, S3–V1.10–P278*).

A signed statement of compliance for drug substance manufacture at the Midland site is included in *Attachment 2. Statement of Compliance, The Dow Chemical Company, Midland, Michigan, S3–V1.10–P274.*

Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will have no impact on compliance with current emission requirements.

b. Introduction from Manufacture of Drug Product

Allegra-D tablets will be manufactured and packaged by HMRI, 10236 Marion Park Drive, Kansas City, Missouri 64137. These manufacturing operations are conducted according to current Good Manufacturing Practices and in compliance with applicable federal, state and local laws, regulations and permits.

Allegra-D tablets will be packaged for commerce in 30 ct., 60 ct., 100 ct. and 500 ct. high density polyethylene (HDPE) bottles and in unit dose blister packages. The 30 ct. and 60 ct. bottles will be secured with child resistant closures (CRC). The 100 ct. and 500 ct. bottles will be secured with non child resistant closures (non CRC). All bottles are sealed with a foil induction inner seal. The unit dose blister packaging will be used for commercial and sampling requirements.

The following provides details of emissions in the air, aquatic and terrestrial compartments as a result of production of the drug product; statement of controls exercised; citation of and statement of compliance with applicable emission requirements; and effect of approval on compliance with current emissions limits.

i. Air Emissions

List of components of emitted streams:

Emission points are given in the confidential EA.

Component	CAS #
Fexofenadine Hydrochloride	138452-21-8
Pseudoephedrine Hydrochloride	345-78-8
Microcrystalline Cellulose	9004-34-6
Carnauba Wax	8015-86-9
Magnesium Stearate	557-04-0
Pregelatinized Starch	9005-84-9
Stearic Acid Flakes	57-11-4
Colloidal Silicon Dioxide	7631-86-9
Croscarmellose Sodium	74811-65-7
Opadry YS-1-7006	N/A
Water, purified‡	7732-18-5
‡ Removed during processing	

Statement of controls exercised:

Compliance with air emissions is achieved by product design, process design, operating discipline limiting flow rates and concentrations of air streams to within regulatory limits or by engineered emission control systems for those streams exceeding regulatory limits at the process.

Air emissions from the Allegra-D tablet production process will consist of exhausted air containing water vapor, particulates and organic materials.

Compliance with particulate emission standards is achieved utilizing filters operating at 99% efficiency for particulate matter sized 10 microns and below and 99.9% for larger particulates. All process air streams are conveyed through the filters before being released to the environment. Particulate matter collected by the filters and used fabric filter media are disposed of by incineration.

There are no volatile organic emissions from the tablet production; however, such emissions are generated by the Quality Control Laboratory analysis processes. Quality control analytical work will include methodologies currently used for other existing products at this facility. No volatile organic solvents not currently in use will be utilized for this product. Assay, physical testing and stability testing will use small quantities and dilute concentrations of acetonitrile which may volatilize and be exhausted to the atmosphere. These laboratory operations are performed with local ventilation exhausts which do not employ emission control systems. Compliance with organic emission limits is achieved through engineering design and employment of Good Laboratory Practices procedures.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

HMRI Kansas City facilities air emissions are currently regulated by permit from the Kansas City, Missouri Health Department Air Quality Section (#94/95-AQ-79). Kansas City has been delegated authority for implementation of Missouri state air laws and regulations, which implement the Federal Clean Air Act by the Missouri Department of Natural Resources; the facility is in full compliance with the city permit and state and federal laws.

Occupational exposures are regulated by Federal Occupational Safety and Health Act Standards (OSHA). Exposures are controlled by engineering design or the use of appropriate personal protective equipment. The facility is in compliance with the applicable regulations. Material Safety Data Sheets are available in *Attachment 4. MSDS for Fexofenadine Hydrochloride Drug Substance and Allegra-D Drug Product, S3–V1.10–P278.*

A signed statement of compliance for drug product manufacture at the Kansas City facilities is included in *Attachment 3. Statement of Compliance, Hoechst Marion Roussel Inc., Kansas City, Missouri, S3–V1.10–P276.*

Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will have insignificant effects on compliance with the Kansas City facility's current regulatory requirements. The facility will remain in full compliance with its permit and local, state and federal regulations.

ii. Aquatic Emissions

List of components of emitted streams:

Emission points are given in the confidential EA.

Component	CAS #
Fexofenadine Hydrochloride	138452-21-8
Pseudoephedrine Hydrochloride	345-78-8
Microcrystalline Cellulose	9004-34-6
Carnauba Wax	8015-86-9
Magnesium Stearate	557-04-0
Pregelatinized Starch	9005-84-9
Stearic Acid Flakes	57-11-4
Colloidal Silicon Dioxide	7631-86-9
Croscarmellose Sodium	74811-65-7
Opadry YS-1-7006	N/A
Water, purified‡	7732-18-5
Water, for cleaning	7732-18-5
‡ Removed during processing	

Statement of controls exercised:

The Kansas City facility discharges wastewater to a local publicly owned treatment works (POTW). Site discharges are regulated by a permit issued by the Kansas City, Missouri Water Pollution Control Department (expiration date January, 1998). Wastewater is treated at the Blue River Treatment Plant operated by Kansas City, Missouri. Discharges from the Blue River Treatment plant are to the Missouri River under an NPDES permit.

Wastewater from the Allegra-D tablet production will consist of cleaning solutions containing residual amounts of raw materials and coating solutions. All process discharges are neutralized and pH adjusted to a pH range of 6 to 10 pH units before discharging to the POTW system.

Citation of and statement of compliance with applicable emission requirements at federal, state and local levels:

Discharges to the POTW system are in compliance with a permit issued by the Kansas City, Missouri Water Pollution Control Department (expiration January, 1998), the State of Missouri, Law and Regulations (Department of Natural Resources) and with the Federal Water Pollution Control Act.

