CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-909

PHARMACOLOGY REVIEW

INTEROFFICE MEMO

TO:	NDA 21909
FROM:	C. Joseph Sun, Ph. D.
SUBJECT:	Supervisory Pharmacologist NDA Review Memo
DATE:	May 21, 2007

I concur with the pharmacologist's conclusion that the pharmacology and toxicology of fexofenadine have been adequately studied based on the comprehensive toxicity data of terfenadine, its parent compound, and limited data of fexofenadine. All the inactive ingredients in the drug product are either GRAS or present in approved marketing oral products. Therefore we recommend approval for the drug product from a preclinical standpoint.

Fexofenadine is a selective H1 receptor antagonist. It is more potent than terfenadine in displacing mepyramine from rat cerebral cortex in an in vitro receptor binding study. Fexofenadine is equipotent to terfenadine in antagonizing the histamine-induced bronchoconstriction in guinea pigs. Fexofenadine did not prolong QTc in dogs and rabbits and had no effects on calcium channel current, delayed potassium channel current or action potential duration in guinea pig myocytes or the delayed rectified potassium channel cloned from human heart.

Chronic toxicity of terfenadine has been extensively studied in animals. Terfenadine was extensively metabolized to fexofenadine. Therefore, the chronic toxicity of fexofenadine is assessed based on the chronic toxicity studies of terfenadine in dogs and the toxicity comparison between fexofenadine and terfenadine in dogs and mice. In dogs, no significant toxicity was observed other than emesis in the 6-month toxicity study of fexofenadine. By comparison, significant toxicities (convulsions and lethality) were observed within 2-3 weeks after dosing of terfenadine at a much lower dose in the 2-year study. Furthermore, in a 3-month mouse study, comparable decrease in body weight occurred where the exposure of fexofenadine from much lower doses of terfenadine was twice that from fexofenadine administration. These toxicity and exposure comparisons in dogs and mice indicate that fexofenadine was less or no more toxic than terfenadine.

Reproductive toxicity of fexofenadine was evaluated based on the reproductive studies of terfenadine. Fertility in mice was not affected, and no terotogenic effects were reported in mice, rats and rabbits following oral administration of terfenadine with significant exposure of fexofenadine being present. However, dose-related decreases in pup weight gain and survival were observed in rats. Thus, a pregnancy category C designation is appropriate.

Fexofenadine was not genotoxic in four mutagenicity studies (Ames test, forward mutation assay of CHO cells, chromosome aberration test of rat lymphocytes and in vivo mouse micronucleus test).

Fexofenadine demonstrated no carcinogenic potential in two oral carcinogenicity studies of terfenadine in rats and mice where significant exposure to fexofenadine was achieved.

The above-mentioned preclinical findings have been incorporated in the carcinogenesis, mutagenesis and impairment of fertility and pregnancy category C sections in the labeling.

There are no outstanding preclinical issues.

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

/s/

Joseph Sun
5/21/2007 12:38:24 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-909
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	9/28/06
PRODUCT:	Allegra Orally Disintegrating Tablet (proposed)
INTENDED CLINICAL POPULATION:	Patients suffering from seasonal allergic rhinitis or chronic idiopathic urticaria
SPONSOR:	Sanofi Aventis
DOCUMENTS REVIEWED:	Vol. NA.
REVIEW DIVISION:	Division of Pulmonary and Allergy Products
PHARM/TOX REVIEWER:	Lawrence F. Sancilio, Ph.D.
PHARM/TOX SUPERVISOR:	Chng-long J. Sun, Ph.D.
DIVISION DIRECTOR:	Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER:	Lori Garcia

Date of review submission to Division File System (DFS): 5/21/07

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
Recommend approval with the recommended labeling changes.

B. Recommendation for nonclinical studies
None.

C. Recommendations on labeling
Modify the label with the recommended changes.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Fexofenadine, a H_1 receptor antagonist, was the active metabolite of terfenadine; an antihistamine that was withdrawn from the market since it produced Torsades des Pointes due to prolongation of the QTc interval. Fexofenadine did not prolong the QTc interval in animals, and consequently, lacks the potential for producing Torsades des Pointes.

Toxicity of fexofenadine was based on the toxicity of terfenadine since terfenadine was rapidly metabolized to fexofenadine, its major metabolite. In dogs, terfenadine was more toxic than fexofenadine. In a 1-month gavage study fexofenadine at oral doses of 90, 300 and 900 mg/kg/day induced emesis occurring at all doses. No other toxic effects were noted. Terfenadine in a one-month oral study, the AUCs for fexofenadine from terfenadine administration was equal to or greater than the AUCs of fexofenadine from fexofenadine administration. In a 6-month toxicity study, fexofenadine at doses of 100, 300 and 900 mg/kg, orally, were not toxic, other than producing emesis. When terfenadine was tested at 30 and 100 mg/kg, orally in a 2-year study in dogs, convulsions and lethality occurred at 100 mg/kg within 2-3 weeks necessitating lowering the dose to 80 mg/kg to the surviving animals. Testicular atrophy was seen in 2/3 dogs at the 80 mg/kg dose. By comparison, the AUC for fexofenadine for the 80 mg/kg dose of terfenadine was comparable (35 ug.h/ml vs 44 ug.h/ml) to the AUC for fexofenadine from the administration of 100 mg/kg of fexofenadine in the 6-month study showing that fexofenadine was less toxic than terfenadine.

In a 3-month dietary study in mice, the toxicity of terfenadine (M, 247 mg/kg; F, 321 mg/kg) was compared with fexofenadine (M, 848, 4367 and 8722 mg/kg; F, 1080, 5154 and 10,324 mg/kg). The AUC of fexofenadine from terfenadine administration (247 mg/kg) was twice that from the dose of terfenadine (848 mg/kg). At this dose of terfenadine and fexofenadine, there was a comparable decrease in body weight gained.

In rats, no toxicity studies were conducted with fexofenadine and terfenadine to make a comparison. In a 3-month oral study in rats, doses of 30, 100 and 300 mg/kg of terfenadine produced minimal toxicity as evidenced by increased reticulocyte levels and weight changes in the seminal vesicles, heart, prostate, pituitary, thyroid and adrenal glands. There was no histopathology observed.

In the carcinogenicity studies in mice and rats, significant exposure to fexofenadine was achieved through the dietary administration of terfenadine. In both species, terfenadine was not carcinogenic at doses of 50 and 150 mg/kg.

In reproductive toxicity studies, significant exposure to fexofenadine was achieved through the administration of terfenadine. In mice, rats and rabbits at oral doses up to 200, 300 and 300 mg/kg of terfenadine, respectively, were not teratogenic. Fertility in rats was not affected at oral doses up to 300 mg/kg.

Fexofenadine was not mutagenic in the Bacterial Reverse Mutation, the (CHO/HGPRT) Forward Mutation and the Rat Lymphocyte Chromosomal Aberration in vitro assays and in the Mouse Micronucleus in vivo assay.

B. Pharmacologic activity

Fexofenadine is a selective H_1 receptor antagonist. In binding studies, fexofenadine was twice as potent as terfenadine in displacing mepyramine from rat cerebral cortex membrane, and orally, equipotent to terfenadine in antagonizing the histamine-induced bronchoconstriction in guinea pigs. The antihistaminic activity was also demonstrated in the isolated guinea pig tracheal and in the guinea pig wheal assays; both enantiomers of fexofenadine produced antihistaminic activity that was comparable to the racemic fexofenadine.

C. Nonclinical safety issues relevant to clinical use

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-909
Review number: 1
Sequence number/date/type of submission: 000, 9/28/06/original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Sanofi Aventis

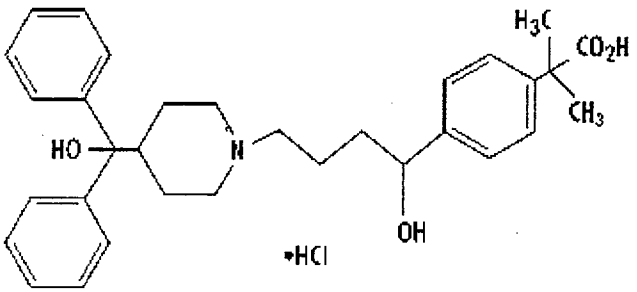
Manufacturer for drug substance: Sanofi Aventis

Reviewer name: Lawrence F. Sancilio, Ph.D.
Division name: Division of Pulmonary and Allergy and Drug Products.
Review completion date: 5/21/07

Drug:

Trade name: Allegra Orally Disintegrating Tablet (proposed)
Generic name: Fexofenadine.
Code name: MDL 16,455A.
Chemical name: (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride.
CAS registry number: 83799-24-0
Molecular formula/molecular weight: $C_{32}H_{39}NO_4.HCl$/ 538.13

Structure:



Relevant INDs/NDAs/DMFs: NDA 19,949, NDA 20-625, NDA 20-872, NDA 21-963.

Drug class: H_1 receptor antagonist.

.Intended clinical population: Patients suffering from seasonal allergic rhinitis (SAR) or chronic idiopathic urticaria (CIU).

Clinical formulation: The following table was excerpted from the sponsor's submission. All the inactive ingredients were acceptable. The fexofenadine was incorporated in a ——formulation prior to making the tablet. The —— of the —— formulation contains 30 mg of fexofenadine. b(4)

Table 1 - Composition of Fexofenadine HCl Orally Disintegrating Tablets, 30 mg

COMPONENTS	COMPOSITION		FUNCTION	REFERENCE TO STANDARDS (2)
	Proportion (% w/w)	Per Unit (mg)		
Fexofenadine HCl	[redacted]	[redacted]	Active Substance	Aventis
Microcrystalline Cellulose			[redacted]	USP/NF
Sodium Starch Glycolate				USP/NF
Povidone K-30				USP/NF
[redacted]				Ph. Eur./JPE[1]
Magnesium Stearate				USP/NF [2]
Alcohol [redacted] Anhydrous	N/A	N/A[4]		CIMA[3]
Total	[redacted]			
[redacted] Fexofenadine HCl, [redacted]	[redacted]	[redacted]	Active Substance	CIMA
Mannitol[5]			[redacted]	USP/NF
[redacted] Mannitol[5]				USP/NF
Crospovidone				USP/NF
Microcrystalline Cellulose[6]				USP/NF
Sodium Bicarbonate, No. 1				USP/NF
Citric Acid, Anhydrous [redacted]				USP/NF
[redacted]				
Aspartame				USP/NF
Magnesium Stearate				USP/NF
Natural and Artificial Orange Flavor				GRAS[7]
Artificial Cream Flavor				GRAS[7]
Total	[redacted]	[redacted]	[redacted]	

1. At the time of manufacture the [redacted] is tested as per the DAB(Deutsches Arzneibuch)/JPE compendial requirements. Since then the Ph Eur has added a monograph for [redacted] In the future, this excipient will be tested according to the Ph. Eur./JPE specifications.
2. [redacted] tad alcohol as per USP. Complies to USP for [redacted] content. The alcoh[redacted] is a non-compendial excipient. Alcohol [redacted] is a [redacted] (volume/volume), which conforms to 27 CFR 21.35. b(4)
4. Removed during processing.
5. Amount adjusted based on the assay of the [redacted] fexofenadine HC[redacted]
6. [redacted] microcrystalline cellulose is used for tablet manufacture.
7. Generally Recognized as Safe (GRAS)

Route of administration: Oral.

Maximum Daily Dose: Children: 6-11 years old: 30 mg twice a day (SAR, CIU).

Studies reviewed within this submission: None. All nonclinical studies were referred to the reviews of NDA 20-625 and NDA 20-872 which are attached.

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Refer to reviews of NDA 20-625 and/or NDA 20-872.

Drug activity related to proposed indication: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.2.3 Secondary pharmacodynamics: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.2.4 Safety pharmacology

Neurological effects: Refer to reviews of NDA 20-625 and NDA 20-872.

Cardiovascular effects: Refer to reviews of NDA 20-625 and NDA 20-872.

Pulmonary effects: Refer to reviews of NDA 20-625 and NDA 20-872.

Renal effects: Refer to reviews of NDA 20-625 and NDA 20-872.

Gastrointestinal effects: Refer to reviews of NDA 20-625 and NDA 20-872.

Abuse liability: NA.

Other: NA.

2.6.2.5 Pharmacodynamic drug interactions: NA.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: NA

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.4.2 Methods of Analysis: NA.

2.6.4.3 Absorption: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.4.4 Distribution: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.4.5 Metabolism: Refer to reviews of NDA 20-6 25 and NDA 20-872.

2.6.4.6 Excretion: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.4.7 Pharmacokinetic drug interactions: NA.

2.6.4.8 Other Pharmacokinetic Studies: NA.

2.6.4.9 Discussion and Conclusions: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.4.10 Tables and figures to include comparative TK summary: NA.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: Refer to reviews of NDA 20-625 and NDA 20-872.

Genetic toxicology: Refer to review of NDA 20-625 and NDA 20-872.

Carcinogenicity: Refer to reviews of NDA 20-625 and NDA 20-872.

Reproductive toxicology: Refer to reviews of NDA 20-625 and NDA 20-872. .

Special toxicology: Refer to review of NDA 20-872.

2.6.6.2 Single-dose toxicity: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.6.3 Repeat-dose toxicity: Refer to reviews of NDA 20-625 and NDA 20-872. .

2.6.6.4 Genetic toxicology: Refer to review of NDA 20-625.

2.6.6.5 Carcinogenicity: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.6.6 Reproductive and developmental toxicology: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.6.7 Local tolerance: NA.

2.6.6.8 Special toxicology studies: Refer to review of NDA 20-872.

2.6.6.9 Discussion and Conclusions: Refer to reviews of NDA 20-625 and NDA 20-872.

2.6.6.10 Tables and Figures: NA.

2.6.7 TOXICOLOGY TABULATED SUMMARY: NA.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Fexofenadine is a selective and potent H_1 receptor antagonist. In the formulation, all the excipients are either GRAS or present in approved marketed oral products. From a preclinical standpoint, there are no safety or toxicity issues when administered at the recommended doses. The label is modified with deletions to conform to the Agency's standard.

Unresolved toxicology issues (if any): None.

Recommendation: Approval of NDA 21-909 with the recommended labeling changes.

Label

There were no additions; the following deletions are in **bold** and ~~strikethrough~~.

[redacted]

b(4)

b(4)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS: REVIEWS OF NDA 20-872 AND NDA 20-625

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original

Reviewer: Lawrence F. Sancilio, Ph.D.

DIVISION: PULMONARY DRUG PRODUCTS, HFD-570

Reviewer Completion Date: 7/6/99

NDA No. 20-872

Information to Sponsor: YES ( ), NO (X)

Serial No./Date/Type of Submission: Original, 7/17/98

Sponsor: Marion Merrell Dow Inc.
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

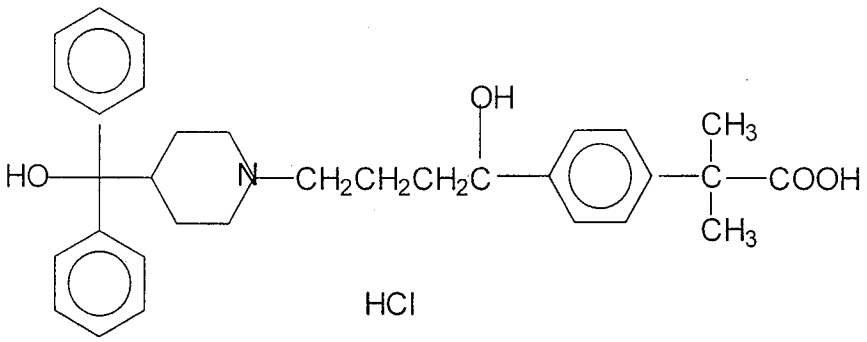
Drug Name: Fexofenadine HCl, MDL 16,455A, TAM (terfenadine active metabolite)

Chemical Name: Benzeneacetic acid, 4-[1-(hydroxydiphenylmethyl)-1-piperidinyl]butyl'- , - dimethyl-, hydrochloride salt ±

CAS Registry No.:138452-21-8

Molecular Weight: 538.13, $C_{32}H_{39}NO_4$. HCl

Structure:



RELEVANT NDAS: 20-625, 18-949

Pharmacological Class: H1 receptor antagonist

Indication: Treatment of seasonal rhinitis and chronic idiopathic urticaria.

CLINICAL FORMULATION AND COMPONENTS

CORE	*WEIGHT, MG/TABLET*			
Fexofenadine HCl	30	60	120	180
Microcrystalline Cellulose Avicel PH101				
Pregelatinized Starch				
Croscarmellose Sodium, intragranular				
M icrocrystalline Cellulose Avicel PH102				
Croscarmellose Sodium, extragranular				
Mg Stearate				

b(4)

COATING SUSPENSION

Colloidal Silicon Dioxide	
Hydroxypropyl Methylcellulose E-15	
Hydroxypropyl Methylcellulose E-5	
Povidone	
Titanium Dioxide	
Polyethylene Glycol 400	
Pink Iron Oxide Blend	
Yellow Iron Oxide Blend	

b(4)

The above components are present in quantities equal to or less than the amounts present in approved products.

Route: Oral, 30, 60, and 180 mg tablets b(4)

Maximum Recommended Daily Doses: Adults >12 years old, 180 mg (3.6 mg/kg).
Children 6-11 years old, 60 mg (3.0 mg/kg).