Occupational exposures are regulated by Federal Occupational Safety and Health Act Standards (OSHA). Exposures are controlled by engineering design or the use of appropriate personal protective equipment. The facility is in compliance with the applicable regulations. Material Safety Data Sheets are available in *Attachment 4. MSDS for Fexofenadine Hydrochloride Drug Substance and Allegra-D Drug Product, S3–V1.10–P278.*

A signed statement of compliance for drug product manufacture at the Kansas City facilities is included in *Attachment 3. Statement of Compliance, Hoechst Marion Roussel Inc., Kansas City, Missouri, S3–V1.10–P276.*

Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will have an insignificant effect on compliance with the Kansas City facility's compliance with its current permit and regulatory requirements.

iii. Terrestrial Emissions

List of components of emitted streams:

Component	CAS #
Fexofenadine Hydrochloride	138452-21-8
Pseudoephedrine Hydrochloride	345-78-8
Microcrystalline Cellulose	9004-34-6
Carnauba Wax	8015-86-9
Magnesium Stearate	557-04-0
Pregelatinized Starch	9005-84-9
Stearic Acid Flakes	57-11-4
Colloidal Silicon Dioxide	7631-86-9
Croscarmellose Sodium	74811-65-7
Opadry YS-1-7006	N/A
Water, purified‡	7732-18-5
‡ Removed during processing	

Statement of controls exercised:

Solid wastes from Allegra-D tablet manufacturing consist of small quantities of excipients from Quality Control area and associated wastes from manufacturing and processes. These wastes are collected, possibly recycled, or shipped offsite for incineration. Landfilling is precluded by procedures and would be utilized as emergency back up only.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Terrestrial discharges are in compliance with the Federal Resource Conservation and Recovery Act (Solid Waste Program: US EPA ID No. MOD-007119555) and Missouri Environmental Laws and Regulations (Missouri Hazardous Waste License No. 001603).

Occupational exposures are regulated by Federal Occupational Safety and Health Act Standards (OSHA). Exposures are controlled by engineering design or the use of appropriate personal protective equipment. The facility is in compliance with the applicable regulations. Material Safety Data Sheets are available in *Attachment 4. MSDS for Fexofenadine Hydrochloride Drug Substance and Allegra-D Drug Product, S3–V1.10–P278.*

A signed statement of compliance for drug product manufacture at the Kansas City site is included in *Attachment 3. Statement of Compliance, Hoechst Marion Roussel Inc., Kansas City, Missouri, S3–V1.10–P276.*

Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will not have a significant effect on compliance with the Kansas City facility's current regulatory requirements.

c. Employee Protection

Drug Substance Sites:

At The Dow Chemical Company, Midland, Michigan site, personnel in chemical production facilities are provided with appropriate personal protective equipment including safety glasses and goggles, safety shoes, protective gloves and clothing. Facilities and equipment are designed to minimize employee exposure to hazardous dust, fumes and vapors through engineering, work practices and administrative controls. Industrial hygiene monitoring of exposure to hazardous agents is routinely conducted at all production facilities. For certain non-routine or emergency situations, approved respiratory protection is provided to employees, and they are trained and fitted for use of the applicable respiratory protection device.

Employees are trained in the proper operation of equipment to minimize potential safety, health or environmental risks. Extensive safety training is mandated in all production facilities. Material Safety Data Sheets are available on-site for all chemicals handled in the production facilities.

Drug Product Site:

All associates receive extensive training for both normal and emergency situations as required to perform their respective operations. Associates receive general safety and chemical handling training as well as specialized training of the specific chemical hazards of the chemicals with which they work. HMRI provides worker protection by providing engineering controls wherever possible for potential hazards associated with noise, hazardous materials or ergonomic hazards. Associates are provided all necessary personal protective apparel to ensure compliance with company requirements and that required by Occupational Safety and Health Act (OSHA), Hazard Communication Standard and Laboratory Standard. Also, emergency training and provisions are provided to respond in the event of injury, fire or chemical release to the air, water, or land as required under the applicable federal, state, and local laws.

HMRI has programs and procedures in place to anticipate and prevent potential adverse environmental impacts associated with this proposed action. HMRI has established emergency plans to be implemented in the event of an injury, spill or fire that may happen at any site or while material is transported around the world. In-plant operation, including distribution and waste management operations, are carried out by trained personnel under the supervision of qualified personnel with training in both normal and emergency operations. Any incident that would require additional specialized expertise, would be provided by local fire, rescue, medical and emergency authorities or emergency response contract specialists.

d. Introduction From Disposal of Drug Substance and Drug Product

The expected introduction concentration (EIC) from disposal is considered to be negligible and is not calculated as waste will be incinerated at facilities that are regulated by the EPA and appropriate State agencies.

Drug Substance

Rejected, returned or expired fexofenadine hydrochloride drug substance (if not reprocessed) at the Midland, Michigan manufacturing site will be incinerated at the Dow Chemical Incineration Complex:

The Dow Chemical Company, Midland, Michigan 48667
EPA ID No.: MID 000724724

Permitted by: State of Michigan Department of Natural Resources
Air Use Permit Nos.: 93-73, 471-79, 403-78, 403-78A, 678-83, 887-89, 441-88, 336-81A (no expiration)
Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)
Incinerator emission limits are given in the confidential EA.

Rejected, returned or expired drug substance (if not reprocessed) at the Kansas City, Missouri manufacturing site will be incinerated at:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730
EPA ID No.: ARD069748192
Permitted by Arkansas Department of Pollution Control and Ecology
Hazardous Waste Management Permit: 10-H, CSN 70-0098 (expiration June 26, 1998)
Construction and Operations Permit: 1009A (until terminated or modified)
NPDES Permit: AR0037800 (expiration October 31, 1995; permit remains in effect due to submission of a complete reapplication in accordance with the appropriate regulations and administrative policies)
Incinerator emission limits are given in the confidential EA.

Drug Product

Rejected, expired or returned drug product (if not reprocessed) will be returned to HMRI, 10236 Marion Park Drive, Park C, Kansas City, Missouri 64137 for evaluation and disposal. Materials identified for disposal will be shipped to the following facilities for incineration:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730
EPA ID No.: ARD069748192
Permitted by Arkansas Department of Pollution Control and Ecology
Hazardous Waste Management Permit: 10-H, CSN 70-0098 (expiration June 26, 1998)
Construction and Operations Permit: 1009A (until terminated or modified)
NPDES Permit: AR0037800 (expiration October 31, 1995; permit remains in effect due to submission of a complete reapplication in accordance with the appropriate regulations and administrative policies)
Incinerator emission limits are given in the confidential EA.

At US hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures and in the home, 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, although minimal quantities of unused drug may be disposed of in the sewer system.

e. Introduction From Use of Drug Product

Allegra-D is administered orally and may be used by individuals throughout the United States. The estimated fifth year market volume of Allegra-D tablets in the US is estimated to amount to approximately [confidential]. The estimate for use is based on total fifth year production estimates for all dosage forms and strengths of fexofenadine hydrochloride in this application and in the previously approved Allegra™ application. The estimated total fifth year production of fexofenadine hydrochloride is [confidential].

Fexofenadine hydrochloride is minimally metabolized. The methyl ester of fexofenadine hydrochloride (3.59% dose) and MDL 4,829 (1.47% dose) were the only potential metabolites of fexofenadine hydrochloride measured. Biliary and renal excretion are considered the principle routes of elimination for fexofenadine hydrochloride. Pseudoephedrine undergoes minimal hepatic metabolism with the majority of that being demethylation to the active metabolite norpseudoephedrine. (Kanfer, Dowse et al; Bnezra and McRae.) The majority of pseudoephedrine is excreted unchanged in the urine. (Bye, Hill, et al; Lo, Land, Bye; Dlebeke and Debackere; Lucarotti, Colaizzi, et al; Lai, Stoll, et al; Brater, Kaojarern, et al.) Excreted drug substance would be introduced into the environment primarily through municipal sewage treatment plants or septic tanks.

The calculation of the expected introduction concentration (EIC) entering into the aquatic environment from patient use is based on total fifth year production of fexofenadine hydrochloride and does not include consideration of metabolism or environmental depletion mechanisms that occur in the waste treatment process. The EIC for the aquatic environment, assuming all drug substance produced is used, even distribution throughout the US per day, and no metabolism or depletion mechanisms, is calculated as follows:

EIC - Aquatic (ppm) = A x B x C x D
where: A = kg/year production [confidential]
B = $1/1.115 \times 10^{11}$
C = year/365 days
D = 10^6 mg/kg

The EIC from patient use of fexofenadine hydrochloride, based on the projected total fifth year production of fexofenadine hydrochloride is [confidential]. Therefore this EA does not qualify for the Tier 0 approach.

7. Fate of Emitted Substances in the Environment

As the EIC for fexofenadine hydrochloride is calculated to be [confidential], this EA does not qualify for the Tier 0 approach and information and data regarding environmental fate and effects is included.

Metabolism of fexofenadine hydrochloride and pseudoephedrine hydrochloride is minimal and primarily parent substance is expected to enter the environment from patient use. In addition, based on physical/chemical properties of fexofenadine hydrochloride, no structurally related substances are expected to exist in the environment. Therefore environmental fate and effects are considered only for the parent substance, fexofenadine hydrochloride.

Physical/Chemical Properties

The physical and chemical properties of fexofenadine hydrochloride have been evaluated and are reported in detail in the Chemistry, Manufacturing and Controls Section. Study reports are included in the confidential EA. Except where noted, all studies were conducted by Marion Merrell Dow Inc., Cincinnati, Ohio or Kansas City, Missouri. Those data which are environmentally relevant are summarized here, and in a data summary chart in *Attachment 5. Fexofenadine Hydrochloride Data Summary Chart, S3–V1.10–P288.*

Water Solubility

The solubility of fexofenadine hydrochloride in water is 2.44 mg/mL at 25°C.

Hydrolysis

Fexofenadine hydrochloride is not expected to hydrolyze due to the absence of hydrolyzable groups such as esters, amides, etc. The estimated hydrolysis rate constant is <10E-5/second.

Dissociation Constant

Fexofenadine hydrochloride is a diprotic compound having both an acidic functional group and a basic functional group. The compound will be a cation at low pH (less than 3), a zwitterion at intermediate pH (between 5 and 9), and an anion at high pH (greater than 11). The dissociation constants were determined, using pH/solubility data, to be 4.25 and 9.53.

n-Octanol/Water Partition Coefficient

The n-octanol/water partitioning coefficients for fexofenadine hydrochloride, a diprotic zwitterionic compound was determined over the pH range 2 to 12. From the observed partitioning coefficients, the intrinsic partitioning coefficients were calculated for the positively charged, neutral and negatively charged species to be: $k_0 = 2.612$, $k_1 = 1.980$ and $k_2 = 5.49$, respectively. The partition coefficients were calculated to be 2.1, 2.0, and 2.8 (log kow (log P) of 0.32, 0.30 and 0.44) at pH 5, 7, and 9, respectively.

Vapor Pressure

A study was conducted by The Dow Chemical Company, Midland, Michigan to measure the vapor pressure of fexofenadine hydrochloride by the Knudsen-Effusion/Weight Loss Method. The vapor pressure was found to be $< 5 \times 10^{-10}$ mmHg at 78.2° C.

Melting Temperature

Upon heating, fexofenadine hydrochloride melts with decomposition at a DSC onset temperature above 190°C (scan rate = 10° C/min).

Ultraviolet -Visible Absorption Spectrum

Fexofenadine hydrochloride shows UV absorbance maxima at 259 nm and 254 nm.

Environmental Depletion Mechanisms

Based on the physical/chemical properties of fexofenadine hydrochloride, there appears to be no environmental depletion mechanism and it will most likely amass predominantly in the aquatic environment. A biodegradation in water study indicated biodegradation in water is insignificant (< 4%), therefore fexofenadine hydrochloride is not expected to be depleted in the aquatic environment.

Biodegradation in Water:

An aerobic biodegradation study in water on [14C]-fexofenadine hydrochloride was conducted by Analytical Bio-Chemistry Laboratories Inc., Columbia, Missouri and the report is included in the confidential EA. No mineralization was observed during the 28-day test period. [14C]-MDL 16,455A was biotransformed slightly with a polar and nonpolar degradate comprising 2.6% and 0.7%, respectively of the applied radioactivity.

Expected Environmental Concentration (EEC)

The EIC of fexofenadine hydrochloride is calculated assuming no metabolism or environmental depletion mechanisms, and is [confidential]. The EEC of fexofenadine hydrochloride is calculated assuming no dilution. Therefore, EIC = EEC = Maximum Expected Environmental Concentration (MEEC) = [confidential].

Summary of Environmental Fate

Aquatic Environment:

Since the majority of fexofenadine hydrochloride will be discharged to public sewage treatment plants as a result of patient usage, the majority of environmental transport and biotransformation processes will occur primarily in the aquatic compartment. As fexofenadine hydrochloride is soluble in water and is not expected to hydrolyze, photodegrade under normal environmental conditions, or biodegrade in water, fexofenadine hydrochloride is most likely to amass predominantly in the aquatic environment.

Terrestrial Environment:

The n-octanol/water partition coefficient of fexofenadine hydrochloride at pH 7 is 2.0; log P (or log K_{ow}) is 0.30. The adsorption coefficient (K_{oc}) is calculated from the partition coefficient by the equation Log K_{oc} = 0.554 Log K_{ow} + 1.377 and is 1.54. The K_{oc} and solubility in water predicts fexofenadine hydrochloride would be mobile and would not be expected to bioconcentrate or bind to soil.

Atmospheric Environment:

Fexofenadine hydrochloride's low vapor pressure and solubility in water preclude the air compartment from being affected by volatilization of this substance at the public sewage treatment plant. Manufacturing controls would prevent significant releases to the air during the manufacturing process.