Background

Fexofenadine HCl is the active metabolite of terfenadine, a marketed H_1 receptor blocker, with little or no sedative properties. It is currently being marketed as a capsule. This submission is for fexofenadine HCl as a tablet.

STUDIES REVIEWED WITHIN THIS SUBMISSION

Pharmacology

Antihistaminic activity of enantiomers of fexofenadine on histamine skin wheals in guinea pigs, No. C-96-0110-R, vol. 14.

Antihistaminic activity of enantiomers of fexofenadine on isolated guinea pig ileum, No. C-96-0079-R, vol.14.

Effects of fexofenadine on contractions induced by neurotransmitters and mast cell derived mediators in the isolated guinea pig trachea, No. J-96-009-R, vol. 14.

Effect on pilocarpine-induced salivation in mice, No. C-95-0205-R, vol. 14.

Tachykinin receptor binding affinity, No. C-95-0255-R, vol. 14.

Binding to selected receptors, No. C-95-0047-R, vol. 14.

SAFETY PHARMACOLOGY

Effects of fexofenadine, terfenadine, ebastine and epinastine on arterial pressure, heart rate, ECG, PR and QT intervals in anesthetized rabbits, No. C-97-0001-R, vol. 14.

Autonomic and cardiovascular effects of i.v. fexofenadine in anesthetized dogs, No. C-95-0339-R, vol. 14.

Effect of fexofenadine, loratidine and ebastine on human cardiac potassium channel HERG, No. C-98-0025-R, vol. 14.

Effect of fexofenadine, loratidine, descarboethoxyloratidine, astemizole and cetirizine on HERG and Kv4.3 channels, No. B-98-0077-R, vol. 14.

Lack of activity of terfenadine and fexofenadine on action potential of guinea pig papillary muscle, No. C-90-0231-R, vol. 14.

PHARMACOKINETICS AND METABOLISM

Plasma concentrations and bioavailability of i.v. and p.o. administered fexofenadine in mice, K-95-0625-N, vol. 19.

Single p.o. pharmacokinetics study in pregnant rabbits on day 19 of gestation, K-96-0798-N and K-96-0413, vol. 22.

Plasma concentrations and bioavailability in beagle dogs administered i.v. and p.o. MDL46619, fexofenadine methyl ester, K-97-0521-N, vol. 19.

Potential formation of the methyl ester of fexofenadine in dogs following single p.o. administration of fexofenadine, K-96-0077-N, vol. 27.

Distribution of ^{14}C fexofenadine in rats by whole-body autoradiography following an i.v. dose of 1 mg/kg and a p.o. dose of approximately 10 mg/kg, K-97-0092-N, vol. 25.
Distribution of ^{14}C fexofenadine in Male rats by whole-body autoradiography following an p.o. dose of 10 mg/kg (b.i.d. x 4.5 days), K-97-0094-N, vol. 26.

Distribution of ^{14}C fexofenadine by whole-body autoradiography following an p.o. dose of approximately 10 mg/kg to pregnant rats on days 12 and 18, K-97-0093-N, vol. 26.

Metabolism of fexofenadine in bile duct cannulated rats, K-97-0390-D, vol. 26.

Isolation and identification of metabolites in urine and bile of Sprague-Dawley rats after p.o. administration of ^{14}C fexofenadine, K-97-0385-N, vol. 26.

Potential formation of trace amounts of the methyl ester of fexofenadine in dogs given a single p.o. dose of fexofenadine, vol.27.

In vitro metabolism of fexofenadine in human hepatic microsomes, K-95-0137-D, vol. 27.

Spectral binding studies of fexofenadine and structurally related compounds in human hepatic microsomes, K-97-0234-D, vol. 27.

Plasma concentrations in guinea pigs of the enantiomers of fexofenadine following the p.o. administration of each enantiomer and fexofenadine, K-97-0261-D, vol. 27.

TOXICOLOGY

SINGLE DOSE

Acute i.v. toxicity of fexofenadine in rats, No. K-98-0079-T, vol. 14.

MULTIDOSE

Three-month dietary study in mice comparing terfenadine with fexofenadine HCl, No. K-98-0164-T and K-97-0446-N (Plasma Levels), vol. 15 and 21.

One-month p.o. gavage toxicity in beagle dogs, No. K-96-0489-T, vol. 17.

Plasma concentrations of fexofenadine and MDL46,619 in a 1-month p.o. study in beagle dogs, K-96-0805-N, vol. 23.

Six-month p.o. toxicity in dogs, No. K-95-0897-T, vol. 18, Toxicokinetics, vol. 23.

Plasma concentrations of fexofenadine and MDL46,619 in a 6-month p.o. study in beagle dogs, K-95-0870-N, vol. 23.

SPECIAL STUDIES

Primary eye irritation study in New Zealand white rabbits, No. B-97-0083-T, vol. 18.

Primary dermal irritation study in New Zealand white rabbits, No. B-97-0084-T, vol. 18.

Dermal sensitization study in guinea pigs, No. B-97-0088-T, vol. 18.

STUDIES NOT REVIEWED WITHIN THIS SUBMISSION SINCE THEY WERE NOT RELEVANT OR DO NOT ADD MORE INFORMATION TO THIS NDA.

Plasma concentrations of fexofenadine in mice following dietary administration for 4-weeks, K-96-0799-N, vol. 19.

Toxicokinetics of fexofenadine in mice following dietary administration for 4-weeks, K-96-0417-N, vol. 20.

Two-week palatability study of fexofenadine in mice, K-96-0416-N, vol. 20.

Toxicokinetics of fexofenadine in rats following dietary administration for 4-weeks, K-96-0800-N, vol. 21.

Toxicokinetics of fexofenadine in rats following dietary administration for 4-weeks, K-96-0415-N, vol. 21.

Two-week palatability study of fexofenadine in rats, K-96-0414-N, vol. 21.

Pilot in situ study on the site-specific absorption of fexofenadine in M Sprague-Dawley rats, K-95-0564-D, vol. 22.

Relative bioavailability of fexofenadine in beagle dogs given various tablet and capsule formulations, K-96-0168-N, vol. 23.

Relative bioavailability of fexofenadine in beagle dogs given various tablet and capsule formulations, K-96-0807-N, vol. 23.

Relative p.o. bioavailability of prototype fexofenadine SR in beagle dogs, K-96-0808-N, vol. 24.

Relative p.o. bioavailability of prototype fexofenadine SR in beagle dogs, K-96-0870-N, vol. 24.

Relative p.o. bioavailability of prototype fexofenadine SR formulations in beagle dogs, K-96-0118-N, vol. 24.

Relative bioavailability of fexofenadine HCl in beagle dogs given prototype formulations, K-96-0942-N, vol. 24.

Influence of cremophore el and polysorbate 80 on the in vitro permeability of fexofenadine HCl across $Caco_2$ monolayer, K-96-0946-N, vol. 25.

Influence of beta-cyclodextrin, hydroxypropyl beta cyclodextrin and sodium lauryl sulfate on the in vitro permeability of fexofenadine HCl across $Caco_2$ monolayer, K-96-09991-N, vol. 25.

Effect of sodium camphorsulfonate, sodium acetate and ursodeoycholic acid on the absorption of fexofenadine HCL in the $Caco_2$ in vitro model, K-96-0366-N, vol. 25.

Distribution of ^{14} C fexofenadine by whole-body autoradiography following an intrapulmonary dose of approximately 10 mg/kg to an 18 day pregnant rat, K-97-0095-N, vol. 26.

Relative p.o. bioavailability of fexofenadine HCl in dogs with and without the addition of bile salts, K-96-0036-D, vol. 27.

Relative p.o. bioavailability of fexofenadine in beagle dogs, K-96-0806-N, vol. 23.

Relative bioavailability of nanoparticle formulations of fexofenadine in beagle dogs administered in the stomach, jejunum and ileum, K-96-0412-N, vol. 24.

Further analysis of the pharmacokinetics of the enantiomers of terfenadine and its acid metabolite in beagle dogs, K-97-0262-D, vol. 26.

Two-week s.c. probe toxicity in rats, No. B-96-0003-T, vol. 18, Toxicokinetics, vol. 22.

REVIEW

Note: The doses of fexofenadine HCl stated in the report represent those of the free base.

Pharmacology

Antihistaminic activity of enantiomers of fexofenadine on histamine skin wheals in guinea pigs, No. C-96-0110-R, vol.14.

The following table shows comparable and dose-related decrease in the histamine wheal test was observed with fexofenadine and its 2 enantiomers at p.o. doses of 0.4, 0.8, 1.6 and 3.2 mg/kg p.o.

COMPOUND	PERCENT DECREASE IN WHEAL RESPONSE			
	mg/kg p.o.: 0.4	0.8	1.6	3.2
Fexofenadine	19.2	30.8	38.0	44.0
(-) Fexofenadine	19.9	29.5	36.1	48.7
(+) Fexofenadine	23.7	35.6	40.6	53.2

Conclusion

In the intradermal histamine wheal test in guinea pigs, the potency of fexofenadine was comparable to each enantiomer.

Antihistaminic activity of enantiomers of fexofenadine on in isolated guinea pig ileum, No. C-96-0079-R, vol.14.

In the histamine-induced contraction of isolated guinea pig ileum assay, the pA_2 for the (-) enantiomer (MDL 100,899A) was 7.62 as compared to 7.97 for the (+) enantiomer (MDL 100,902A) in blocking the effect of histamine. Thus, the in vitro antihistaminic activity of the (+) enantiomer (MDL 100,902A) was slightly more potent than the (-) enantiomer (MDL 100,899A).

Effects of fexofenadine on contractions induced by neurotransmitters and mast cell derived mediators in the guinea pig trachea, No. J-96-009-R, vol. 14.

In the isolated guinea pig tracheal strip model, fexofenadine at concentrations up to $3x\ 10^{-5}M$ did not reduced the contractions due to acetylcholine, neurokinin A, substance P and leukotriene, D_4, antigen challenged sensitized tracheas, U46619 (a thromboxane A_2 analog), compound 48/80 and capsaicin by > 48%. In this model the antihistaminic ED_{50} for fexofenadine was 29.8 nM.

Effect on pilocarpine-induced salivation in mice, No. C-95-0205-R, vol. 14.

In anesthetized mice, fexofenadine at 3 mg/kg s.c. did not affect pilocarpine-induced salivation. Atropine was active at 0.1 mg/kg s.c.

Tachykinin receptor binding affinity, No. C-95-0255-R, vol. 14.

Fexofenadine and terfenadine were inactive at 1μM on the NK-1 receptor using guinea pig lung and on the NK-2 receptor using HSKR-1 cells which are mouse 3T3 fibroblasts.

Binding to selected receptors, No. C-95-0047-R, vol. 14.

Fexofenadine had no affinity for the following receptors and the L-type Ca channel since the IC 50s were > 10μM: α_1 adrenergic, α_2 adrenergic, β adrenergic, α_1 adrenergic, muscarinic m_1, muscarinic m_2, muscarinic m_3, muscarinic m_4, $5HT_{1A}$ and $5HT_{2A}$. Similar results were seen with the enantiomers of fexofenadine, and cetirizine.

Summary of Pharmacology

The results are summarized in the following table.

Model	Activity
Histamine Wheal Test in Guinea Pigs	At 0.4, 0.6, 08, 1.6 and 3.2 mg/kg p.o., fexofenadine and the (-) and (+) enantiomers were equipotent in decreasing the skin response to intradermal histamine.
Isolated Guinea Pig Ileum (-) fexofenadine (+) fexofenadine	 pA_2: 7.62 pA_2: 7.97
Guinea Pig Trachea	ED_{50}: > 3 x 10^{-5} M against the contractions induced by acetylcholine, neurokinin A, substance P, leukotriene, D_4, antigen challenged sensitized trachea, U46619 (a thromboxane A_2 analog), compound 48/80 and capsaicin. ED_{50} against histamine contractions: 2.48 x 10^{-8} M
Pilocarpine-Induced Salivation in Mice	Inactive at 3 mg/kg s.c.
Binding Studies using fexofenadine and terfenadine	Inactive at 1x 10^{-6} against NK-1 and NK-2 receptors
Binding Studies using fexofenadine, (-) fexofenadine and (+)fexofenadine and cetirizine	Inactive 1x 10^{-5} against α_1 adrenergic, α_2 adrenergic, β adrenergic, L-type Ca channel, α_1 adrenergic, muscarinic m_1, muscarinic m_2, muscarinic m_3, muscarinic m_4, $5HT_{1A}$ and $5HT_{2A}$ receptors.

SAFETY PHARMACOLOGY

Effects of fexofenadine, terfenadine, ebastine and epinastine on arterial pressure, heart rate, ECG, PR interval and QT interval in anesthetized rabbits, No. C-97-0001-R, vol. 14.

METHOD

M New Zealand white rabbits (2.8-3.6 kg) were used. Each compound, dissolved in 84% PEG 200 and 16% DMSO administered in volumes ranging from 0.05 to1 ml, was each tested in 4-5 rabbits. Fexofenadine (0.1, 0.2, 0.7, 2.0 and 7.0 mg/kg, total dose: 10 mg/kg) and terfenadine (0.1, 0.2, 0.7 and 2.0 mg/kg, total dose: 3.0 mg/kg) were administered i.v. in increasing doses to the same animal. Initially, after the animal was stabilized, the baseline blood pressure and heart rate were recorded for 5 min. Atrial pacing rates of 325 for 30 sec. was then initiated. At the end of the atrial pacing, the ventricles were paced at 325 bpm for 2 min (atrial-ventricular pacing). At the end of 2 min, the atrial pacing rate was increased to 350 bpm for 30 sec. At the end of the atrial pacing, the ventricles were paced at 350 bpm for 2 min (atrial-ventricular pacing). The stimulus to the ventricle was delayed 30 msec from the atrial stimulus. This was followed by the first dose of the compound. After an 11-min observation period, the 2 pacing rate procedures were initiated. This was repeated for the second, third, fourth and possibly the fifth dose. During the non-paced portion, the mean arterial pressure and heart rate were determined. The PR interval was determined during the atrial-pacing period, and the QT interval was determined during the atrial-ventricular pacing. The mean maximum change in heart rate and blood pressure were determined during the nonpaced dose portion. The steady state refers to state of the cardiovascular system at the end of the 11 minute observation period following the i.v. administration of each dose.

RESULTS

The results for fexofenadine and terfenadine summarized in the following table indicate that unlike terfenadine, fexofenadine did not affect the PR and QT intervals. Data for ebastine and epinastine were not reviewed.

Effect on Blood Pressure and Heart Rate

Parameter	% Change from Baseline Fexofenadine					% Change from Baseline Terfenadine				
	0.1[b]	0.2	0.7	2.0	7.0	0.1[b]	0.2	0.7	2.0	7.0
Steady State Mean Arterial	0	0	0	0	0	0	0	0	-19[a]	ND
Blood Pressure	0	0	0	0	0	0	0	0	-6[c]	ND
Spontaneous Heart Rate	0	0	0	0	0	0	0	-33[a]	-61[a c]	ND
Maximum Response	0	0	0	0	-4[c]	0	0	0	0	-13[c]

[a] P<05 when compared to vehicle dose
[b] Dose, mg/kg, i.v. given to the same animal
[c] Determined by difference from the respective control group which also showed a significant bradycardia or hypotension.

Parameter	% Change from Baseline Fexofenadine					% Change from Baseline Terfenadine				
	0.1[a]	0.2	0.7	2.0	7.0	0.1[a]	0.2	0.7	2.0	7.0
PR Interval, 325 bpm	0	0	0	0	0	0	0	0	+21[b]	ND
350 bpm	0	0	0	0	0	0	0	0	CNP	ND
QT Interval, 325 bpm	0	0	0	0	0	0	0	+14[b]	+19[b]	ND
350 bpm	0	0	0	0	0	0	0	+11[b]	+20[b]	ND

ND, Did not determine

CNP, COULD NOT PACE.

[a] Dose, mg/kg, i.v. given to the same animal
[b] P<005 from vehicle control

CONCLUSION

In the rabbit fexofenadine at a cumulative dose of 10 mg/kg i.v. did not affect the mean arterial blood pressure, heart rate and PR and QT intervals. Terfenadine under similar conditions did reduce the blood pressure and increased the PR and QT intervals.

Autonomic and cardiovascular effects of i.v. fexofenadine in anesthetized dogs, No. C-95-0339-R, vol. 14.

METHOD

Anesthetized beagle dogs (8-14.2 kg) received the vehicle (5% mannitol, 2 M and 2 F) or fexofenadine (2 M and 2 F). The control group received the vehicle by a bolus followed by an infusion over 90 minutes. The treated group received by infusion a low (0.093 mg/kg bolus + 0.036 mg/kg/hr for 1.5 h), mid (0.185 mg/kg bolus + 0.107 mg/kg/hr for 1.5 h) and high (0.648 mg/kg bolus + 0.356 mg/kg/hr for 1.5 h) dose of fexofenadine. Prior to and after each dose, the following agonists were administered i.v. followed by bilateral carotid occlusion: phenylephrine (3 and 10 μg/kg), acetylcholine (0.3 and 1 μg/kg), isoproterenol (0.03 and 0.1 μg/kg) and tyramine (50 μg/kg). Plasma levels were determined at 5, 15, 30, 50 and 60 min after each dose. Their Cmaxs were compared with the Cmax seen with the recommended dose of 60 mg bid.