8. Environmental Effects of Released Substances

The EIC of fexofenadine hydrochloride is [confidential], therefore this EA does not qualify for the Tier 0 approach and environmental effects information and data are included. As no environmental depletion mechanism was identified and fexofenadine hydrochloride will most likely amass predominantly in the aquatic environment, Tier 1 acute toxicity studies are included in this section. Other toxicity and environmental effects data are also included.

Nonclinical Toxicology Studies with MDL 16,455A

An acute oral toxicity study in mice and rats was conducted by the Merrell Dow Research Institute, Merrell Dow Pharmaceuticals Inc., Cincinnati, Ohio. The approximate oral LD_{50} for mice and rats was > 5146 mg/kg. The toxicology of fexofenadine hydrochloride has been evaluated and is reported in detail in the Section 5.C. Toxicology.

Microbial Growth Inhibition

A microbial growth inhibition study was conducted by Analytical Bio-Chemistry Laboratories Inc., Columbia, Missouri and the report is included in the confidential EA. No inhibition was observed for *Pseudomonas fluorescens, Bacillus megaterium, Azotobacter chroococcum, Aspergillus clavatus, Penicillium canescens* and *Chaetomium globosum* at any concentration of fexofenadine hydrochloride up to and including 1000 mg/L. Therefore the minimum inhibitory concentration (MIC) for these species was >1000 mg/L. The MIC for *Anabaena flos-aquae* was 400 mg/L.

Aquatic Toxicology Studies with Fexofenadine hydrochloride

Daphnia magna

An acute toxicity study in *Daphnia magna* was conducted by Analytical Bio-Chemistry Laboratories Inc., Columbia, Missouri and the report is included in the confidential EA. The 48-hour EC_{50} for fexofenadine hydrochloride was 780 mg/L. The 48-hour no-observed effect concentration was 330 mg/L.

The NOEC in *Daphnia magna* divided by the MEEC of fexofenadine hydrochloride is greater than the Tier 1 assessment factor of 1000. Therefore, Tier 2 testing was not conducted.

Freshwater Fish

An acute toxicity study in the bluegill fish (*Lepomis macrochirus*) was conducted by Analytical Bio-Chemistry Laboratories Inc., Columbia, Missouri and the report is included in the confidential EA. The 96-hour LC_{50} for fexofenadine hydrochloride was > 940 mg/L. The 96-hour no-observed effect concentration was 570 mg/L.

The NOEC in bluegill fish divided by the MEEC of fexofenadine hydrochloride is greater than the Tier 1 assessment factor of 1000. Therefore, Tier 2 testing was not conducted.

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ALLEGRA-D™
(combination fexofenadine hydrochloride 60 mg and pseudoephedrine hydrochloride 120 mg tablets)

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment (Nonconfidential)

Conclusions on Environmental Impact:

The MEEC of fexofenadine hydrochloride is calculated assuming no metabolism, environmental depletion mechanism or dilution. Therefore the MEEC = EIC = [confidential]. For *Daphnia* and bluegill fish, the NOEC divided by the MEEC is greater than the Tier 1 assessment factor of 1000 for both species, so no further testing was conducted. Introduction of fexofenadine hydrochloride into the environment from patient use is not expected to have adverse effects in the environment.

Fexofenadine hydrochloride is likely to biotransform significantly, based on the presence of functional groups in the molecule that are likely to undergo microbial mediated biodegradation. In addition, the dissociation constant results indicate the compound, having acidic and basic functional groups, will exist as cation at low pH (< 3), a zwitter ion at pH 5 and 9, and as anion at pH 11 or higher. These functional groups will also facilitate microbial attack and biodegradation.

Fexofenadine hydrochloride has UV-VIS absorbance in the region of 259 and 254 nm and is therefore not amenable to direct photodegradation. However, the compound may undergo indirect photodegradation in the wastewater treatment plant (WTP) as there are several sensitizers that will absorb light and transfer the excitation energy to the target compound, facilitating extensive degradation. Thus photodegradation and biodegradation in the activated sludge aeration tanks will lead to significant depletion of the compound. Also, the sludge solids will undergo further degradation in the anaerobic digesters, facilitating further depletion of the compound through anaerobic microbial degradation. Fexofenadine hydrochloride will be reduced significantly in the WTP by these mechanisms.

Fexofenadine hydrochloride is likely to partition partly into water and partly into sludge solids, based on the water solubility (2,440 ppm) and octanol/water partition coefficient (log K_{ow} ranges from 0.3 to 0.44). The solubility of the compound relative to the amount excreted into the wastewater treatment plants will ensure partition into wastewater effluent. The K_{ow} values will tend to partition a small amount of the drug into the sludge solids.

The WTP effluents will undergo a thousand fold dilution in the surface water at the effluent out fall (Operation of Wastewater Treatment Plants, A Manual of Practice; Water Pollution Control Federation, 1975), resulting in a worst case concentration of [confidential] in the surface water. This concentration will be further reduced due to dilution of the WTP out fall. Biodegradation and photodegradation are possible depletion mechanisms of the compound in surface water.

In the United States, approximately 40% of WTP sludge is applied to agricultural fields, 30% is disposed of in the landfill, and the remainder is incinerated. At the current application rate of municipal sludge in soil, there will be a thousand fold dilution (The Nature and Properties of Soil, Nyle C. Brady, Macmillan, 1974). This will result in a [confidential] concentration even if all the compound is partitioned into sludge. As soils have a diverse group of microorganisms ie,

fungi, actinomycete, and bacteria, the biodegradation potential is much higher than water which contains mostly bacteria.

The worst case EEC of the compound in surface water and soil [confidential] is several orders of magnitude lower than the NOEC of the most sensitive microorganism tested. This indicates that the compound is not toxic to microorganisms and will not inhibit microbial mediated degradative processes in these environmental matrices.

The worst case EEC of the compound in surface water [confidential] is several orders of magnitude lower than the NOEC for the aquatic species *Daphnia* (330,000,000 ppt) and fresh water fish (570,000,000 ppt). This indicates the compound is not toxic to aquatic species.

Based on the above conclusions, no environmental impact is expected due to the use and disposal of fexofenadine hydrochloride.

9. Use of Resources and Energy

a. Drug Substance

There will not be a significant impact on total usage of energy or utilities by the Michigan Division site of The Dow Chemical Company as a result of the manufacture of fexofenadine hydrochloride. The total steam and electrical power consumption for this purpose will be less than 1% of the overall site usage. No new land use will be required for the proposed new action.

The Michigan Department of Natural Resources Wildlife Division was contacted to determine if endangered or threatened species inhabit the area of drug substance manufacture. A search of the Michigan Natural Features Inventory database (Natural Heritage Program, Wildlife division) was conducted. The database indicated there are records of the threatened sedge *Carex serosa* in the Chippewa and Tittabawasee Rivers. The records documenting this species' presence are very old, and the Department of Natural Resources' assessment is the sedge should not be impacted by the manufacturing site.

The National Register of Historic Places includes at least 17 listings of historical sites in Midland County, Michigan. Consultation with the Midland County Historical Society indicated the nearest historical site is approximately one mile from the plant's property. The proposed action is not expected to have a significant impact on these historical sites, as the controls on the manufacturing process should prevent any adverse effects to these sites.

b. Drug Product

The proposed action will not have a significant impact on total usage of energy or utilities by the Kansas City site. The manufacturing process for both Allegra™ and Allegra-D is expected to require an additional 10% utility requirement above the existing total site utilities usage. Site utility capacity is sufficient to provide this increased usage without need for expansion. No new land use will be required for the proposed new action.

The Missouri Department of Conservation lists the barn owl as a rare species in Jackson County. Consultation with the Department of Conservation indicated there are other species in the area also, but their experience indicated there are none in the immediate vicinity of the manufacturing site. Department staff examined map and computer files for federal and state threatened and endangered species, and determined that no sensitive species or communities are known to occur on the immediate site or surrounding area.

There are at least 134 historical sites in Jackson County, Missouri listed in the National Register of Historic Places. In addition, 13 sites in Jackson County are pending nomination in the Federal Register. The nearest historical site is located approximately one mile from the manufacturing site. The proposed action should not have a significant impact on these sites, as the controls on the manufacturing process will prevent any adverse effects to these sites.

10. Mitigation Measures

An emergency preparedness plan is in place both for the fexofenadine hydrochloride production unit and The Dow Chemical Company Michigan Division Site, which includes on-site fire and emergency response personnel. All storage vessels are equipped with secondary containment to prevent groundwater contamination. All operating personnel are trained on both proper industrial hygiene protocols and emergency response procedures.

HMRI has programs and procedures in place to anticipate and prevent potential adverse environmental impacts associated with this proposed action. HMRI has established emergency plans which are implemented in the event of an injury, spill or fire that may happen at any site or during transport around the world. All plant operations, including distribution and waste management, are carried out by trained personnel under the supervision of qualified personnel with training in both normal and emergency procedures. Material Safety Data Sheets for drug substance and drug product are available *(Attachment 4. MSDS for Fexofenadine Hydrochloride Drug Substance and Allegra-D Drug Product, S3–V1.10–P278)*. Any incident that would require additional specialized expertise would be provided by local fire, rescue, medical and emergency authorities or emergency response contract specialists.

11. Alternatives to the Proposed Action

The alternative to the proposed action is nonapproval and the prevention of Allegra-D from being available for the use in the relief of symptoms of seasonal allergic rhinitis. Since the proposed action is not expected to have any adverse effects on the environment, no alternatives are proposed.

12. List of Preparers

Hoechst Marion Roussel, Inc., Kansas City, Missouri

Donald L. Krueger, PE
Environmental Specialist
BS Chemical Engineering, University of Missouri, 1967
22 years experience

Vicki J. Selzer, DVM
Sr Associate Scientist, Toxicology
DVM Kansas State University College of Veterinary Medicine, 1985
BS Life Science and Physical Science, Kansas State University, 1980
9 Years Experience

Dhiren N. Shah, PhD
Director, Global Regulatory CMC
PhD Physical and Industrial Pharmacy, Purdue University, 1979
MS Industrial Pharmacy, Columbia University, New York, 1971
B.Pharm. Gujarat University, India, 1968
18 years experience

Hoechst Marion Roussel, Inc. at The Dow Chemical Company, Midland, Michigan

Charles E. Aiman, PhD
Director of Bulk Drug Supplies
PhD Organic Chemistry, University of Kansas, 1962
32 years experience

The Dow Chemical Company, Midland, Michigan

Kirsten L. Lang
Sr Production Engineer
BS Chemical Engineering, University of New Mexico, 1987
7 years experience

Ron M. Lacher
Sr Process Specialist
BS Chemical Engineering, South Dakota School of Mines and Technology, 1972
MS Chemical Engineering, South Dakota School of Mines and Technology, 1977
8 years experience

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment (Nonconfidential)

Persons and Agencies Consulted

Joan M. Fischer
Marion Merrell Dow Inc.
North American Business Development

State of Michigan Department of Natural Resources
Wildlife Division

Dennis Figg
Endangered Species Coordinator
Missouri Department of Conservation
Natural History Division

Kansas City Landmark Society

Midland County (Michigan) Historical Society

Chamber of Commerce
Kansas City, Missouri

Chamber of Commerce
Grandview, Missouri

U.S. Department of Commerce
Bureau of the Census
Population Division

Ranga R. Velagaleti, PhD
Director, Environmental Fate and Assessment
Analytical Bio-Chemistry Laboratories, Inc.
Columbia, Missouri

13. Certification

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the Environmental Assessment.

The undersigned official certifies that the Environmental Assessment summary document (Exhibit 14: Allegra-D Environmental Assessment FOI [nonconfidential] Copy) and Attachments 1 through 5 contain nonconfidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6.

Preparation of Environmental Assessment:

Signature: Vicki J. Selzer Date: 12/3/97
Vicki J. Selzer, DVM
Scientist, Toxicology

Review and Approval of Environmental Assessment:

Signature: Steven D Barkyoumb Date: 12/3/97
Steven D. Barkyoumb, DVM, PhD
Sr Director, Drug Safety

Signature: Paul F Neihouse Date: 12/3/97
Paul F. Neihouse, PharmD
Assistant Director,
US Drug Regulatory Affairs

NDA 20-786

ALLEGRA-D™
(combination fexofenadine hydrochloride 60 mg and pseudoephedrine hydrochloride 120 mg tablets)

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Attachment 1. Dosage Form Components of Allegra-D Tablets

Hoechst Marion Roussel, Inc.

NDA 20-786

ALLEGRA-D™
(combination fexofenadine hydrochloride 60 mg and pseudoephedrine hydrochloride 120 mg tablets)

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Dosage Form Components of MDL 16,455A Tablets:

Component	CAS #
Fexofenadine Hydrochloride	138452-21-8
Pseudoephedrine Hydrochloride	345-78-8
Microcrystalline Cellulose	9004-34-6
Carnauba Wax	8015-86-9
Magnesium Stearate	577-004-0
Pregelatinized Starch	9005-84-9
Stearic Acid Flakes	57-11-4
Colloidal Silicon Dioxide	7631-86-9
Croscarmellose Sodium	74811-65-7
Opadry YS-1-7006	N/A
Water, purified	7732-18-5

Attachment 2. Statement of Compliance, The Dow Chemical Company, Midland, Michigan

DOW

The Dow Chemical Company
Midland, Michigan 48667

June 12, 1995

FEXOFENADINE HYDROCHLORIDE DRUG SUBSTANCE- ENVIRONMENTAL ASSESSMENT

Fexofenadine hydrochloride drug substance is manufactured at the Dow Chemical Company's Michigan division facilities, Midland, Michigan, in compliance with all applicable state and federal environmental regulations.