RESULTS

Fexofenadine had no effect on the blood pressure and heart rate response to bilateral carotid occlusion, phenylephrine, acetylcholine, isoproterenol and tyramine. The ratios of the $Cmaxs_{ss}$ for fexofenadine in the dog to that (299 ng/ml) for the clinical human dose (60 mg bid) ranged from 0.65-1.0 for the low dose to 6.0 to 8.1 for the high dose.

CONCLUSION

Fexofenadine at high plasma levels relative to the human plasma level had no effect on the response to the response to various autonomic agonists and bilateral carotid occlusion in anesthetized dogs.

Effect of fexofenadine, loratidine and ebastine on human cardiac potassium channel I_{kr} HERG, No. C-98-0025-R, vol. 14.

The ID_{50}s for blocking the human cardiac potassium channel I_{kr} HERG (mouse fibroblast) listed in the following table show that fexofenadine was the weakest inhibitor of the 3 compounds tested.

COMPOUND	IC_{50}, nM	Potency
Ebastine	82.8	2753
Loratidine	3,000	7.6
Fexofenadine	22,800	1

CONCLUSION

Fexofenadine possesses very weak human cardiac potassium channel I_{kr} HERG blocking activity.

Effect of fexofenadine, loratidine, descarboethoxyloratidine, astemizole and ceterizine on HERG and Kv4.3 channels, No. B-98-0077-R, vol. 14.

The HERG (I_{kr}) and Kv4.3 (I_{to}) channel models were expressed in mouse L cell clones cotransfected with the neomycin resistance gene.

The results in the following table indicate that fexofenadine was a relatively weak HERG (I_{kr}) and Kv4.3 (I_{to}) channel inhibitors relative to terfenadine and astemizole.

COMPOUND	IC_{50}, nM	
	HERG (I_{kr})	Kv4.3 (I_{to}) channel
Astemizole	5	17,000
Terfenadine	35	3,000
Fexofenadine	30,000	112,000
Loratidine	15,000	9,000
Loratidine Metabolite	19,000	22,000
Cetirizine	>300,000	336,000

CONCLUSION

Fexofenadine possesses weak HERG (I_{kr}) and Kv4.3 (I_{to}) channel inhibitory properties.

Lack of activity of terfenadine and fexofenadine on action potential of guinea pig papillary muscle, No. C-90-0231-R, vol. 14.

At concentrations up to 10^{-5}M (the highest concentration tested) neither terfenadine nor fexofenadine affected the APD_{90} (action potential duration at 90% duration) and the V_{max} (maximum upstroke velocity of action potential).

Conclusion

Fexofenadine did not affect the APD_{90} and V_{max} of the guinea pig papillary muscle. However, the data for terfenadine were inconclusive since in the Overall Summary Section, it was indicated that terfenadine adhered to the tubing used in the study.

SUMMARY OF SAFETY PHARMACOLOGY

The results are summarized in the following table.

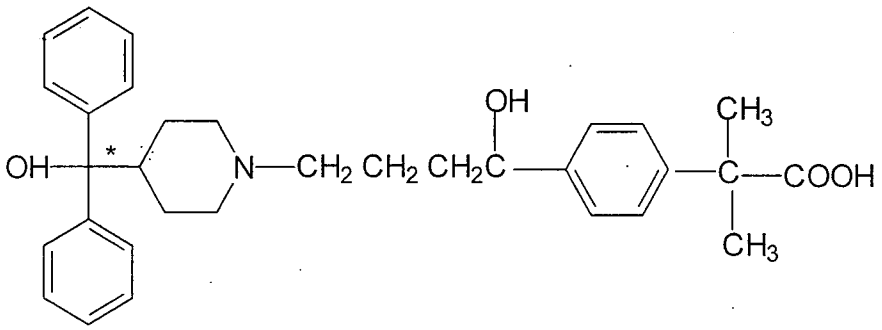
Model	Activity
Anesthetized Rabbits	At a cumulative dose of 10 mg/kg i.v., fexofenadine produced no effect on the blood pressure, heart rate, and PR and QT intervals. The PR and QT intervals were determined during atrial pacing or atrial-ventricular pacing. Terfenadine produced hypotension at the cumulatice does of 1mg/kg i.v. and increased PR interval and increased QT interval at cumulative doses of 1 and 3 mg/kg , respectively.
Anesthetized Dogs	At i.v. doses (bolus + infusion) that produced Cmaxs that were 0.65-1 to 6-8 times that seen at the clinical dose, there was no effect on the blood pressure and heart rate and the response to bilateral carotid occlusion, phenylephrine, acetylcholine, isoproterenol and tyramine.
HERG Human Cardiac Potassium Channel I_{kr} (mouse fibroblast L cell line)	IC_{50}: 22.8 μM, 0.0004 as potent as ebastine 0.013 as potent as loratidine
HERG I_{kr} Channel (mouse fibroblast L cell line)	IC_{50}: 30 μM, 0.001 as potent as terfenadine .
Kv4.3 (I_{to}) Channel (mouse fibroblast L cell line)	IC_{50}: 112 μM, 0.018 as potent as terfenadine .
Guinea Pig Papillary Muscle	At 10^{-5}M both fexofenadine and terfenadine did not Affect the APD_{90} (action potential duration at 90% duration) and the V_{max} (maximum upstroke velocity of action potential). The data for terfenadine are questionable since terfenadine was found to adhere to the tubing of the apparatus.

PHARMACOKINETICS AND TOXICOKINETICS

In the pharmacokinetics studies, fexofenadine in plasma was determined utilizing [redacted] method. The limits of quantitation ranged from 0.5-1 to 100 ng/ml. b(4)

The lower limit of quantitation ranged from 1-2 ng/ml in dog plasma, 25 ng/ml in the rat, rabbit and mouse plasma.

In the distribution and excretion studies, the C^{14} * was in the fexofenadine molecule as shown in the following structure.



ABSORPTION

Plasma concentrations and bioavailability of i.v. and p.o. administered fexofenadine in mice, K-95-0625-N, vol. 19.

METHOD

Fasted M CD-1 mice were used. Blood was taken from 5 mice/time point at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h following i.v. or p.o. administration. Fexofenadine was dissolved in saline for i.v. administration, in water for the 30 mg/kg p.o. dose and for the 5000 mg/kg dose in 0.5% methylcellulose in 0.2% Tween 20 aqueous solution.

RESULTS

The results are shown in the following table indicate that by the p.o. route, there was limited absorption as the dose was increased. Administering the high dose as a suspension in contrast to administering the low dose as a solution may have contributed to this limited absorption. By the i.v. route , fexofenadine was rapidly cleared. Systemic absorption by the p.o. route was low; this may also be attributed to high extra-hepatic clearance since the systemic plasma clearance after the i.v. dose was 53 ml/min/kg as compared to the normal hepatic plasma flow of 35 ml/min/kg.

Parameter	Dose		
	1 mg/kg i.v.	30 mg/kg p.o.	5000 mg/kg p.o.
C max, ng/ml	923	282	5191
T max, h	0	0.5	0.5
$AUC_{0\text{-}inf}$, ng/h/ml	283	1588	30,220
Time (h) where the last measureable level was detected.	1	6	8
% Bioavailability	100	19	2.1

CONCLUSION

Fexofenadine showed low systemic bioavailability by the p.o. route. The bioavailability was inversely related to the dose.

Single p.o. pharmacokinetics study in pregnant rabbits, K-96-0413-N, vol. 22, Toxicokinetics, K-96-0798-N, vol. 22.

Laboratory the Study was conducted: [redacted] and , Nonclinical Pharmacokinetics Pharmacodynamics Dept., Hoechst Marion Roussel, Kansas City, Mo. b(4)

Method

Species/Sex/ Body Weight : Pregnant Hra: (NZW)SPF rabbits weighing 3.3-4.2 kg were used. Each group consisted of 8 animals. On day 19 of gestation, fexofenadine was given p.o.
Lot No.: Fexofenadine HCl, Fr 9412.
Route: Oral by gavage.
Vehicle: 0.5% methylcellulose in 0.5% Tween 20.
Doses: Fexofenadine HCl: 300 (LD) and 1500 (HD) mg/kg
Duration of Study: 5 days.

The following parameters were determined.

Clinical Observations: Daily for 5 days.
Food Consumption: By inspection.
Plasma Levels: For each dose group: Day 1, 1, 4, 8, 12, 24 and 36 h (4 rabbits); 0.5, 2, 6, 10, 16, 30 and 48 h (4 rabbits)
Necropsy: Animals were examined to confirm pregnancy.

RESULTS

Clinical Signs: Decreased or no feces, LD, 2/8, HD, 8/8.
Decreased food consumption, LD, 2/8, HD, 8/8

Necropsy: All animals were pregnant.

PHARMACOKINETICS

	Dose, mg/kg p.o.	
PARAMETER	**300**	**1500**
Cmax, µg/ml	6.5	17.4
T max, h	1	2
$AUC_{0\text{-}48\ h}$, µg.h/ml	37.4[a]	174.4

[a] At this dose terfenadine produced an AUC of 101.6 µg.h/ml (K-94-0159-D, 1994)

CONCLUSION

Fexofenadine administered 300 and 1500 mg/kg p.o. to pregnant rabbits on day 19 of gestation produced a dose related decrease in food consumption and fecal output. The AUCs were dose related and doses proportional. The AUC for 300 mg/kg p.o. of fexofenadine was less than that seen with a comparable dose of terfenadine.

Plasma concentrations and bioavailability in beagle dogs administered i.v. and p.o. MDL46619 (fexofenadine methyl esther), K-97-0521-N, vol. 25.

Object of Study: To determine whether by administering the methyl ester of fexofenadine, MDL46619, would increase the plasma levels of fexofenadine thereby enhancing exposure to fexofenadine.

Laboratory the Study was conducted: Preclinical Development Dept., Hoechst Marion Roussel, Kansas City, Mo.

Method

Species/Sex/ Body Weight: 4 M Beagle dogs (11.5-13.7 kg) were used in crossover study with a washout period of 1-2 weeks between trials.
Lot No.: MDL 46,619, 02.
Route: Oral by gavage or i.v.

Vehicle: Oral route: 1.5%-glacial acetic acid/propylene glycol/ hydroxypropyl-∃-cyclodextrin,

0.5 mg/kg/kg.

Intravenous route: 1.5%-glacial acetic acid/98.5% propylene glycol, 0.5 ml/kg over 10 min.

Doses: MDL 46,619: 1.35 and 13.5 mg/kg p.o. and 1 mg/kg i.v.

Plasma Levels: Oral route: Blood samples were collected at 5, 15, 30 min and 1, 1.5, 2, 3, 4, 6, 8,

12, 24, 48, 72 and 96 h.

Intravenous route: Blood samples were collected at < 1, 2, 15 and 30 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 h.

RESULTS

The pharmacokinetics for MDL 46,619 are summarized in the following table.

Parameter	Dose of MDL 46,619, Route		
	1 mg/kg, i.v.	**1.35 mg/kg, p.o.**	**13.5 mg/kg, p.o.**
Cmax, ng/ml	201	11.3	266
T max, h	0.01	0.88	1.1
$AUC_{0\text{-}inf}$, ng.h/ml	288	48.3	1393
T ½, h	4.0	3.3	4.1
MRT, h	4.5	4.8	5.2
CL, ml/min/kg	53.1	NA	NA
Vss, L/kg	14.2	NA	NA
% Bioavailability	100	12.4	ND

NA not available

ND, Not determinable since the AUC was non-linear with the increasing dose.

By the p.o. route, MDL 46,619 was rapidly absorbed; the disproportionate increase in the AUC indicates saturable elimination. The absolute bioavailability at the LD was low, 12.4%; due to the non-linearity of the AUC, the absolute bioavailability could not be determined for the HD.

From the i.v. study, the steady state volume of 14.2 L/kg, exceeds the volume of total body water in the dog, 0.6 L/kg, indicating that MDL 46,619 readily distributes into the tissues. The clearance of 53.1 ml/min/kg which is twice the normal hepatic plasma flow of 25 ml/min/kg suggests extra hepatic metabolism. The terminal lives for the p.o. and i.v. routes were similar.

Plasma was also analyzed for fexofenadine since MDL 46,619 was the methyl ester of fexofenadine. As seen in the following table MDL 46,619 was converted to fexofenadine following i.v. or p.o. administration.

Parameters For Fexofenadine	MDL 46,619 Dose, Route		
	1 mg/kg i.v.	1.35 mg/kg p.o.	13.5 mg/kg
Cmax, ng/ml	217	172	3544
T max, h	2.5	1.8	2.4
$AUC_{0\text{-}inf}$, ng.h/ml	1643	1282	21,183
T ½, h	10.1	14.6	18.1
MRT, h	9.2	11.5	6.8

THE CMAX AND AUC OBSERVED FOR FEXOFENADINE FOLLOWING THE ADMINISTRATION OF 13.5 MG/KG P.O. OF MDL 46,619 WAS APPROXIMATELY ½ THAT OBSERVED UNDER SIMILAR CONDITIONS FOR 8.7 MG/KG P.O. OF FEXOFENADINE ($AUC_{0\text{-}INF}$, 45,197 NG.H/ML, REPORT NO. K-93-0145-D-1993).

CONCLUSION

MDL 46,619, the methyl ester of fexofenadine, possesses low p.o. bioavailability and attains saturable elimination with increasing doses. MDL 46,619 is biotransformed to fexofenadine but does not offer greater systemic exposure to fexofenadine. Since MDL 46,619 is metabolized to fexofenadine, it qualifies as an impurity at the proposed specification of 0.2%.

Potential formation of the methyl ester of fexofenadine in dogs following single p.o. administration of fexofenadine, K-96-0077-N, vol. 27.

Laboratory the Study was conducted: Preclinical Development Dept., Hoechst Marion Roussel, Kansas City, Mo.

Method

Species/Sex/ Body Weight: 5 M Beagle dogs (9-13 kg) were used in crossover study with a washout period of 23 days between trials.

Compound: Radioactive fexofenadine; MDL 46,619 was present as an impurity. At the HD the amount of MDL 46,619 administered was approximately 13.7 μg which accounted for 0.00029% of the dose.
Route: Oral by gavage
Dose and Vehicle: 1.75 mg/kg in 1 ml of water followed by 10 ml of tap water or 392 mg/kg in 6 ml of a aqueous 0.5% Methocel suspension followed by 10 ml of tap water.
Plasma Levels: Oral route: Blood samples were collected at 1, 2, 4 and 8 h.
Feces and Urine: Collected at –16 h, 0, 0-12, 12-24, 24-48 h, 48-72 h, 72-96 h and 96-120 h.

RESULTS

The plasma levels and excretion of fexofenadine are summarized in the following tables.

TIME, H	**Plasma levels, ng Eq/g**	
	1.75 mg/kg	**392 mg/kg**
1	1.65	20.5
2	1.40	24.5
4	0.96	18.5
8	0.15	2.3

PARAMETER	**% of Dose, (0-120 h)**	
	1.75 mg/kg	**392 mg/kg**
Urine	8.61	0.91
Feces	85.97	95.39
Cage Wash	1.19	1.39
Total	95.77	97.69

The wide difference in doses (1.75 mg/kg vs 392 mg/kg) of fexofenadine, with only a 14-20 x difference in plasma levels indicates decreased absorption with increasing doses of fexofenadine. This was supported be a marked decrease in urinary excretion and an increase in fecal excretion. Further, the feces at the HD were white-colored indicative of unabsorbed fexofenadine .

MDL 46,619 was not detected at the LD in the feces. At the HD, the average amount of MDL 46,619 recovered was 116% of the dose administered.

CONCLUSION

In the dog absorption of fexofenadine following oral administration decreased with increasing dose. MDL 46,619, the methyl ester of fexofenadine, although an impurity in the fexofenadine substance and potentially a metabolite, was not a metabolite of fexofenadine.

Distribution

Distribution of ^{14} C fexofenadine in Male rats by whole-body autoradiography following an i.v. dose of 1 mg/kg and a p.o. dose of approximately 10 mg/kg, K-97-0092-N, vol. 25.

METHOD

Male rats, 188-227 g, received 1 mg/kg i.v. or 10 mg/kg p.o. of C^{14} fexofenadine (Batch No. 26024-0). Fexofenadine was administered as a aqueous/ethanol solution. Following i.v. administration 1 animal was sacrificed at 0.25, 0.5 and 2 h later; in the orally dosed rats, 1 animals was sacrificed at 0.5, 2, 24 and 48 h. Levels of fexofenadine and/or metabolite(s) were determined with radioluminography.

RESULTS

The results shown in the following table show the distribution of radioactivity in decreasing order of concentration following p.o. or i.v. administration. In both routes, no radioactivity was found in the brain.

Route/Time After Administration	DISTRIBUTION OF RADIOACTIVITY IN ORGANS LEVELS IN DECREASING ORDER
Oral Route 0.5 h	Esophagus, stomach, small intestines, liver, urinary bladder
2.0 h	Stomach, small intestines, kidneys (renal cortex> renal pelvis)
24 h.	Lower part of small intestine, large intestine, liver
48 h	no radioactivity
Intravenous Route 0.25 h	small intestines, urinary bladder, kidney, liver; other tissues had concentrations < 1μg equivelants/g
0.5 h	small intestines, urinary bladder, kidney, liver; concentrations > 0.3 μg equivalents/g: myocardium, salivary glands, skeletal muscle, lung, pancreas and thyroid
2 h	intestines, urinary bladder, liver; concentrations > 0.1 μg equivelants/g: myocardium, skeletal muscle, lung, pancreas and thyroid

CONCLUSION

Following p.o. or i.v. administration, fexofenadine was distributed in the gastrointestinal tract, kidney and liver. Fexofenadine was not distributed in the brain.