The unlawful release of contaminants to the environment is prevented by the use of appropriate emission control devices such as vent gas scrubbers, particulate filters and activated waste water treatment.

The process to manufacture fexofenadine hydrochloride drug substance is covered by Air Use Permits issued by the State of Michigan (Air Quality Division of the Michigan Department of Natural Resources pursuant to the delegation of authority from the Michigan Air Pollution Control Commission - Act 348, P.A. 1965, as amended); Air Use Permit No. 1371-91A. The process is in compliance with these rules, which are consistent with and at least as stringent as applicable federal standards under the Clean Air Act.

This process is in compliance with the Resource Conservation and Recovery Act (RCRA) of 1976, Title II (Solid Waste Disposal) and the State of Michigan Public Act 64, the Solid Waste Management Act.

The process is in compliance with the Federal Water Pollution Control Act and the Michigan Water Resources Commission Act (under the National Pollution Discharge Elimination System Permit No. MI 4(0000868).

D.C.Price
Manager
Pharmaceutical Chemicals Technology Center
827 Building
The Dow Chemical Co.
Midland, MI 48667

NDA 20-786

ALLEGRA-D™
(combination fexofenadine hydrochloride 60 mg and pseudoephedrine hydrochloride 120 mg tablets)

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Attachment 3. Statement of Compliance, Hoechst Marion Roussel Inc., Kansas City, Missouri

Hoechst Marion Roussel

FEXOFENADINE HYDROCHLORIDE DRUG PRODUCTS, ENVIRONMENTAL ASSESSMENT

Fexofenadine Hydrochloride drug products are manufactured at the Hoechst Marion Roussel, Inc., Kansas City facilities in compliance with all applicable local, state and federal occupational and environmental regulations.

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

The release of contaminants to the environment from the Kansas City facility is controlled by the use of appropriate emission control devices such as particulate filters, thermal destruction devices, wastewater treatment and by internal procedures and polices as necessary for compliance.

The process to manufacture the fexofenadine hydrochloride drug products is covered by air permits issued by the City of Kansas City, Missouri, Health Department, Air Quality Section (Permit #502), under authority delegated to the City by the Missouri Department of Natural Resources and the US Environmental Protection Agency. The manufacturing process is in compliance with these permits and the underlying rules and regulations, the permits and regulations are consistent with and at least as stringent as applicable federal standards under the Clean Air Act.

The manufacturing process is in compliance with the Resource Conservation and Recovery Act (RCRA) of 1976, Title II (Solid Waste Disposal) and the State of Missouri Hazardous Waste Management Law and the Solid Waste Law, Title 16.

The manufacturing process is in compliance with a wastewater discharge permit issued by the City of Kansas City, Missouri, Water and Pollution Control Department (expires January 1998). The wastewater discharge permit is consistent with and as stringent as applicable state regulations under Title 10 of the Missouri Code of State Regulations and federal regulations under the Clean Water Act.

The manufacturing facilities are likewise in compliance with applicable occupational health and safety regulations and laws. The site is governed by federal Occupational Safety and Health Administration (OSHA) regulations under 29 CFR 1910.

Donald L. Krueger, P.E.
Environmental Specialist

Daniel G. Maher
Vice President, KC Operations
Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
Kansas City, Missouri 64137

Attachment 4. MSDS for Fexofenadine Hydrochloride Drug Substance and Allegra-D Drug Product

Material Safety Data Sheet

PREPARATION DATE: 18 November, 1996

SECTION 1: Chemical Product and Company Identification

Common Name: (used on the label)	Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride
(Trade Name & Synonyms)	**Allegra-D™** Terfenadine Acid Metabolite (TAM) MDL16,455A
Chemical Name:	*fexofenadine hydrochloride*: (+/-)-4-[1-hydroxy-4[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride *pseudoephedrine hydrochloride*: [S-(R*,R*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrochloride
Manufacturer's Name:	Hoechst Marion Roussel
Address:	10236 Marion Park Drive Kansas City, Missouri 64137
Emergency Telephone Numbers:	Call St. Paul-Ramsey Medical Center for a 24 hour/day DOT Emergency Response Hotline.
Within the U.S. and Canada use:	1-800-228-5635 ext. 254
Outside the U.S. and Canada use:	1-612-221-3999 ext. 254
Other Information Calls:	816-966-5755 or 816-966-5000

SECTION 2: Composition/Information on Ingredients

Material:	Allegra-D™
Composition:	fexofenadine hydrochloride (60 mg) and pseudoephedrine hydorchloride (120 mg)
Nature of Hazard:	Allegra-D is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itch nose/palate/throat, itchy/watery/red eyes, and temporary relief of nasal congestion. Allegra-D should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired.

SECTION 3: Hazards Identification

Appearance:	two-layer tablet, one white layer and one tan layer with a clear film coating on the tablet; tablets are engraved with "xxxx" on the white layer
Packaging:	Allegra-D tablets are available in: high density polyethylene (HDPE) bottles of 30; bottles of 60; bottles of 100, bottles of 500, and clear blister packs of 100

Acute Exposure: The approximate LD50 for mice and rats was > 5146 mg/kg.
Single oral doses of 1000 mg/kg and 2000 mg/kg in male dogs showed no clinically apparent MDL16,455A related effects.

Chronic Exposure: Oral MDL16,455A was well tolerated clinically up to 300 mg/kg/day for 15 days, with only single sporadic episodes of emesis in dogs, given 300 mg/kg/day.

See Toxicological Information, Section 11.

SECTION 4: First Aid Measures

Inhalation: Breathe fresh air.
Eyes: Flush thoroughly with water for 15 minutes, seek medical attention.
Skin: Remove contaminated clothing, wash affected area with soap and water.
Ingestion: If material is ingested, seek medical attention.

In the event of overdose: consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended.

SECTION 5: Fire Fighting Measures

Extinguisher Media: Carbon Dioxide, Dry Chemical Powder, Alcohol or Polymer Foam. Water may be effective for cooling.

Special Fire Fighting Procedures: Wear self-contained breathing apparatus and protective clothing to prevent contact with the skin.

Unusual Fire and Explosion Hazards: Hydrogen chloride gas and nitrogen oxides may be released.