Distribution of ^{14}C fexofenadine in Male rats by whole-body autoradiography following an p.o. dose of 10 mg/kg (b.i.d. x 4.5 days), K-97-0094-N, vol. 26.

METHOD

Four M Sprague Dawley rats, 205-218 g received 10 mg/kg p.o./day of C^{14} fexofenadine (Batch No. 26024-0) by gavage twice a day for 4.5 days. Fexofenadine was administered as a aqueous/ethanol solution. Following administration, 1 animal was sacrificed at 0.5, 2, 24 and 72 h. Levels of radioactive fexofenadine and/or metabolite(s)

were determined by [redacted] at the level of the kidney, adrenal, eye, brain and thyroid. b(4)

RESULTS

The results in the following table show the distribution of radioactivity of concentration following p.o. administration of 10 mg/kg /day of fexofenadine twice a day for 4 .5 days.

Route/Time After Oral ADMINISTRATION	DISTRIBUTION OF RADIOACTIVITY IN ORGANS
0.5 h	Stomach and intestine, liver (0.91 µg equiv./g), esophagus
2.0 h	liver (1.3 µg equiv./g), esophagus, intestines
24 h.	liver (0.082 µg equiv./g)
72 h	no radioactivity

CONCLUSION

Following p.o. of 10 mg/kg twice a day for 4.5 days of C^{14} fexofenadine, radioactivity was initially distributed in the gastrointestinal tract, liver and esophagus. By 24 h, radioactivity was seen only in the liver. At 72 h, no radioactivity was detected suggesting that excretion was complete.

Distribution of ^{14} C fexofenadine by whole-body autoradiography following a p.o. dose of approximately 10 mg/kg to 12 and 18 days pregnant rats, K-97-0093-N, vol. 26.

METHOD

Three 18-day and three 12- day pregnant Wistar rats (252-316 g) g received 10 mg/kg p.o. of C^{14} fexofenadine (Batch No. 26024-0) by gavage. Fexofenadine was administered as a aqueous/ethanol solution. Following administration 1 animal from each group was sacrificed at 0.5, 2 or 24 h. Levels of radioactive fexofenadine and/or metabolite(s) were determined by [redacted] at the level of the kidney, adrenal, eye, brain and thyroid. Immediately after killing each dam, 1 fetus was examined separately. b(4)

RESULTS

THE DATA SHOWING THE DISTRIBUTION OF RADIOACTIVITY IN THE DAMS AND FETUSES ARE SHOWN IN THE FOLLOWING TABLE.

Route/Time After Oral ADMINISTRATION	DISTRIBUTION OF RADIOACTIVITY IN ORGANS
Day 18 of Pregnancy	
0.5 h	Stomach and intestine, liver (2.09 μg equiv./g), esophagus, kidney and urinary bladder Fetus: no radioactivity
2.0 h	small intestine >liver (1.23 μg equiv./g), esophagus, urinary bladder Fetus: no radioactivity
24 h	Large intestine> liver (0.03 μg equiv./g) Fetus: no radioactivity
Day 12 of Pregnancy	
0.5 h	Stomach and intestine, liver (0.86 μg equiv./g), esophagus Fetus: no radioactivity
2.0 h	Stomach and intestine, liver (2.1 μg equiv./g), Fetus: no radioactivity
24 h	Liver (levels were too low to determine) Fetus: no radioactivity

CONCLUSION

Following the p.o. administration of 10 mg/kg of radioactive fexofenadine to 12- and 18-day pregnant rats, radioactivity was distributed predominantly in the gastrointestinal tract and liver.

NO RADIOACTIVITY WAS DISTRIBUTED TO THE FETUSES. THIS DISTRIBUTION WAS SIMILAR TO THAT SEEN IN M RATS.

METABOLISM AND EXCRETION

Metabolism of C^{14} fexofenadine in bile duct cannulated rats, K-97-0390-D, vol. 26.

METHOD

Groups of 4 M rats (250-350g) were used in the study. Two groups were bile duct-cannulated; they received 5 or 30 mg/kg p.o. of fexofenadine. The third group was sham operated and received 5 mg/kg p.o. of fexofenadine. The fourth group was normal and received 5 mg/kg p.o. of fexofenadine.

Sample collections were made at various times. The times for each group are listed in the following table.

Parameter	Group, 1 and 2	Group 3	Group 4
Bile	-1-0, 0-4, 4-8, 8-24 h		
Urine	0-8, 8-24 h	0-8, 8-24 h	0-8, 8-24 h
Feces	0-8, 8-24 h	0-8, 8-24 h	0-8, 8-24 h
Liver	24 h	24 h	24 h
Kidney	24 h	24 h	24 h
GI Tract	24 h	24 h	24 h
GI Contents	24 h	24 h	24 h
Carcass	24 h	24 h	24 h

RESULTS

The % of dose expressed as radioactivity excreted is shown in the following table. Excretion was predominantly in the feces. Part of this excretion was by way of the bile. Urinary excretion was very low.

Parameter	**Mean % of Dose**			
	GROUP 1	***GROUP 2***	***GROUP 3***	***GROUP 4***
Urine	2.4	7.3	0.74	1.8
Bile	17.6	10.8		
Feces	54.5	48.1	84.9	83.1
GI Tract	0.89	1.05	0.18	0.36
GI Contents	11.0	20.2	2.0	6.4
Liver	0.10	0.34	0.03	0.04
Kidney	0.01	0.05	0.002	0.005
Cage Wash	1.1	2.4	0.68	1.5

Five metabolites were identified; the glucuronide of hydroxy fexofenadine, phenyl hydroxy fexofenadine, MDL 106949, MDL 47397 and MDL 102038. Their levels in the urine and feces are summarized in the following table.

Metabolite Parent Compound	**Range of the % of Dose in the 4 Groups**		
	Urine	Bile	Feces
Glucuronide of hydroxy fexofenadine	<2.67-<0.06	2.64-4.88	ND
phenyl hydroxy fexofenadine	ND-<0.58	0.97-1.91	ND-3.07
MDL 106949	<0.2-0.67	1.45-2.87	1.66-4.54
MDL 47397	ND	<0.04-<0.05	ND
MDL 102038	ND	<0.01-<0.05	ND
Fexofenadine	<1.58-3.2	4.45-6.92	48.9-78.1

ND,
Not detectable

CONCLUSION

In normal and bile duct cannulated rats, fexofenadine undergoes minimal metabolism. Although 5 metabolites were detected, their levels in the urine, bile duct and feces were low or not detectable. Fexofenadine was excreted predominantly unchanged in the feces.

Isolation and identification of metabolites in urine and bile of Sprague-Dawley rats after p.o. administration of ^{14}C fexofenadine, K-97-0385-N, vol. 26.

METHOD

Description of the method was not clearly described. Sprague-Dawley Rats received 30 mg/kg p.o. of fexofenadine. Eight hour urine collection was pooled from 2 rats; bile collection was made from 4-8 h in one rat and 0-4 h and 4-8 h in a second rat and pooled. Samples were analyzed for metabolites using HPLC, LC/MS with electrospray ionization techniques.

Results

Fexofenadine was the major component in urine and bile. In the urine, there were 3 metabolites: MDL 4,829, MDL102038 and, MFD 106,949, hydroxylated fexofenadine at the methyl group. The bile contained the following metabolites in addition to fexofenadine: MFD106,949, and, hydroxylated fexofenadine and trace amounts of MDL 47,397, and MDL102038, glucuronide of the hydroxylated fexofenadine.

Conclusion

Following p.o. administration of fexofenadine, fexofenadine was the main component in the urine and bile. In the urine and bile, there were 3 metabolites; MFD106, 949, and MDL102,038, were metabolites found in the bile and urine.

In vitro metabolism of fexofenadine in human hepatic microsomes, K-95-0137-D, vol. 27.

METHOD

^{14}C Fexofenadine at concentrations of 5, 10 and 30 μM was incubated with liver microsomes alone and with the 2 S9 fractions, 0.5 mg/ml and 2.0 mg/ml of microsomal protein or liver slices. Studies with the 2 mg/ml preparation involved SKF525, a cytochrome P450 metabolic poison, or troleandomycin, an inhibitor of CYP3A4 enzymes. Analyses were conducted HPLC with radiometric and fluorescence detection..

RESULTS

When fexofenadine was incubated with liver slices for 2 and 24 h, no apparent biotransformation occurred. In the study with the 2 mg/ml of microsomal protein, 2 peaks were seen; one was MDL 4,829 and the other peak was not identified structurally. They may not be metabolites of fexofenadine since the levels of fexofenadine were unchanged. No biotransformation occurred in the presence of SKF 525A or troleandomycin. No peaks were seen when fexofenadine was incubated with liver slices indicating no biotransformation.

CONCLUSION

Fexofenadine was not metabolized in vitro using liver slices or liver microsomal protein.

OTHER STUDIES

Spectral binding studies of fexofenadine and structurally related compounds in human hepatic microsomes, K-97-0234-D, vol. 27.

Method

Spectral binding were conducted using human hepatic microsomes to determine whether fexofenadine interacts with P-450. Binding to the liver enzymes would be manifested by the microsomes manifesting a different spectra as determined by a b(4) **spectrophotometer. This instrument recorded spectra between 380 nm and 490 nm. One of the references was terfenadine. From the spectral changes, the K_s (enzyme dissociation constants) were determined.**

Results

Fexofenadine (2.5 μM to 100 μM) when added to liver microsomal preparation did not produce any characteristic spectral changes. Since no K_s could be determined, fexofenadine does not bind to the P-450 enzyme sites. Under similar conditions, the K_s for terfenadine 4.56 μM indicating that terfenadine binds to the P450 enzyme site.

CONCLUSION

Spectral analysis indicate that fexofenadine unlike terfenadine does not bind to the P-450 enzyme sites.

Plasma concentrations in guinea pigs of the enantiomers of fexofenadine following the p.o. administration of each enantiomer and fexofenadine, K-97-0261-D, vol. 27.

METHOD

Groups of 20 M guinea pigs received 5 mg/kg p.o. of (-)-fexofenadine, (+)-fexofenadine or
(±) –fexofenadine. They were administered as the HCl salt and the volume administered was 2 ml/kg. At 0.5, 1, 2,3 and 4 h, 4 animals from each group were killed, the blood removed by cardiac puncture and the plasma analyzed for the respective enantiomer.

RESULTS

The pharmacokinetics is summarized in the following table.

PARAMETER	Enantiomer Administered			
	Fexofenadine (-)	**Fexofenadine (+)**	**(±) – Fexofenadine (-)**	**(±) – Fexofenadine (+)**
Auc_{0-z}, (ng.h/ml)	587	438	178	206
Cmax, ng/ml	474	279	122	143
T max, h	1	1	0.5	0.5

No (-) enantiomer was present in the plasma of the guinea pigs receiving the (+) enantiomer; the reverse was true for the animals receiving the (-) enantiomer, i.e., no (+) enantiomer was present in the plasma. The AUCs were similar although the Cmax in the (+) enantiomer- treated group was lower than that in the animals receiving the (-) enantiomer. In animals given the racemic fexofenadine, the pharmacokinetics of both enantiomers were similar.

Conclusion

In guinea pigs, the pharmacokinetics of the enantiomers was similar when administered alone or administered as the racemate, and no interconversion occurred.

Summary of Pharmacokinetics and Toxicokinetics

THE RESULTS ARE SUMMARIZED IN THE FOLLOWING TABLES.

ABSORPTION

Species/Dose	Cmax	T max	AUC	F	T ½
	ng/ml	h	µg.h/ml	%	h
MOUSE					
Single Dose, mg/kg					
30 p.o.	0.28	0.5	1.59 [a]	19	
5000 p.o.	5.19	0.5	30.22 [a]	2.1	
1, i.v.	923		0.283		
PREGNANT RABBIT					
Day 19 of Gestation	6.5	1.0	37.4 [b]		
300 mg/kg p.o.[c]	17.4	2.0	174.4 [b]		
1500 mg/kg p.o.[c]					
DOG	11.3	0.9	0.048	12.4	
1.35 mg/kg p.o.	3.3				

[A] AUC WAS 0-INF
[B] AUC WAS 0-48H
[C] ANIMALS SHOWED DECREASED FOOD CONSUMPTION AND LITTLE OR NO FECAL OUTPUT.

PHARMACOKINETICS STUDIES WERE CONDUCTED WITH MDL46619 (FEXOFENADINE METHYL ESTER) IN DOGS TO DETERMINE WHETHER ADMINISTERING MDL 46,619 WOULD INCREASE THE PLASMA EXPOSURE OF FEXOFENADINE BY ADMINISTERING MDL 46,619. MDL 46,619 AT P.O. DOSES OF 1.35 AND 13.5 MG/KG SHOWED LOW BIOAVAILABILITY (APPROXIMATELY 10 %) AND SATURABLE ELIMINATION WITH INCREASING P.O. DOSES. MDL 46,619 READILY DISTRIBUTED IN THE TISSUES SINCE THE STEADY STATE VOLUME EXCEEDED THE VOLUME OF TOTAL BODY WATER. MDL 46,619 WAS RAPIDLY CLEARED (HEPATIC BLOOD FLOW WAS TWICE THE NORMAL FLOW) INDICATING EXTRA HEPATIC CLEARANCE. MDL 46,619 WAS METABOLIZED TO FEXOFENADINE, BUT THE PLASMA EXPOSURE TO FEXOFENADINE

FOLLOWING ITS ORAL ADMINISTRATION WAS LESS THAN THAT OBSERVED WITH A COMPARABLE DOSE OF TERFENADINE.

In a dog study in which MDL 46,619 was administered p.o. as an impurity (0.00029% of the dose of fexofenadine or 13.7 μg) in the fexofenadine. The p.o. doses of fexofenadine were 1.75 mg/kg and 325 mg/kg. Absorption of fexofenadine decreased as the dose increased. This was indicated since the HD was 185 times the LD, and there was only a 12-fold difference in the 1-hr plasma level of fexofenadine. Decreased absorption was further indicated since whitish material was present in the feces. The amount of MDL 46,619 recovered was approximately comparable to the amount administered; this indicates that MDL 46,619 was not a metabolite of fexofenadine. Excretion of the fexofenadine was predominantly fecal.

In distribution studies in M rats, whole-body autoradiography method was used. Following p.o. administration, radioactivity was predominantly found in the gastrointestinal tract and liver for up to 24 h. Kidneys and urinary bladder showed radioactivity up to 2 h. Following i.v. administration, fexofenadine was distributed mainly in the small intestines, liver and urinary bladder at the 0.25, 0.5, 2-h reading. The brain showed no radioactivity. In pregnant rats, fexofenadine was given orally on days 12 or 18 of gestation. Distribution was similar to that seen in the M rats except that on day 12 of gestation, distribution did not occur in the kidneys and urinary bladder of the pregnant animals. No radioactivity was observed in the fetuses. In M rats receiving fexofenadine twice daily for 4.5 days, distribution was in the esophagus, stomach, intestine and liver.

IN METABOLISM STUDIES IN RATS, FIVE METABOLITES WERE IDENTIFIED; THE STRUCTURES OF TWO WERE IDENTIFIED AS THE GLUCURONIDE OF HYDROXYFEXOFENADINE AND PHENYLHYDROXYFEXOFENADINE. THEY WERE EXCRETED IN THE BILE AND/OR FECES. URINARY EXCRETION WAS MINIMAL. A MAJOR PORTION OF DOSE OF FEXOFENADINE WAS EXCRETED UNCHANGED.

IN VITRO STUDIES USING HUMAN LIVER SLICES OR LIVER MICROSOMAL PROTEIN INDICATE THAT FEXOFENADINE WAS NOT METABOLIZED BY THE LIVER. FURTHER, SPECTRAL ANALYSIS USING HUMAN HEPATIC MICROSOMES SHOW THAT FEXOFENADINE UNLIKE TERFENADINE DOES NOT BIND TO THE P-450 ENZYME SITES.

IN GUINEA PIGS, FOLLOWING P.O. ADMINISTRATION OF EACH ENANTIOMER ALONE OR OF THE RACEMATE, THERE WAS NO INTERCONVERSION. THE PHARMACOKINETICS OF EACH ENANTIOMER WHEN ADMINISTERED ALONE WAS SIMILAR TO THAT SEEN WHEN ADMINISTERED AS THE RACEMATE.

TOXICOLOGY

SINGLE DOSE

ACUTE I.V. TOXICITY OF FEXOFENADINE IN RATS, NO. K-98-0079-T, VOL. 14.

Laboratory the Study was conducted: [redacted] b(4)

Dates of Study: 11/15/93- 10/23/98
GLP Compliance: Yes
QA: Yes.

Method

Species/Sex/ Body Weight : M and F Hsd: Sprague –Dawley rats, body weight ranging from 118-149 g for M and 102-120g for F. Each group consisted of 2 M and 2 F.

Route: i.v.
Vehicle: sterile water, pH adjusted to 11.2 with NaOH.
Doses: 10, 12.5, 50, 200, 400, 800, 2000 mg/kg/day.
Volume Administered: 1-20 ml/kg.
Lot No.: 98052070
Study Dates: Oct. 31-Nov.2,1997
Duration of Observation: 14 days.

Results

The results are summarized in the following table.

Dose mg/kg i.v.	Observations
10	No effect.
25	No effect.
50	M, lacrimation tonic, clonic, jumping and rolling convulsions; death, 2/2, day 1 F, twitching; death 2/2, day 1
200	M, F, bloody lacrimation, tonic, clonic, jumping and rolling convulsions; death, 4/4, day 1
400, 800, 2000	M, F, bloody lacrimation, gasping and tonic and clonic convulsions; death, all rats dead on day 1.
Necropsy	No macroscopic findings were seen in all animals

Conclusion

In rats, fexofenadine was lethal in all animals within 24 h at i.v. doses ≥ 50 mg/kg; toxicity were clonic and tonic convulsions. Macroscopically, no changes were seen. At 10 and 25 mg/kg, no toxicity was noted. The i.v.LD_{50} is between 25 and 50 mg/kg and no organs were targeted.

MULTIDOSE

Three- month dietary study in mice comparing terfenadine with fexofenadine HCl, No. K-98-0164-T and K-97-0446-N (Plasma Levels), vol. 15 and 21.

Laboratory the Study was conducted: Hoechst Marion Roussel, Deutschland GmbH, Global Preclinical Development Germany, Frankfurt am Main, Germany and US Pharmacokinetics, Hoechst Marion Roussel, Kansas City, Mo.

Dates of Study: 4/2/7- 7/31/97
GLP Compliance: Yes
QA: Yes.

Method

Species/Sex/ Body Weight : M and F CD-1 mice, 55-6 week old, mean weight of M: 24.3g and mean weight of F:19.7 g. Each group consisted of 15 M and 15 F. 15 additional M and F in the treated groups and 5 additional M and F in the control groups were used in the toxicokinetics study.
Route: Oral by dietary administration..
Dietary Doses: Fexofenadine HCl: 0.5% (LD), 2.5% (MD) and 5% (HD) equal to 848, 4,367 and 8,722 mg/kg/day for the M and 1,080, 5,154 and 10,324 mg/kg/ day for the F.
Terfenadine: 0.15% equal to 247 mg/kg/day for the M and 321 mg/kg/ day for the F.
The expected fexofenadine AUC values will be up to 5 x those obtained in the 18-month terfenadine study.
Lot No.: Fexofenadine HCl, 98052070; Terfenadine, KK0869M201
Duration of Study: 3-months.
Analysis of Concentration in Diet: Day 2 and approximately 1 and 2 months in the study.

The following parameters were determined.

Clinical Observations: Daily
Body Weight: Weekly
Food Consumption: Weekly.
Hematology and Clinical Chemistry: Week 12 (5 M and 5 F/ group) and in surviving animals after 4 week recovery.
Plasma Levels: Day 90 at 1, 5, 9, 13 and 24 h. A HPLC/fluorescence method was used with a assay LOQ of 25 ng/ml /100µl sample.

Necropsy: Three months after treatment, the first surviving 10 M and 10 F/ group were killed; the remaining animals were killed 4-weeks later as the recovery group. All organs were examined macroscopically.

Organ Weights: The following organs were weighed: heart, lungs, liver, kidneys, spleen, adrenals, testes, ovaries and brain.

Histology: The organs examined are listed in the table at the end of the Toxicology Section.

Results

Mortality: Fexofenadine: M, C, 1(death due to accident), MD, 1, HD, 1; F, C, 1. Deaths were not treatment related.

Body Weight Gained (0-Day 85): Fexofenadine: M, LD, -9.9%, MD, -19.8%, HD, -18.9%
F, No effect.
Terfenadine: M,-12.6%; F, No effect.
Recovery Period: Fexofenadine, M, full recovery at all doses.
Terfenadine, M, full recovery.

Food Consumption: Fexofenadine: No effect; Terfenadine, No effect.

Hematology: Fexofenadine: Hemoglobin: M, LD, +4.8%, MD, +5.4%, HD, +6.8%. F, No effect.
Terfenadine: No effect.
Recovery Period: Fexofenadine, M, full recovery at all doses.

Clinical Chemistry: No effect seen with fexofenadine and terfenadine.

Necropsy

Organ Weights: M, Kidneys, Relative Weight, HD, +16%

Histology: No histopathology was noted.

Plasma Levels of fexofenadine: The $AUC_{0\text{-}24h}$s are summarized in the following table. In both sexes, the AUCs for fexofenadine were maximum at the MD. M receiving fexofenadine or terfenadine showed higher AUCs than F. At dose where there is a comparable decrease in body weight gained, the AUC for fexofenadine was approximately 1/2 that of fexofenadine from the administration of terfenadine.

Compound	Dose mg/kg p.o.		AUC_{0-24h} ng.h/ml	
	M	*F*	M	F
Fexofenadine	848	1,080	14,662	10,577
	4,367	5,154	90,894	67,253
	8,722	10,324	82,714	61,297
Terfenadine	247	321	28,873	18,787

Summary and Conclusion

In a 3-month study in mice, the toxicity and pharmacokinetics of 0.5%, 2.5% and 5% fexofenadine in the diet was compared with 0.15% of terfenadine. Both compounds produced a decrease in body weight gained in the M. Maximum AUCs for fexofenadine occurred at the MD; the M receiving fexofenadine or terfenadine showed higher AUCs than the F. This may account for the increased sensitivity in the M. For the dose that produced comparable decreases in body weight gained, the AUC for fexofenadine was approximately ½ that of fexofenadine seen in the terfenadine-treated mice. For fexofenadine, the NOAEL was 848 mg/kg in the M and 1080 mg/kg in the F; no organ was targeted. Animals in the recovery group showed that the decreased body weight gained in fexofenadine- and terfenadine- treated animals were reversible.

One-month p.o. gavage toxicity in beagle dogs, No. K-96-0489-T, vol. 17. Toxicokinetics: vol. 23.

Laboratory the study was conducted: [redacted] b(4)

Dates of Study: 2/23-3/26/96
GLP Compliance: Yes
QA: Yes

Method

Species/Sex/ Body Weight: M and F Beagle dogs, body weight ranging from 10.5-15.4 kg for M and 6.7-8.4 kg for F .

No. of animals /group: 3 M and 3 F/control and treated groups;
Doses (mg/kg) 0 (2 ml/kg + 15 ml of tap water), 90 (LD), 300 (MD) and 900 mg/kg/day in 3 equally divided doses.
Lot No., % Purity: (Lot 80110), 99.9% Fexofenadine, 0.1% MDL: 46,619 (fexofenadine methyl ester)

Formulation (vehicle): 98.5% Polyethylene glycol 400 and 1.5% glacial acetic acid

The following observations were made:

Clinical Signs: Daily
Ophthalmologic Exam.: Once prior to dosing and during week 4.
Body Weight: Once prior to dosing and weekly thereafter.
Food Consumption: Once prior to dosing and weekly thereafter.
Electrocardiography: Twice (days –12 and –2) prior to and 1-2 h after dosing on days 2 and 30.
Hematology: Days –12, -2, 7, 15, 22 and 29.
Clinical Biochemistry: Days –10, -2 and 29.
Urinalysis: Days –10, -2 and 29.
Toxicokinetics: Days 1 and 7; Blood was collected at 0.5, 1, 2, 4 and 8 h after the first dose.

Plasma llq (lower limits of quantification) was 0.5-1 ng/ml.

Necropsy

Organ Weights at Termination: The following organs were weighed: adrenals, heart, brain with brainstem, kidneys, liver, ovaries, pituitary, prostate, spleen, testes, thymus, thyroid and uterus (cervix).

Histopathology: See table at the end of the Toxicology Section.

RESULTS

Mortality: Week 2, 1 HD, F and Week 3, 1HD, M. died or was killed for humane reasons. These deaths were not compound related.

Clinical Signs: Emesis [white material], M+F, C, 1/6, LD, 3/6, MD. 3/6, HD, 6/6. Some of this white material was apparently fexofenadine. This effect was seen during the study.

Feces (green): M+F, C, 1/6, LD, 0/6, MD. 4/6, HD, 3/6.

Body Weight Gained: Week 0- 4: F, C, -0.17 kg, HD, +0.26 kg.
M, no change.

Food Consumption: No effect.

Ophthalmologic Exam: No effect.

Electrocardiography: No effect.

Hematology: No effect.

Clinical Biochemistry: No effect.

Urinalysis: No effect.

Toxicokinetics: The results are summarized in the following table. The llq (lower limit of quantitation) was 0.5 ng/ml. For fexofenadine , the AUC in both sexes were dose related but not dose proportional. Fexofenadine accumulated upon repeated dosing. At the HD the AUC in the F were higher than those in the M. The levels of the impurity, MDL 46,619 were so low that AUCs could not be determined.

Daily Dose mg/kg, Orally	Fexofenadine $AUC_{0-8\ h}$, µg.h/ml				MDL46,619[a] Cmax, ng/ml			
	Day 1		Day 29		Day 1		Day 29	
	M	F	M	F	M	F	M	F
90	40.2	36.3	82.9	63.8	<0.5	<0.5	<0.5	<0.5
300	56.2	75.3	121.2	92.1	<0.6	1.0	1.4	1.1
900	83.4	74.0	126.7	188.3	<0.6	<0.5	1.1	1.2

[a] AUCs could not be determined

Necropsy

Organ Weights: No effect.

Gross Pathology: No significant changes.

Histopathology: No significant changes.

CONCLUSION

In a 1 month p.o. study in beagle dogs, 90, 300 and 900 mg/kg of fexofenadine containing 0.1% MDL 46,619 as an impurity, were administered daily in 3 equally divided doses. Emesis was seen at all doses and green feces occurred at the MD and HD. The NOAEL was 90 mg/kg, and no organ was targeted. This study was intended to but did not qualify the impurity, MDL 46,619, since a 3 month toxicity study is necessary for qualification.

Six-month p.o. toxicity in dogs, No. K-95-0897-T, vol. 18, Toxicokinetics, vol. 23.

Laboratory the study was conducted [redacted] b(4)

Initiation Date of Study: 11/14/94
GLP Compliance: Yes
QA: Yes

Method

Species/Sex/ Body Weight : M and F Beagle dogs, body weight ranging from 9.2- 13.2 kg for M and 6.9-11.1 kg for F .
No. of animals /group: 5 M and 5 F/control and treated groups;
Doses (mg/kg) C, 0 (6ml/kg), 100 (LD), 300 (MD) and 900 mg/kg/day in equally divided doses every 12 h.
Lot No., % Purity : (Lot RF9412), 99.87% Fexofenadine
Formulation (vehicle): 0.5% aqueous methylcellulose
The following observations were made:
Mortality: Daily.
Clinical Signs: Daily
Ophthalmologic Exam: Once prior to dosing and at end of treatment.
Body Weight: Weekly.
Food Consumption: Daily beginning day –14.
Electrocardiography: Twice (days –12 and –2) on all dogs prior to initiation of test. During the study, C and HD animals were tested 2-3 h postdose on days 1, 31, 90 and 178.
Hematology and Clinical Biochemistry: Days –13, -2, 29, 182 and 210.
Urinalysis: Days –13, 29, 182 and 210.
Toxicokinetics: Days 1, 30 and 183. Blood was collected at 1, 2, 4 and 7 h after the first dose.

Necropsy

Organ Weights at Termination: The following organs were weighed: adrenals, heart, brain with brainstem, kidneys, liver, ovaries, pituitary, prostate, spleen, testes, thymus, thyroid and uterus (cervix).

Histopathology: See table at end of the Toxicology Section. The first 3 dogs/sex/group were necropsied at the end of 6 months; the remaining dogs were necropsied at 7 months,1 month after recovery.

RESULTS

Test Article Analyses: 91-113% of theoretical value.

Mortality: 2 Dogs were killed for humane reasons; deaths were due to the results of incubation error and not compound related.

Clinical Signs: Emesis [white material], M+F Total number of emetic episodes increased from controls at all doses in a dose related manner. Vomitus contained white to yellow material; this may be unabsorbed fexofenadine .
Feces were discolored at the MD and HD; they were white to yellow color indicative of unabsorbed fexofenadine.

Body Weight: No effect.

Food Consumption: No effect.

Ophthalmologic Exam: No effect.

Electrocardiography: No effect.

Hematology: No effect.

Clinical Biochemistry: No effect.

Urinalysis: No effect.

Toxicokinetics: The results shown in the following table indicate that the AUCs were similar in M and F, and that fexofenadine showed accumulation in both sexes at the HD upon chronic administration.

DAILY DOSE Mg/kg, Orally	Fexofenadine $AUC_{0\text{-}12\ h}$, µg.h/ml			
	Day 1		Day 183	
	M	F	M	F
100	58.6	55.1	55.4	77.9
300	61.2	92.6	108.0	154.0
900	96.4	106.0	231.0	246.0

Necropsy

Organ Weights: No effect.

Gross Pathology: No significant changes.

Histopathology: No significant changes.

CONCLUSION

In a six-month study in beagle dogs, doses of 100, 300 and 900 mg/kg/day of fexofenadine were administered by gavage in divided doses. Fexofenadine was emetogenic at all doses. The vomitus contained white material suggesting unabsorbed fexofenadine. The feces was white to yellow in color indicating unabsorbed fexofenadine. The AUCs were dose related but not dose proportional, and accumulation occurred at the HD in M and F. The NOAEL was 100 mg/kg p.o., and no organ was targeted.

SUMMARY OF TOXICOLOGY

In an i.v. acute toxicity study rats, doses ≥ 50 mg/kg, fexofenadine was toxic and lethal. No toxicity was seen at 25 mg/kg. The animals manifested lacrimation, tonic and clonic seizures. No target organ was identified.

Multidose toxicity studies were conducted in the mouse and dog. In the mouse, a 3-month dietary study was conducted whereby the doses were to 848, 4,367 and 8,722 mg/kg for the M and 1,080, 5,154 and 10,324 mg/kg for the F. For comparison, one dose of terfenadine was included (247 mg/kg for the M and 321 mg/kg for the F). Fexofenadine was slightly more toxic than terfenadine since it decreased body weight gained in M. The AUC for LD of fexofenadine was ½ the fexofenadine AUC seen in the terfenadine-treated animals indicating a difference in bioavailability. The NOAEL for fexofenadine was the LD, and there was no target organ of toxicity.

Two gavage studies were conducted in dogs. In the 1- month study, p.o. doses of 90, 300 and 900 mg/kg of fexofenadine with 0.1% MDL 46,619 as an impurity were emetic; at the MD and HD, the feces were green. Accumulation occurred in the HD, F. Little or no MDL 46,619 was detected in the plasma. The NOAEL was 90 mg/kg p.o., and no organ was targeted.

In the 6-month study, the p.o. doses of fexofenadine were 100, 300 and 900 mg/kg. The results were similar to those in the 1-month study, i.e., emesis, change in fecal color and accumulation in the HD, M and F. The exception was that the feces were white to yellow in appearance in contrast to green indicating unabsorbed fexofenadine. The NOAEL was 100 mg/kg p.o. No organ was targeted. Increasing the duration of the study from 1- to 6-months did not increase the toxicity in dogs

Histopathology –List of tissues examined

Study No.	0164-T	B-960003-T	K-95-0897-T			
Species	Mouse 3-Month	Dog, 1 Month	Dog, 6 Month			
Adrenals	X	X	X			
Aorta	X	X	X			
Axillary lymph node						
Brain	X	X	X			
Cecum	X	X				
Cervix						
Colon	X	X				
Diaphragm	X		X			
Duodenum	X	X	X			
Epididymis	X	X	X			
Esophagus	X		X			
Eye	X	X	X			
Fallopian Tubes						
Gall Bladder	X	X	X			
Gross Lesions		X				
Harderian Gland						
Head						
Heart	X	X	X			
Hypophysis						
Ileum	X	X	X			
Injection Site						
Jejunum	X	X	X			
Knee Joint	X					
Kidneys	X	X	X			
Lachrymal Gland		X				
Large Intestine			X			
Larynx						
Liver	X	X	X			
L nodes, mesesnteric	X	X	X			
L nodes, mandibular	X	X				
L nodes, ilical	X					
Lungs	X	X	X			
Mandibular Gland						
Mammary Gland		X	X			
Medulla oblongata	X					
Optic Nerves	X					

Ovaries	X	X	X			
Pancreas	X	X	X			
Parathyroid	X	X	X			
Pituitary Gland	X	X	X			
Prostate	X	X				
Rectum	X	X				
Salivary Gland,	X	X				
Sciatic Nerve	X	X	X			
Seminal Vesicles	X					
Skeletal Muscle	X	X	X			
Skin		X	X			
Skin with Mammary gland	X					
Spinal Cord	X	X	X			
Spleen	X	X	X			
Sternum with bone marrow	X	X	X			
Stomach	X	X	X			
Testes	X	X	X			
Thymus	X	X	X			
Thyroid	X	X	X			
Tongue	X	X	X			
Tonsil						
Trachea	X	X	X			
Urinary Bladder	X	X	X			
Uterus	X	X	X			
Vagina	X	X	X			
Abnormalities						
Inguinal L. node		X				
Rib Marrow		X				

Special Studies

Primary eye irritation study in New Zealand white rabbits, No. B-97-0083-T, vol. 18.