Vapor Pressure: Not applicable.
Vapor Density: Not applicable.
Flashpoint: Not applicable.
Auto-ignition temperature: Not available.

SECTION 6: Accidental Release Information

Steps to be taken in case material is released or spilled: Sweep into suitable container and seal.

Waste Disposal Methods: Dispose according to local, state and/or federal regulations.

SECTION 7: Handling and Storage

Avoid contact with skin, or eyes.
Do not breathe the dust.
Incompatibility: Strong bases, strong acids at elevated temperatures, strong oxidizers.
Hazardous decomposition products: Hydrogen chloride gas, nitrogen oxides.
Hazardous polymerization: Will not occur.

Store Allegra-D tablets at controlled room temperature, 20-25°C (68-77°F). Protect from excessive heat. Foil-backed blister packs should be protected from excessive moisture.

SECTION 8: Exposure Controls/Personal Protection

Respiratory Protection: Atmospheric levels should be maintained below the exposure guideline. When respiratory protection is required, for certain operations, a NIOSH approved respirator, equipped with HEPA cartridges must be used.
Ventilation: Provide local exhaust ventilation to control airborne levels below the exposure guidelines.
Protective gloves: Use gloves impervious to this material.
Safety glasses must be used when handling this material.
Additional protective clothing and equipment: Disposable jump suit.

OSHA Permissible Exposure Limit: Not available.
ACGIH Threshold Limit Value: Not available.
Other exposure limits: Marion Merrell Dow Interim Industrial Hygiene Guide-5.0 mg/m3 of air.
This is based on a calculation using 300 mg/kg/day as a no observable effect level.
Chemical listed as a carcinogen or potential carcinogen: No.
National Toxicology Program: No.
I.A.R.C. Monographs: No.
OSHA: No.

SECTION 9: Physical and Chemical Properties

Appearance:	fexofenadine hydrochloride: white to off-white crystalline powder pseudoephedrine hydrochloride: fine, white to off-white crystalline powder or crystals
Odor:	pseudoephedrine hydrochloride: faint characteristic odor

SECTION 9: Physical and Chemical Properties continued ....

Physical State:	Solid.
pH:	Not applicable.
Vapor Pressure:	Not applicable.
Boiling Point:	Not applicable.
Melting Point:	Onset approximately 195°C-196°C (with decomposition) when heated at a rate of 10°C/minute.
Specific Gravity:	Not applicable.
DSC:	Sample exhibits a single endotherm above 190°C
TGA:	Sample loses less than 0.5% weight when heated up to 150°C.

Solubility: (Expressed as anhydrous HCl salt)

Chloroform	1.6 mg/ml
Hexane	1.0×10^{-4} mg/ml
Methanol	> 450 mg/ml
Tetramethylsilane	3.5×10^{-4} mg/ml
Propylene glycol	185 mg/ml at 25°C
Propylene glycol/acetic acid (98.5:1.5 v/v)	187 mg/ml at 25°C
Ethanol	> 300 mg/ml at 25°C.
Water	3.63 mg/ml at 25°C

SECTION 10: Stability and Reactivity

Stability (Conditions to avoid): Temperatures >190°C
Incompatibility: Strong bases, strong acids at elevated temperatures, strong oxidizers.
Hazardous decomposition products: Hydrogen chloride gas, and nitrogen oxides.
Hazardous polymerization: Will not occur.

SECTION 11: Toxicological Information

The approximate oral LD50 for mice and rats was > 5146 mg/kg.

LD50, Single oral administration, mice, male and female > 4500 mg/kg

Dogs-Female-Single oral dose (2 dogs/dose) of 300 and 500 mg/kg-No clinical signs of toxicity or adverse effects on body weights or food consumption.
Single oral dose of 1000 mg/kg and 2000 mg/kg, male dogs, showed no clinically apparent MDL16,455A related effects.

Dogs-1/sex/dose-daily oral doses of 10 or 30 mg/kg/day for 10 days
daily oral doses of 100 or 300 mg/kg/day for 15 days

SECTION 11: Toxicological Information continued .....

Conclusion: Oral MDL16,455A was well tolerated clinically up to 300 mg/kg/day for 15 days, with only single sporadic episodes of emesis in dogs given 300 mg/kg/day.

Dogs-Oral-3/sex/dose were given a total of 0, 90, 300, or 900 mg/kg/day
Conclusion: MDL16,455A was well tolerated with only a minimal reversible clinical effects at 900 mg/kg/day.

No reproductive toxicology studies have been done.

CONTRAINDICATIONS
ALLEGRA-D is contraindicated in patients with known hypersensitivity to any of its ingredients. Due to its pseudoephedrine component, ALLEGRA-D is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment (Ref. ND monograph; CL-D) (see **Drug Interactions** section). It is also contraindicated in patients with severe hypertension, or severe coronary artery disease, and in those who have shown hypersensitivity or idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include: insomnia, dizziness, weakness, tremor, or arrhythmias.(CL-D Labeling)

WARNINGS
Sympathomimetic amines should be used judiciously and sparingly in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (See Contraindications). Sympathomimetic amines may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension (Ref. ND monograph CL-D Labeling).

Use in Elderly:
The elderly are more likely to have adverse reactions to sympathomimetic amines (REF. CL-D).
SECTION 11: Toxicological Information continued .....

PRECAUTIONS
General
Due to its pseudoephedrine component, ALLEGRA-D should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see WARNINGS). Patients with decreased renal function should be given a lower initial dose (one tablet per day) because they have reduced elimination of fexofenadine and pseudoephedrine (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION) (Ref. CL-D Labeling).

Information for Patients
Patients taking ALLEGRA-D tablets should receive the following information: ALLEGRA-D tablets are prescribed for the relief of symptoms of seasonal allergic rhinitis. Patients should be

SECTION 11: Toxicological Information continued .....

instructed to take ALLEGRA-D tablets only as prescribed. (Ref. CL-D Labeling) **Do not exceed the recommended dose.** If nervousness, dizziness, or sleeplessness occur, discontinue use and consult the doctor (Ref. ND monograph). Patients should also be advised against the concurrent use of ALLEGRA-D tablets with over-the-counter antihistamines and decongestants (Ref. CL-D). The product should not be used by patients who are hypersensitive to it or to any of its ingredients. Due to its pseudoephedrine component, this product should not be used by patients with narrow-angle glaucoma, urinary retention, or by patients receiving a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of MAO inhibitor. It also should not be used by patients with severe hypertension or severe coronary artery disease (Ref. CL-D).

Patients should be told that this product should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant. Patients should be cautioned not to break or chew the tablet. Patients should be directed to swallow the tablet whole. Patients should also be instructed to store the medication in a tightly closed container in a cool, dry place, away from children (Ref. 3B9a).