GLP Compliance: No.
QA: Yes.

Method

Species/Sex/ Body Weight : M and F New Zealand White rabbits ranging from 2.6-3.4 kg for M and for F. There were 3 M and 3 F in the treated group. No control group was used in the study.
Lot No., % Purity : (Lot 98052070), 98-102% Fexofenadine
100 mg of fexofenadine HCl powder was instilled into the subconjunctival sac of the right eye of each animal. The left eye was not treated and served as the control. The cornea, iris and conjunctiva of the treated eyes were examined and scored using the Draize Ocular Irritation Grading System at 1, 24, 48 and 96 h postdosing and on days 5-8. The maximum attainable total irritation score was 110 for each animal.

RESULTS

The results in the following table show that fexofenadine was mildly irritating to the eye with a maximum mean score of 13.3. The irritation score peaked at 1-h post dosing and by day 7, irritation was still present although minimal. Complete recovery was achieved at day 8.

Time Post DOSING	**Mean Irritation Score** *N=6*
1 h	13.3
24 h	9.5
48 h	6.3
72 h	5.0
96 h	4.0
5 days	3.7
6 days	1.7
7 days	0.8
8 days	0

Conclusion

Fexofenadine HCl was mildly irritating when instilled into the eyes of rabbits. The irritation lasted 7 days.

Primary dermal irritation study in New Zealand white rabbits, No. B-97-0084-T, vol. 18.

GLP Compliance: No.
QA: Yes.

Method

Species/Sex/ Body Weight : M and F New Zealand White rabbits ranging from 2.58-3.05 kg for M and for F. There were 3 M and 3 F in the treated group. No control group was used in the study.
Lot No., % Purity : (Lot 98052070), 98-102% Fexofenadine
0.2 g of fexofenadine was placed in a [redacted] with the cotton pad removed and secured with an adhesive bandage to a previously shaved one-inch square skin on the dorsal trunk of each rabbit. After 4 h , the fexofenadine was removed gently with a moistened gauze pad. At 1, 24, 48 and 72 h later, the marked skin site was examined for edema and erythema using the Scale Scoring Dermal Reactions system of 0-4 for each symptom. b(4

RESULTS

At 1, 24, 48 and 72 h following the placement of 0.2 g of fexofenadine for 4 h, the edema and erythema score was 0 out of a maximum score of 8 for each period indicating no irritation.

Conclusion

Fexofenadine was not irritating when applied topically to the shaved skin of rabbits.

Dermal sensitization study in guinea pigs, No. B-97-0088-T, vol. 18.

GLP Compliance: No.
QA: Yes.

Method

Species/Sex/ Body Weight : M and F Hartley guinea pigs from 310-420 g were used. There were positive (1-chloro-2,4 dinitrobenzene, DNCB) and negative control groups in the study.
Lot No., % Purity : (Lot 98052070), 98-102% Fexofenadine

The groups used in the study are presented in the following table. Each induction group received the respective agent applied to the shaved skin (left side) 3 times a week for 3 weeks. The material was exposed to the skin for 6 h. The fexofenadine was administered by [redacted] with the cotton pad removed. The patch was then secured with an adhesive bandage. The other materials were applied by the same technique except that the cotton pad was not removed. 17 days after the last application, the respective challenging agent was administered to the shaved skin on the right side. The sites were examined for signs of dermal reactions 24 and 48 h after each application during the induction and challenge phases. b(4)

Induction Group and Number	No. of Animals M	F	Challenging Agent
I Fexofenadine, 100 mg	10	10	Fexofenadine, 100 mg
II Water, 0.4 ml	5	5	Fexofenadine, 100 mg
III Water, 0.4 ml	5	5	Water, 0.4 ml
IV DNCB (0.25%), 0.4ml	3	3	DNCB

RESULTS

Both sexes showed similar dermal responses. During the induction phase Groups I, II and III showed no signs of skin reaction. Group IV-treated animals, the positive control, showed erythema and edema, which increased in intensity as the number of applications increased. By the 9th application, the mean score at 48 h was 4.0 with evidence of necrosis.

Following the administration of the respective challenges, Groups I, II and III showed no tissue reactions at 24 and 48 h. Group IV-treated animals (positive control) showed a positive dermal response with edema and eschar. The response would be classified as extreme indicating a good response for the positive control group and a valid experiment.

Fexofenadine was not a skin sensitizer in guinea pigs.

SUMMARY OF SPECIAL STUDIES

Applying fexofenadine powder to rabbit eyes was slightly irritating. When was applied to shaved skin of rabbits, fexofenadine was not irritating. Fexofenadine was not a skin sensitizer in guinea pigs.

OVERALL SUMMARY AND EVALUATION

Fexofenadine, a H_1 receptor antagonist, is being marketed as a 60-mg capsule with a daily dose of 60-mg capsule twice a day. This NDA is for fexofenadine as a 60-mg tablet with the same daily dosage: [redacted] b(4)

[redacted] that was withdrawn from the market since it tended to produce [redacted] b(4)
This was due to prolongation of the QTc interval, an action that has lead to ventricular fibrillation and death. This was attributed to the ability of [redacted] to inhibit the IKr channel in the heart leading to the cardiac irregularity. Under normal conditions, [redacted] was immediately metabolized to fexofenadine. Since this biotransformation b(4)
involved the hepatic cytochrome P-450 enzyme, CYP3A4, patients taking [redacted] with drugs that inhibit the CYP3A4 enzyme were especially susceptible to developing cardiac arrhythmias. Fexofenadine was developed since it did not block the IK channel or prolong the QTc interval in animals, and consequently, lacks the potential for producing the cardiac arrhythmias.

The H_1 receptor antagonist potency of fexofenadine in in vitro and in in vivo models, respectively, ranged from 0.3 to 2 and 0.4 to 1 times that of terfenadine. However, fexofenadine was less potent than terfenadine in preventing anaphylaxis in guinea pigs and in preventing the release of histamine from rat mast cells. Studies with the enantiomers of fexofenadine show that the antihistaminic activity of the (+) enantiomer was comparable to and slightly more potent than the (-) enantiomer in in vivo and in in vitro studies, respectively. In binding studies neither fexofenadine nor it enantiomers had affinity to the following receptors: NK-1, NK-2 ,
α_1 adrenergic, α_2 adrenergic, β adrenergic, L-type Ca channel, α_1 adrenergic, muscarinic m_1, muscarinic m_2, muscarinic m_3, muscarinic m_4, $5HT_{1A}$ and $5HT_{2A}$.

Fexofenadine did not prolong the QTc interval in dogs and rabbits and it was relatively very weak or inactive in blocking the K^+ channels in vitro or affect the APD_{90} of the guinea pig papillary muscle. In the general pharmacology studies involving the central nervous, autonomic, cardiovascular, gastrointestinal, coagulating and renal systems, fexofenadine did not demonstrate potential clinical adverse effects.

In pharmacokinetics studies, fexofenadine was poorly bioavailable orally in the mouse (19%) and rat (2.9%) as compared with the dog (50%) and humans (33%). However, when administered as a solution in propylene glycol/1.5% acetic acid in contrast to a capsule, the p.o. bioavailability in dogs increased 2.7 fold. Pretreating dogs with ketoconazole doubled the bioavailability and also increased the systemic exposure of fexofenadine. In pregnant rabbits, the exposure to fexofenadine from administering fexofenadine alone was less than those seen with comparable doses of terfenadine. In guinea pigs, the exposure to enantiomers when given p.o. alone was similar to that seen when the racemate was administered and no interconversion occurred.

In distribution studies in rats, using radiolabeled fexofenadine, radioactivity was found in the intestines and liver and bladder following p.o. (single or multidose) or i.v. administration. (single) dose. Fexofenadine/metabolites were not distributed in the brain. Similar finding were seen in pregnant rats.

In rats, fexofenadine was metabolized to 5 metabolites and excretion was predominantly in the feces. A portion of this excretion in the feces was by way of the bile. Administering MDL 46,619, the methyl ester of fexofenadine, to dogs did not increase

the systemic exposure of fexofenadine. When fexofenadine was administered, no significant levels of the impurity, MDL 46,619, were found in the feces. In in vitro studies, fexofenadine was not metabolized by human hepatic microsomes nor did it bind with the P-450 hepatic enzymes. This indicates that no potential adverse action would occur between fexofenadine and drugs that inhibit these liver enzymes.

In an i.v. acute toxicity study in mice, fexofenadine was lethal at doses ≥ 50 mg/kg; 25 mg/kg was not toxic. At the lethal dose, convulsions were seen. Its p.o. LD50 in mice was> 5146 mg/kg indicating low systemic bioavailability. Low p.o. toxicity was seen in rats and dogs, where their LD50s were >5146 mg/kg and > 2000 mg/kg, respectively. In a 10-day multidose study, 10-300 mg/kg p.o. in dogs, no toxicity was observed.

In a 3-month dietary study in mice, the toxicity of terfenadine (M, 247 mg/kg; F, 321 mg/kg) was compared with fexofenadine (M, 848, 4367 and 8722 mg/kg; F, 1080, 5154 and 10,324 mg/kg). Both compounds produced a decrease in body weight gained; in addition, fexofenadine produced a dose-related decrease in hemoglobin. Based on the AUCs, fexofenadine showed greater systemic bioavailability from terfenadine than from its own administration.

In the earlier p.o. multidose studies, the toxicity of fexofenadine was determined by administering terfenadine since terfenadine was quickly metabolized to fexofenadine and produced high exposure to fexofenadine. Rats receiving 10, 100 and 300 mg/kg for 3 months produced an AUC at 300 mg/kg that was > 4- times higher than the clinical dose. Little toxicity was see as evidenced by increased reticulocyte count, and weight changes in the seminal vesicles, heart , prostate, pituitary, thyroid and adrenal glands. No histopathology was noted.

In a 1-month gavage study in dogs, fexofenadine was administered as solution doses of 90, 300 and 900 mg/kg/day administered in 3 divided doses. Fexofenadine contained a 0.1% impurity, MDL 46,619, which was the methyl ester of fexofenadine. Emesis occurred at all doses, and the feces were green at the MD and HD. No other toxic effects were noted. There was evidence of accumulation of fexofenadine in the plasma, especially in the HD, F. Terfenadine in a similar study decreased thymus weight at 300 and 900 mg/kg. Terfenadine was more toxic than fexofenadine, since at the doses of terfenadine which affected the thymus, the AUCs of fexofenadine from terfenadine administration were equal to or greater than the AUCs of fexofenadine from fexofenadine administration.

In a 6-month gavage study in dogs, fexofenadine was administered as a suspension of 100, 300 and 900 mg/kg/day given in 2 divided doses. The feces in the MD and HD were white to yellow in color indicating poor absorption. Other than emesis, no toxicity was observed. Accumulation occurred in the HD M and F. This accumulation in the HD, F was also seen in the 1-month study. No comparison of the 1- and 6- month's toxicity profile of fexofenadine could be made with terfenadine at similar periods. However, in a 2-year oral study, terfenadine was tested at 30 and 100 mg/kg. At 100 mg/kg, terfenadine

was convulsive and lethal within 2-3 weeks. The dose was subsequently reduced from 100 to 80 mg/kg. The NOEL was 30 mg/kg. The $AUC_{0\text{-}24h}$ for the 80 mg/kg dose of terfenadine was approximately 35 μg.h/ml and that for 100 mg/kg of fexofenadine was approximately 44 μg.h/ml (Sancilio, 1/12/94 review of IND 43,573, p 23). Extrapolating the AUC (35 μg.h/ml) of fexofenadine from 80 mg/kg of terfenadine to that for 100 mg/kg of terfenadine, the AUC for fexofenadine would be approximately 44 μg.h/ml. Since the AUCs for fexofenadine for 100 mg/kg of terfenadine and 100 mg/kg fexofenadine would be comparable, terfenadine is more toxic than fexofenadine in the dog.

In the carcinogenicity studies in mice and rats, exposure to fexofenadine was achieved through the administration of terfenadine. In both species, the doses administered in the diet were 50 and 150 mg/kg. No neoplasms were seen. At 150 mg/kg, p.o., the respective ratios of the AUCs for mice and rats to that for the adult dose (3.6 mg/kg) were 1.7 and 3.5 for the M and 3.4 and 2.7 for the F and that for the children dose (3.0 mg/kg) were 3.0 and 6.1 for the M and 6.0 and 4.8 for the F.

In the reproductive toxicity studies, exposure to fexofenadine was achieved through the administration of terfenadine. In mice, rats and rabbits at oral doses up to 200, 300 and 300 mg/kg, respectively, no teratogenicity was observed. The respective AUCs for 300 mg/kg in rats and rabbits were 3.6 and 30.5 times the maximum human therapeutic exposure. Fertility in rats was not affected at oral doses up to 300 mg/kg. At 150 and 300 mg/kg, toxicity was seen in the dams; in the fetuses, there was decreased body weight and decreased survival.

Fexofenadine was not mutagenic in the Salmonella-Escherichia coli/mammalian microsome reverse mutation, the (CHO/HGPRT) forward mutation and the rat lymphocyte chromosomal aberration in vitro assays and in the mouse bone marrow micronucleus in vivo test.

Special studies indicate that fexofenadine applied as a powder to the eyes or to the shaved skin of rabbits was either slightly or not irritating. Fexofenadine applied dermally was not a sensitizer in guinea pigs.

Recommendation

Based on the preclinical data, there is no objection to approval of fexofenadine tablets.

Comments for further studies: None.

Labeling

The following changes are recommended. The ratios of the AUC in animals to the AUC in adults and children that were used in the label are summarized in the following table.

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

SANCILIO

JUN 2 4 1996

DIVISION OF PULMONARY DRUG PRODUCTS
EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
REVIEW

NDA 20-625

Date of Submission: 7/31/95

Information to be Conveyed to Sponsor: YES (X), NO ( )

Reviewer: Lawrence F. Sancilio, Ph.D.

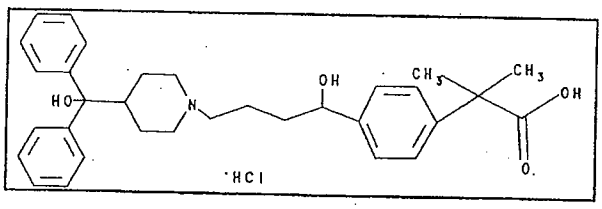
Date Review Completed: 6/24/96

Sponsor: Marion Merrell Dow Inc.
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Drug Name: Fexofenadine HCl, MDL 16,455A, TAM (terfenadine active metabolite)
MDL 9,918 (terfenadine)

Chemical Name: Benzeneacetic acid, 4-[1-(hydroxydiphenylmethyl)-1-piperidinyl]butyl'-α,α-dimethyl-, hydrochloride salt ±

Structure:



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

CAS No.: 138452-21-8

Related INDs and NDAs: IND [redacted] (fexofenadine HCl), NDA 18-849 (terfenadine) b(4)

Pharmacological Class: H1 receptor blocker

Indication: Treatment of Seasonal Rhinitis

Route: Oral

Formulation: 60 mg capsule containing croscarmallose sodium, gelatin, lactose, microcrystalline cellulose and pregelatinized starch.

Amended Reviews, Reviewer Dates:

NDA 19-949, Terfenadine, C. G. Oberlander, 4/28/83
Com
IND
IND
IND

b(4)

Background

Fexofenadine is the active metabolite of terfenadine, a marketed H_1 receptor blocker with little or no sedative properties. The uniqueness of fexofenadine is that unlike terfenadine, fexofenadine does not prolong QT_c intervals or inhibit the delayed rectifier potassium current channel. Consequently, fexofenadine is unlikely to produce Torsades de point, a cardiac arrhythmia seen in terfenadine patients under certain conditions.

List of Unpublished Reports and Pertinent Preclinical Articles Submitted

PHARMACOLOGY

The following were reviewed.

1. Mechanism of the cardiotoxic actions of terfenadine, JAMA 1993;269:1532-1536, vol. 16, p P174.

2. Interactions of the nonsedating antihistamines astemizole and loratadine with a voltage-dependent K+ channel cloned from human heart, No. C-94-0645-D, vol. 16, p 207.

3. Antiallergic effects of terfenadine on immediate type hypersensitivity reactions. Immunopharmacol. Immunotoxicol. 9:257-279, 1987, vol. 16, p 220.

4. Intracellular calcium release induced by histamine releasers and its inhibition by some antiallergic drugs, Ann Allergy 56:464-469, 1986, vol. 16, p 379.

The following were not reviewed since they were previously reviewed or were not relevant.

Second-generation H1-receptor antagonists, Annals of Allergy 1991; 66:5-19, vol. 15, p 79 .

Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In: The Pharmacological Basis of Therapeutics, 7th ed., Gilman AG, Goodman LS, Rall TW, and Murad F, ed. MacMillan Publishing Co., New York, 1985, vol. 15, p 95.

Cardiotoxic effects with convulsions in terfenadine overdose, Br Med J. 1989:298, vol. 15, p 133.

Pharmacokinetics and biotransformation studies of terfenadine in man, Arzneim-Forsch/Drug Res. 1982,32: 1185-1190, vol.15 p 133.

Effects of intravenous infusion of terfenadine and MDL 16,455A on QTc interval in anesthetized rabbits, N. C.-93-0235-R, vol. 15, p 140.

Effect of intravenous terfenadine infusion on QTc interval in anesthetized dogs, No. C-93-0234-R, vol. 16, p 180.

Effect of repeated ascending doses of terfenadine and MDL 16,455A, the acid metabolite of terfenadine, on the electrocardiogram of dogs, No. C-93-0248-R, vol. 15, p 164.

Effect of terfenadine, MDL 16,455A, and the stereoisomers MDL 15,171 and MDL 15,172 on action potential and membrane currents in guinea pig ventricular cells, No. C-91-0084-R, vol. 15, p 193.

Time course of the antihistaminic effects of MDL 16,455A and terfenadine on histamine skin wheals in guinea pigs, No. C-93-0145-R, vol. 15, p 206.

Oral effects of terfenadine and MDL 16,455A on histamine wheals in guinea pigs, No. C-84-0054-R, vol. 15, p 218 .

The effects of MDL 16,455A on the vascular effects of histamine and phenylephrine in the dog hindlimb preparation, No. C-84-0068-R, vol. 15, p 233.

The effects of terfenadine or chlorpheniramine on the vascular effects of phenylephrine and histamine in the dog hindlimb preparation, No. C-83-0054-R, vol. 15, p 245.

Antagonism of histamine-induced bronchoconstriction by MDL 9,918 and MDL 16,455A in anesthetized guinea pigs, No. C-93-0215-R, vol. 15, p 260.

Competitive receptor binding studies with MDL 16,455A and its enantiomers to rat brain

histamine-H1 receptors, No. C-93-0247-R, vol. 15, p 271.

Antihistaminic effect of MDL 16,455A, a major metabolite of terfenadine, No. C-84-0066-R, vol. 15, p 279.

Primary CNS evaluation of MDL 16,455A, No. C-93-0233-R, vol. 15, p 1.

General pharmacology of an antiallergic drug terfenadine, No. J-92-0010-R, vol. 16, p 11.

Effects of terfenadine and MDL 16,455A on histamine wheals in guinea pigs, No. C-84-0067-R, vol. 16, p 121.

Effect of MDL 16,455A on the isolated guinea pig ileum, No. C-77-0015-R, vol. 16, p 132.

Effect of RMI 16,218A on the isolated guinea pig ileum. A comparison with terfenadine, No. C-77-0014-R, vol. 16, p 146.

Block of a human delayed rectifier K+ channel by terfenadine and its metabolites, No. C-93-0182-R, vol. 16, p 165 .

Cumulative dose-response curves: Technique for the making of dose-response curves in isolated organ and the evaluation of drug parameters. Arch Int Pharmacodyn Ther 1963;143:299-330, vol.15, p 304.

PHARMACOKINETICS

Absorption/Excretion

1. Pharmacokinetics in Beagle dogs following oral administration of terfenadine, No. J-91-0005-D, vol. 19, p 277.

Distribution

1. Tissue distribution of radioactivity in the rat following a single oral dose of [14C]MDL 16,455A, No. K-93-0668-D, vol. 16, p 244.

2. One-month dietary pharmacokinetic study of terfenadine in CD-1 mice (PK 206), No.K-93-0411-D, vol. 17, p 259

3.One-month dietary pharmacokinetic study of terfenadine in Sprague-Dawley rats (PK 233), No. K-93-0409-D, vol. 17, p 275.

4. Terfenadine and fexofenadine plasma concentrations following a 10 mg/kg oral dose of terfenadine in male Sprague-Dawley rats, No. K-93-0528-D, vol. 19-P123

Metabolism

1. Incubation of fexofenadine with rat and human hepatic microsomes, No. K-93-0186-D, vol. 20, p 202.

The following were not reviewed since they were previously reviewed or were not relevant.

Plasma concentrations of MDL 16,455 in male and female Sprague-Dawley rats given a single 5 g/kg oral suspension doses of MDL 16,455A (PK-236), No. K-93-0364-D, vol. 17 p 86.

Acute oral toxicity of MDL 16,455A administered to dogs, No. C-90-0240-T, vol. 17, p 101.

Plasma concentrations of MDL 16,455 in female Beagle Dogs given a 500 mg/kg oral suspension dose of MDL 16,455A (PK-235), No. K-93-0370-D, vol. I7, p 114.

Plasma concentration of MDL 16,455 and terfenadine in Beagle dogs given 80 mg/kg/day capsule doses of terfenadine for one month (PK 234), No. K-93v0431-D, vol.17, p 292.

Maternal and fetal plasma concentrations of MDL 16,455 and terfenadine in Sprague-Dawley rats given daily 300 mg/kg oral doses of terfenadine (PK-251), No.K-94-0222-D, vol. 18, p 1.

Maternal and fetal plasma concentrations of MDL 16,455 and terfenadine in Dutch-Belted rabbits given daily oral 300 mg/kg doses of terfenadine (PK-250), No. K-94-0159-D, vol., 18 p 27.

b(4)

MDL 16,455, MDL 17,523, and terfenadine in mouse plasma, No. WARS-2135V, vol.18, p 186.

The pharmacokinetics and oral bioavailability of MDL 16,455A in Sprague-Dawley rats, No. K-93-0442-D, vol. 19, p 54.

The bioavailability and urinary excretion of terfenadine acid metabolite (MDL 16,455A) and terfenadine in Sprague-Dawley rats, No. K-93-0071-D, vol. 19, p 80.

Terfenadine and Fexofenadine plasma concentrations following a 10 mg/kg oral dose of Terfenadine in male Sprague-Dawley rats, No. K-93-0528-D, vol.19, p 123.

A comparison of the absorption and elimination of oral MDL 16,455A and terfenadine in Beagle dogs, No. K-93-0145-D, vol. 19, p 141.

Plasma concentrations of MDL 16,455 in Beagle Dogs given 90, 300, or 900 mg/kg/day oral doses of MDL 16,455A in a one-month toxicity study (TI93-033), No. K-93-0460-D, vol. 19, p 195.

Physiological parameters in laboratory animals and humans, Pharm Res. 10:1093-1095,1993, vol. 19, p 216.

Metabolism studies on terfenadine (II), No. J-94-0006-D, vol.19, p 220.

Pharmacokinetics in Beagle dogs following oral administration of terfenadine, No. 91-0005-D, vol. 19, p 277.

Protein binding of MDL 16,455 in serum of healthy, drug-free human subjects, No. C-88-0198-D, vol. 20, p 21.

Metabolic disposition of terfenadine in laboratory animals. Arzneim-Forsch/Drug Res. 32(11):1173-1178, 1982, vol. 20, p 11.

Pharmacokinetics, p 238. In: Drugs and the pharmaceutical sciences, ed. James Swarbrick. 1975:vol 1, vol. 6, p 18.

Predicted human whole body and tissue exposures to radioactivity from an oral dose of 14C-labeled terfenadine, No. K-93-0470-D, vol. 20, p 46.

Metabolic studies on terfenadine (I): Absorption, distribution, metabolism and excretion in rats, No. J-94-0005-D, vol. 20, p 58.

Marion Merrell Dow Inc., No. K-93-0186-D, vol. 20, p 202.

Relative Bioavailability of MDL 16,455 from Two Oral Suspension Formulations in Dogs, No. K-95-0092-D, vol. 20, p 272.

Validation of a method based on liquid chromatography with fluorescence detection for quantification of fexofenadine and terfenadine in rat plasma, No. K-93-0634-D, vol. 20, p 295.

Validation of a method based, on liquid chromatography with fluorescence detection for quantification of fexofenadine and terfenadine in dog plasma, No. K-93-0500-D, vol. 20, p 327.

Validation of a method based on liquid chromatography with fluorescence detection for quantification of terfenadine in rat and dog urine, No. K-95-0441-D, vol. 20, p 361.

The pharmacokinetics and oral bioavailability of MDL 16,455A in Sprague-Dawley rats, No. 93-0442-D. vol. and page number not given.

TOXICOLOGY

Genotoxicity

1. MDL 16,455A: Mutagenicity test in the Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay, No.K-94-059-T, vol. 18, p 51.

2. MDL 16,455A: Evaluation of the Chinese Hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay, No. K-94-0621-T, vol.18, p 80.

3. MDL 16,455A: Evaluation of an in vitro chromosomal aberration assay utilizing rat lymphocytes, No. K-9k-062-T, vol. 18, p 118.

4. MDL 16,455A: Evaluation in the mouse bone marrow micronucleus test, No. K-94-0635-T, vol. 18, p 151.

The following were not reviewed since they were previously reviewed or were not relevant.

Acute oral study with MDL 16,455, terfenadine metabolite I, in mice.
No. J-2-0020-T, vol. 17, p 54.

Acute oral toxicity of MDL 16,455A in mice and rats, No. C-90-0241-T, vol. I7, p 68.

Acute oral toxicity of MDL 16,455A administered to dogs. Project Report C-90-0240-T, vol. 17, p 101.

MDL 16,455A: Exploratory acute oral toxicity study in Beagle dogs, No. -934046-T, vol. 17, p 129.

Fexofenadine: Two-week oral tolerance screen in Beagle dogs, No. 93-0048-T, vol. 17, p 143.

Fexofenadine: One-month oral toxicity study in Beagle dogs, 93-0051-T, vol.17 p 154.

REVIEW

PHARMACOLOGY

1. Mechanism of the cardiotoxic actions of terfenadine, JAMA 1993;269:1532-1536, vol. 16, p 174.

Episodes of Torsades de pointes in humans are the result of a quinidine like action. This was attributed to blockade of the delayed rectifier potassium current. Terfenadine like quinidine blocked the potassium current in isolated feline myocytes while its metabolite, fexofenadine, was inactive at concentrations up to 5μM which is up to 30 times higher than that of terfenadine which produces a half maximal inhibition of the delayed rectifier potassium current in isolated feline myocytes.

2. Interactions of the nonsedating antihistamines astemizole and loratadine with a voltage-dependent K+ channel cloned from human heart, No. C-94-0645-D, vol. 16, p 207.

Using a delayed rectifier K+ channel (fHK) cloned from the human heart, both astemizole and loratidine blocked the K+ channel fHK with an IC_{50} of 1μM. However, the two drugs differed in their effect on current deactivation. Astemizole like terfenadine in a time dependent manner slowed current deactivation while loratidine did not affect the current deactivation.

3. Antiallergic effects of terfenadine on immediate type hypersensitivity reactions. Immunopharmacol. Immunotoxicol. 9:257-279, 1987, vol. 16, p 220.

The activity of terfenadine on immediate hypersensitivity reactions were compared with its 2 metabolites, fexofenadine and Metabolite II. The results are shown in the following table.

Model	Route	Potency (Terfenadine: 1)		
		Fexofenadine	Metabolite II	Ketotifen
Passive Cutaneous Reaction in Rats	p.o.			2
Antigen-Induced Bronchospasm in Guinea Pigs	p.o.	0.5	0.07	2.5
Histamine Release from Rat Mast Cells Induced by Compound 48/80	In Vitro	0.33	Inactive at 100 μM	0.1

Model	Dose /Concentration Activity Was Noted	
	Terfenadine	Ketotifen
Antagonism of ↑Ca Uptake of Mast Cells Induced by Compound 48/80	2-10 μM	Not Tested
↑ Cyclic AMP Levels		
Rat Mast Cells	5-20 mg/kg p.o.	Inactive at 20 mg/kg p.o.
Guinea Pig Lungs	5-20 mg/kg p.o.	Inactive at 20 mg/kg p.o.
↑ Adenylate Cyclase Levels		
Rat Lung, Ex Vivo	5-20 mg/kg p.o.	Inactive at 20 mg/kg p.o.
Phosphodiesterase Activity		
Rat Lung, Ex Vivo	Inactive at 20 mg/kg p.o.	Inactive at 20 mg/kg p.o.

4. Intracellular calcium release induced by histamine releasers and its inhibition by some antiallergic drugs, Ann Allergy 56:464-469, 1986, vol. 16, p 379.

Terfenadine and fexofenadine and not Metabolite II at 10 μM inhibited Ca release from stored intracellular Ca. This was shown with mast cells who require Ca ions to release histamine. Consequently, in a calcium free media the Ca comes from released stored intracellular Ca. By blocking the release of histamine induced by Compound 48/40 in a Calcium free medium, terfenadine and fexofenadine thus exert their effect by inhibiting the release of stored Ca.

Summary of Pharmacology (Reviewed Reports/Articles)

Fexofenadine was different from terfenadine as it did not inhibit the delayed rectifier current in isolated feline myocytes at a concentration (5 μM) that was 30 times higher than an effective concentration of terfenadine. Terfenadine was similar to astemizole and different from loratidine on their effects on the voltage- dependent K+channel cloned from the human heart. Although all 3 drugs inhibit this channel at 1 μM, terfenadine like astemizole slowed the current deactivation while loratidine showed no effect on the current deactivation.

Studies were conducted with terfenadine and its 2 metabolites, fexofenadine and Metabolite II. Orally, terfenadine was twice as potent as fexofenadine and 14 times as potent as Metabolite II in protecting guinea pig from anaphylactic shock. Terfenadine was 3 times as potent as fexofenadine in inhibiting Compound 48/80 induced release of histamine from rat mast cells. Metabolite II was inactive in this model. Studies showed that terfenadine inhibited the release

of histamine by terfenadine and fexofenadine by inhibiting the release of intracellular Ca^{++}. Terfenadine was different from ketotifen since it 1. antagonized the increased uptake of Ca^{++} of mast cells induced by Compound 48/80, 2. increased the cyclic AMP levels of rat mast cells and guinea pig lungs and 3. increased the adenylate cyclase levels of rat lungs ex vivo. Both terfenadine and ketotifen were not phosphodiesterase inhibitors.

PHARMACOKINETICS

Absorption/Excretion

1. Pharmacokinetics in Beagle dogs following oral administration of terfenadine, No. J-91-0005-D, vol. 19, p 277.

Method

M Beagle dogs (12-13 kg) were given a 60 mg tablet of terfenadine. Blood samples were drawn at 0.5, 1, 2, 3, 4, 6, 10, and 24 h. Urine and feces were collected at 24 h for 72 h.

Results

Plasma level for terfenadine was less than 50 ng/ml; no terfenadine was found in the urine and fecal excretion accounted for 0.8% of the dose. The results for the 2 major metabolites, fexofenadine and MDL 4829 (N-dealkylated terfenadine), are summarized in the following table.

Parameter	Fexofenadine	MDL 4829
C_{max}, ng/ml	1770	71
T_{max}, h	2.7	2.5
AUC_{0-24h}, ng.h/ml	13263	857
$T_{1/2}$, h	2.0	12.0
Excretion, % of Dose		
Urine	0-24 h, 3.7% 24-72 h, 0.4%	0-24 h, 6.8% 24-48 h, 1.6% 48-72 h, 0.3
Feces	0-24 h, 34% 24-48 h, 14% 48-72 h, 2%	0-72 h, 0.8%

Conclusion

In beagle dogs, approximately 5 mg/kg p.o. (1 x 60 mg tablet), of terfenadine was rapidly metabolized predominantly to fexofenadine and to minor degree to the N-dealkylated terfenadine. Very little or no terfenadine was found in the plasma, urine and feces. The primary excretory route for the metabolite, fexofenadine, was fecal in contrast to urinary for the N-dealkylated metabolite.

Distribution

1. Tissue distribution of radioactivity in the rat following a single oral dose of [14C]MDL 16,455A, No. K-93-0668-D, vol. 16, p 244.

Ten mg/kg of radioactive fexofenadine were administered by gavage as a single dose to M Sprague-Dawley and Long Evans rats. At various periods up to 72 h, animals were sacrificed and plasma levels and tissues were analyzed for radioactivity. In the Sprague-Dawley rat 23 tissues were examined while in the Long Evans rat levels were determined only in the plasma, eyes, skin (pigmented area) and erythrocytes. The results are summarized in the following table.

Parameter	Sprague Dawley Rat	Long Evans Rat
C_{max}, μg equiv./ml	0.019	0.049
$AUC_{0\text{-}TF}$[a], μg equiv. x hr/ml	0.092	0.179
$T_{1/2}$, terminal, hr	13.3	1.42
Highest Concentration of Radioactivity		
AUC $_{0\text{-}TF}$[a] μg equivalents x hr/g		
Stomach	105	
Small Intestine	149	
Large Intestine	119	
Liver	9.8	
Excretion, 0-72 hr		
% of Radioactive Dose		
Urine	0.87	1.5
Feces	91.7	90.2

[a] AUC from the time 0 to the last measureable C^{14} concentration

2. One-month dietary pharmacokinetic study of terfenadine in CD-1 mice (PK 206), No.K-93-0411-D, vol. 17, p 259

Method

Animals: M (26-32 g)and F (24-29g) CD mice were used.

Compound: Terfenadine (Lot No. Z 0575-007)

Formulation: Terfenadine was administered in the diet at a daily dose of 150 mg/kg; this dose was the HD in the carcinogenicity study.

Plasma Levels: Blood from 12 mice/sex was obtained at 4 h intervals from 8 PM on day 30 to 4 PM on day 31. Concentrations of terfenadine and 2 metabolites, fexofenadine and MDL 17523 were determined from the plasma by HPLC with fluorescence detection. The lower quantification limit for each compound was 25 ng/ml in a sample volume of 0.2 ml.

Results

The results are summarized in the following table.