Drug Interactions Fexofenadine hydrochloride and pseudoephedrine hydrochloride do not influence the pharmacokinetics of each other when administered concomitantly (Ref. Section 8C2, synopsis; 6f2b, overall summary). In two separate studies, fexofenadine hydrochloride 120 mg twice daily (twice the recommended dose) was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with erythromycin or ketoconazole.

The mechanisms of these interactions are unknown, and the potential for interaction with other azole antifungal or macrolide agents has not been studied. These changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials. Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole (Ref. Allegra PI).

ALLEGRA-D tablets (pseudoephedrine component) are contraindicated in patients taking monoamine oxidase inhibitors and for 14 days after stopping use of an MAO inhibitor (Ref. ND monograph). Concomitant use with antihypertensive drugs which interfere with sympathetic activity (eg, methyldopa, mecamylamine, and reserpine) may reduce their antihypertensive effects (Tatrot and Zucchero from CDS). Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis (Ref. CL-D).
Care should be taken in the administration of ALLEGRA-D concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS) (Ref. DC to provide).

SECTION 11: Toxicological Information continued ....

Carcinogenesis, Mutagenesis, Impairment of Fertility
There are no studies on the combination product fexofenadine hydrochloride and pseudoephedrine hydrochloride to evaluate carcinogenesis, mutagenesis, or impairment of fertility (Ref. FEX NDA, Section 5, S5VX-PX Summary of Toxiocology).
The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (based on plasma area-under-the-curve [AUC] values). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses of 50 and 150 mg/kg of terfenadine for 18 and 24 months, respectively; these doses resulted in plasma AUC values of fexofenadine that were up to four times the human therapeutic value (based on a 60 mg twice-daily fexofenadine hydrochloride dose) (Ref. 50, 51 from TAM).

In in-vitro (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and in vivo (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity (Ref. 53-56 from TAM).
In rat fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at oral doses equal to or greater than 150 mg/kg of terfenadine; these doses produced plasma AUC values of fexofenadine that were equal to or greater than three times the human therapeutic value (based on a 60 mg twice-daily fexofenadine hydrochloride dose) (Ref. 52 from TAM).

Pregnancy
Teratogenic Effects: Category C. There was no evidence of teratogenicity in rats or rabbits at oral terfenadine doses up to 300 mg/kg; these doses produced fexofenadine plasma AUC values that were up to 4 and 37 times the human therapeutic value (based on a 60 mg twice-daily fexofenadine hydrochloride dose), respectively (Ref. 57-59 from TAM).
There are no adequate and well-controlled studies in pregnant women. ALLEGRA-D should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects. Dose-related decreases in pup weight gain and survival were observed in rats exposed to oral doses equal to and greater than 150 mg/kg of terfenadine; at these doses the plasma AUC values of fexofenadine were equal to or greater than 3 times the human therapeutic values (based on a 60 mg twice-daily fexofenadine hydrochloride dose) (Ref. 52 from TAM).

SECTION 11: Toxicological Information continued ....

Nursing Mothers

It is not known if this combination product is excreted in human milk. Because many drugs are excreted in human milk caution should be used when fexofenadine is administered to a nursing woman. Pseudoephedrine administered alone distributes into breast milk of lactating human females. Pseudoephedrine concentrations in milk are consistently higher than those in plasma. The total amount of drug in milk as judged by area under the curve (AUC) is 2 to 3 times greater than in plasma. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4% to 0.7%. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when ALLEGRA-D is administered to nursing women (Ref. CL-D).

Pediatric Use

Safety and effectiveness of ALLEGRA-D in pediatric patients under the age of 12 years have not been established (Ref. Allegra PI; CL-D). Across well-controlled clinical trials in patients with seasonal allergic rhinitis, a total of 205 patients between the ages of 12 to 16 years received fexofenadine hydrochloride doses ranging from 20 mg to 240 mg twice daily for up to two weeks. Adverse events were similar in this group compared to patients above the age of 16 years (Ref. Allegra PI).

Geriatric Use

In placebo-controlled trials, 42 patients, age 60 to 68 years, received doses of 20 mg to 240 mg of fexofenadine twice daily for up to two weeks. Adverse events were similar in this group to patients under age 60 years (Ref. Allegra PI).

SECTION 12: Ecological Information

Not available.

SECTION 13: Disposal Considerations

Dispose of according to local, state, and/or federal regulations.

SECTION 14: Transport Information

This material is not regulated as hazardous by U.S.-DOT. A copy of this MSDS should accompany shipments of this material.

SECTION 15: Regulatory Information

No additional information at this time.

SECTION 16: Other Information

The information provided in this Material Safety Data Sheet has been compiled from our experience and the data presented in various technical publications. It is the users responsibility to determine the suitability of this information for the adoption of safety precautions as may be necessary. We reserve the right to revise the Material Safety Data Sheet from time to time as new information becomes available. The user has the responsibility to contact the company to make sure the sheet is the latest one issued.

Attachment 5. Fexofenadine Hydrochloride Data Summary Chart

NDA 20-786

ALLEGRA-D™
(combination fexofenadine hydrochloride 60 mg and pseudoephedrine hydrochloride 120 mg tablets)

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

MDL 16,455A Data Summary Chart

Test	Results
Water solubility (mg/mL at 25°C)	2.44
Hydrolysis Rate Constant (estimated)	<10E–5/second
Dissociation Contstant (pK_a at 25°C)	$pK_1 = 4.25$ $pK_2 = 9.53$
Octanol/Water Partition Coefficient (log K_{ow} at pH 7)	0.30
Vapor Pressure (mmHg)	$<5 \times 10^{-10}$
Melting Temperature (°C)	>190
Ultraviolet–Visible Spectrum (absorption maxima, nm)	259 and 254
Aerobic Biodegradation in Water	
Mineralization (% CO_2)	0
Biotransformation (% degradation products)	3.3
Log K_{oc}*	1.54
Microbial Inhibition (MIC, mg/L) *Pseudomonas fluorescens, Bacillus megaterium, Azotobacter chroococcum, Asergillus clavatus, Penicillium canescens, Chaetromium globosum* *Anabaena flos–aquae*	>1000 400
Daphnia magna EC_{50} (mg/L) *Daphnia magna* NOEC (mg/L)	780 330
Lepomis macrochirus LC_{50} (mg/L) *Lepomis macrochirus* NOEC (mg/L)	>940 570

* Absorption Coefficient calculated from the equation Log K_{oc} = 0.554 Log K_{ow} + 1.377, where K_{ow} = n–Octanol/Water partition coefficient.