Compound	C_{max}, ng/ml M	F	AUC_{24h} ng.h/ml M	F
Terfenadine	< 25	< 25	[a]	[a]
Fexofenadine	355	689	5,655	11,444
MDL 17523	< 25	< 25	[a]	[a]

[a]Could not be determined due to undetectable levels

Conclusion

In a 30 day dietary administration of 150 mg/kg terfenadine to mice, no detectable levels of terfenadine or one of its metabolites, MDL 17523, was detected. Fexofenadine, another metabolite, was found in high levels. The C_{max} and $AUC_{24\,h}$ in the F were approximately 2 x those found in M.

3.One-month dietary pharmacokinetic study of terfenadine in Sprague-Dawley rats (PK 233), No. K-93-0409-D, vol. 17, p 275.

Method

Animals: M (232-275 g)and F (159-201 g) Crl:CD (SD)BR (VAF/PLUS) rats were used.

Compound: Terfenadine (Lot No. 70733)

Formulation: Terfenadine was administered in the diet at a daily dose of 150 mg/kg; this dose was the HD in the carcinogenicity study.

Plasma Levels: Blood from 3 rats/sex was obtained at 4 h intervals from 8 PM on day 28 to 8 PM on day 29. Concentrations of terfenadine and its metabolite, fexofenadine, were determined from the plasma by HPLC with fluorescence detection. The lower quantification limits were 5 ng/ml for fexofenadine and 10 ng/ml for terfenadine in a sample volume of 0.5 ml.

Results

The results are summarized in the following table.

Compound	C_{max}, ng/ml		AUC_{24h} ng.h/ml	
	M	F	M	F
Terfenadine	96	152	1,175	[a]
Fexofenadine	675	702	11,618	9,091

[a] Could not be determined since the levels in many animals were not detectable.

Conclusion

In a 30 day dietary administration of 150 mg/kg terfenadine to rats, the plasma levels for fexofenadine were in both sexes markedly higher than those seen with terfenadine. The respective C_{max}s and $AUC_{24\ h}$s for fexofenadine were essentially similar in both sexes.

4. Terfenadine and fexofenadine plasma concentrations following a 10 mg/kg oral dose of Terfenadine in male Sprague-Dawley rats, No. K-93-0528-D, vol. 19, p 123.

Method

Terfenadine at 10 mg/kg was administered by gavage as a micellar solution to M Sprague-Dawley rats. Groups of 3 rats were sacrificed at 0, 0.25, 0.5, 1, 1.5, 2, 3, 5, 7, 10, 14, 18, and 24 h and the plasma assayed for terfenadine and fexofenadine.

The results are shown in the following table.

Parameter	Terfenadine	Fexofenadine
C_{max}, ng/ml	35.7	257
T_{max}, h	1.5	1.5
$AUC_{0-\infty}$, ng.h/ml	61.3	683.8

Conclusion

In rats terfenadine was administered as a micellar solution at dose of 10 mg/kg p.o. It was

rapidly metabolized to fexofenadine since at 1.5 h, the plasma level of fexofenadine was approximately 7 x higher than the parent compound. In addition the AUC for fexofenadine was approximately 10 x higher that for terfenadine.

Metabolism

1. Incubation of fexofenadine with rat and human hepatic microsomes, No. K-93-0186-D, vol. 20, p 202.

Method

Fexofenadine (30 μM) was incubated with microsomes from rats for 2 h and from humans 1 h. The rat microsomes were from untreated animals and from animals treated with dexamethasone to induce P-450 enzymes. Human microsomes were obtained from 2 normal volunteers. They were characterized for P-450 enzymes.

Results

The results are summarized in the following table.

Microsome Preparation	Results
Rat Untreated, naive (2 h incubation)	No change in fexofenadine substrate
Dexamethasone-treated (1 h incubation)	No change in fexofenadine substrate; Vehicle controls showed a chromatographic peak which co-eluted with MDL 4829 (N-dealkylated fexofenadine). Mass spectroscopy was not performed to confirm the presence of MDL 4829.
Human Untreated, naive (1 h incubation)	8% decrease in fexofenadine substrate; a small peak related to MDL 4829 was detected.

Conclusion

In human microsomes and possibly in rat microsomes, fexofenadine undergoes oxidative dealkylation at a very slow rate.

Summary of Pharmacokinetics

In Beagle dogs receiving approximately 5 mg/kg p.o. (1 x 60 mg tablet) of terfenadine, rapid and complete metabolism occurred since little or no detectable levels of parent compound were found. Two metabolites, fexofenadine and MDL 4829, N-dealkylated terfenadine, were found in the plasma, urine and feces. Fexofenadine was the prominent metabolite as its $AUC_{0\text{-}24\ h}$ was 15 x higher than that for MDL 4829. Fexofenadine excreted mainly in the feces accounted for 50 % of the dose. Most of excretion of MDL 4829 which accounted for 8% of the dose was urinary.

Following the administration of a single dose of 10 mg/kg p.o. of radiolabeled fexofenadine to Sprague-Dawley and Long Evans rats, The Cmax in the Long Evans rat was higher than that in the Sprague-Dawley rat; however, the reverse was seen with their AUCs. The terminal half life in the Sprague-Dawley rat was approximately twice that of the Long Evans rat. In distribution studies, the highest levels based on AUC, terfenadine was seen in the small intestine, large intestine, stomach and liver. None of the assayed tissues from the Long Evans rats showed any radioactivity indicating that fexofenadine was not distributed to any degree in the eyes, skin and erythrocytes. In both strains, excretion was predominantly in the feces as > 90% of the total radioactivity was found in the feces.

In Sprague-Dawley rats terfenadine was administered 10 mg/kg p.o. as a micellar solution. Terfenadine was rapidly metabolized to fexofenadine as the C_{max} and $AUC_{0\text{-}\infty}$ for fexofenadine were approximately 7 x and 10 x that of terfenadine, respectively.

Two dietary 30 day pharmacokinetics studies of terfenadine were conducted in mice and rats. Both species received a daily dose of 150 mg/kg p.o., the dose used in the carcinogenicity studies. In the mouse, terfenadine was metabolized predominantly to fexofenadine since no detectable levels of terfenadine and MDL 17523 were found in the plasma on day 30. F showed an $AUC_{24\ h}$ and C_{max} that were approximately twice those in the M.

In rats, the plasma was assayed for terfenadine and fexofenadine. The C_{max}s for fexofenadine were similar in both sexes; they were approximately 5-7 x higher than terfenadine. However, the $AUC_{24\ h}$s of fexofenadine although similar in both sexes, were 10 x that for terfenadine in the M. However, the AUC_{24h} for terfenadine in the F could not be determined since in many animals, terfenadine levels were not detectable indicating the it was metabolized faster in the F than in the M.

TOXICOLOGY

Genotoxicity

1. MDL 16,455A: Mutagenicity test in the Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay, No.K-94-059-T, vol. 18, p 51.

GLP signed statement: Yes

Study Dates: 3/23/94-4/25/94.

Site the study was conducted: Hazelton Washington, Inc., Vienna, Va.

Method

Organisms: Salmonella typhimurium TA98, TAI00, TA1535 and TA1537 and Escherichia coli WP2uvrA. Liver microsomal enzyme reaction mix (S9 mix) was prepared from M Sprague-Dawley rats injected i.p. with Aroclor.

Positive Controls are listed in the following table:

Organism	With S9, Conc. (μg/plate)	Without S9, Conc. (μg/plate)
Salmonella typhimurium		
TA98	2-Aminoanthracene, (2.5)	2-Nitrofluorene (1.0)
TA100	2-Aminoanthracene, (2.5)	Na azide, (2.0)
TA1535	2-Aminoanthracene, (2.5)	Na azide, (2.0)
TA1537	2-Aminoanthracene, (2.5)	ICR-191 (2.0)
Escherichia coli		
WP2uvrA	2-Aminoanthracene, (25)	N-Nitroquinoline-N- oxide, (1.0)

With each organism the tests were conducted twice in triplicate for the test compound and in duplicate for the positive controls. The response to the positive control should be a 3-fold increase in the number of revertants per plate over that of the vehicle. A positive response and a valid assay were a reproducible dose response and ≥3 X increase in the number of revertant colonies with more than 1 dose.

Compound: Fexofenadine Lot No. 73038

Test for Cytotoxicity: For TA100 and WP2uvrA, 10 concentrations ranging from 6.67 μg - 5000 μg/plate were tested. Cytotoxicity was seen at 3330 and 5000 μg/plate (33-37%) in the absence of S9 and at 5000 μg/plate (15%) in the presence of S9.

Concentrations: 100, 333, 667, 1000 and 3300 μg/plate in the presence and absence of S9 mix for each organism.

Vehicle: Dimethylsulfoxide

Results

Fexofenadine, was not genotoxic in the presence and absence of S9 mcg/plate. The respective positive controls produced more than a 3 fold increase in the number of revertant colonies.

Conclusion

Fexofenadine was not mutagenic in the bacterial assay. This was a valid and acceptable assay.

2. MDL 16,455A: Evaluation of the Chinese Hamster ovarycell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay, No. K-94-0621-T, vol.18, p 80.

GLP signed statement: Yes; Fexofenadine sample was not audited.

Study Dates: 2/15/94-8/26/94.

Site the study was conducted: Health and Environmental Services, The Toxicology Research Laboratory, Midland, Michigan

Method

Chinese hamster CHO-K_1-BH_4 cell line was used. Liver microsomal enzyme reaction mix (S9 mix) was prepared from M Sprague-Dawley rats injected i.p. with Aroclor.

Vehicle: Dimethylsulfoxide

Test Compound: Fexofenadine (Lot No. 73038)

Positive Controls are listed in the following table:

With S9, Conc. (μg/ml)	Without S9, Conc. (μg/ml)
20-Methylcholanthrene , 4	Ethylmethane sulfonate, 621

An acceptable test was a statistical increase in the mutation frequency by the positive control, and the mutation frequency in the negative controls should be within the historical controls. Test compound is positive if it produces a statistical significant, dose related, reproducible increase in mutation frequency. Tests were conducted in duplicate whenever possible at each concentration.

Cytotoxicity Study: 200 cells/petri dish; concentrations tested, 218.75-3500 μg/ml (5 concentrations with and without S9. No cytotoxicity was noted at the concentrations tested.

Results

The highest concentration, 3500 μg/ml, in the absence and presence of S9, showed a 10.3% and 24.2% of control cell survival. The test compound showed no mutagenicity under both conditions and the positive control showed a high number of revertant cells. This was a valid and acceptable assay.

Conclusion

Fexofenadine was not mutagenic in the Chinese Hamster (CHO/HGPRT) forward mutation assay.

3. MDL 16,455A: Evaluation of an in vitro chromosomal aberration assay utilizing rat lymphocytes, No. K-9k-062-T, vol. 18, p 118.

GLP signed statement: Yes; Fexofenadine sample was not audited.

Study Dates: 2/15/94-8/26/94.

Site the study was conducted: Health and Environmental Services, The Toxicology Research Laboratory, Midland, Michigan

Method

Lymphocytes were taken from M Sprague-Dawley rats, 13-15 weeks old. At each concentration the number of cells/assay were 200 for the test compound and 100/ positive

control. Liver microsomal enzyme reaction mix (S9 mix) was prepared from M Sprague-Dawley rats injected i.p. with Aroclor. Two complete assays were conducted, a preliminary and confirmatory test. In the preliminary test the cells were harvested at 24 h after treatment while in the confirmatory test, the cells were harvested at 24 and 48 h post treatment.

Vehicle: Dimethylsulfoxide

Test Compound: Fexofenadine (Lot No. 73038)

Positive Controls are listed in the following table:

With S9, Conc. (μg/ml)	Without S9, Conc. (μg/ml)
Cyclophosphamide, 6	Mitomycin, 0.5

An acceptable test was a statistical increase in the chromosomal aberration frequency by the positive control, and the chromosomal aberration frequency in the negative controls should be within the historical controls. Test compound is positive if it produces a statistical significant, dose related, reproducible increase in chromosomal aberration frequency. Each test was conducted in triplicate.

Mitotic Indexes were determined in both tests. Concentrations tested, Assay 1, 35, 116.7, 350, 1167 and 3500 μg/ml with and without S9. Assay 2, 350, 1167, 3000 and 3500 μg/ml with and without S9.

Results

Mitotic Index (MI): Assay 1: At 3500 μg/ml the MI was reduced by 70% in the absence of S9 and 96.6% in the presence of S9. Assay 2: At 3500 μg/ml the MI was reduced by 65% and 100% in the absence of S9 at 24 and 48 h, respectively. At 3000 and 3500 μg/ml in the presence of S9, the MI was reduced by 100% at 24 and 48 h. At 1167 μg/ml, the MI was reduced by 13% at 24 and 36% at 48 h.

Chromosomal Aberration: Assay 1 and 2: No chromosomal aberration was noted in the absence of and presence of S9. In both tests the positive controls showed a marked increase in the number of chromosomal aberrations in the absence and presence of S9. The assay was valid and acceptable.

Conclusion

Fexofenadine was not clastogenic in the lymphocyte chromosomal aberration assay.

4. MDL 16,455A: Evaluation in the mouse bone marrow micronucleus test, No. K-94-0635-T, vol. 18, p 151.

GLP signed statement: Yes

Study Dates: 2/5/94-9/2/94

Site the study was conducted: Health and Environmental Services, The Toxicology Research Laboratory, Midland, Michigan

Method

Animals: 9 Week old M and F CD-1 Charles River mice (5/sex/group).

Test Compound: Fexofenadine (Lot No. 73038)
Positive Control: Cyclophosphamide

Formulation: Suspension containing 0.5% Methocel/ 0.5%Tween 80, 20 ml/kg for vehicle and fexofenadine treated animals and 10 ml/kg for reference treated animals.

Time of sacrifice: 24, 48 or 72 h for fexofenadine treated animals and 24 h for positive control group. 1000 cells from bone marrow of each animal were examined and the ratio of the number of micronucleated polychromatic erythrocytes (MN-PCE) to the number of normal polychromatic erythrocytes (NPE) was determined.

Doses: Vehicle (20 ml/kg by gavage), 625 mg/kg (LD), 1250 mg/kg (MD), 2500 mg/kg (HD). The HD was selected since a dose of 5000 mg/kg could not be given due to poor consistency of the suspension made it difficult to administer with a dosing needle. Reference: Cyclophosphamide: 120 mg/kg p.o.

Results

Dose ranging study: 2500 mg/kg was not toxic over a 4 day period.

At doses of 625, 1250 and 2500 mg/kg, fexofenadine produced no increase in the number of micronucleated polychromatic erythrocytes in M and F mice. Cyclophosphamide caused a marked increase in the frequency of abnormal erythrocytes (M, 28 vs 0.8; F, 40.3 vs 1.6). This a valid and acceptable study.

Conclusion

Fexofenadine was not mutagenic in the mouse micronucleus test.

Summary of Genotoxicity

Fexofenadine was not mutagenic in the Salmonella-Escherichia coli/mammalian microsome reverse mutation, the (CHO/HGPRT) forward mutation and the rat lymphocyte chromosomal aberration in vitro assays and in the mouse bone marrow micronucleus in vivo test.

OVERALL SUMMARY AND EVALUATION

Terfenadine is a non sedative H_1 receptor blocking drug. Terfenadine is metabolized to fexofenadine, a compound that possesses H_1 receptor blocking properties. Since the biotransformation to fexofenadine through the P450 system is fairly rapid in animals and in humans, the antihistaminic activity of terfenadine is attributed to a large degree to fexofenadine. The advantage of fexofenadine over terfenadine is that it does not possess the undesirable cardiac actions of terfenadine alone. Consequently, the potential for fexofenadine to produce Torsades de pointes, a potential fatal cardiac arrhythmia, is minimal. This cardiac action is seen with terfenadine in allergic patients especially those being treated with drugs like erythromycin that block the P450 enzymes thereby increasing the level of terfenadine.

The H_1 receptor blocking properties of fexofenadine in vitro and in vivo models are summarized in the following table. Its potencies relative to terfenadine ranged from 0.2 to 3.

Model	Activity
Binding Studies Rat Cerebral Cortex Membranes	2 x Potency of Terfenadine
Histamine-Induced Skin Wheal Test in Guinea Pigs	p.o., 0.4-0.6 x Potency of Terfenadine i.v., 3 x Potency of Terfenadine
Histamine-Induced Bronchoconstriction in Guinea Pigs	p.o., Equipotent to Terfenadine
Anaphylactic Shock in Guinea Pigs	p.o., 0.5 x Potency of Terfenadine
Histamine-Induced Contraction of Guinea Pig Ileum	0.3-1 x p.o., x Potency of Terfenadine
Histamine-Induced Vasodepression in Perfused Dog Hindlimb	i.v., Approximately equipotent to Terfenadine

Terfenadine may also exert its effectiveness in allergic diseases by inhibiting the release of histamine from mast cells. Compound 48/80 causes the release of histamine from rat peritoneal mast cells in a calcium free medium. This is due to a release of intracellular released calcium. Terfenadine, fexofenadine and disodium chromoglycate at 10 μM inhibited the release of histamine induced by Compound 48/80; this indicates that these compounds may exert this effect by affecting intracellular calcium or by exerting a stabilizing effect on mast cell. membrane.

Other properties that fexofenadine may possess since they were determined in vivo and ex vivo only for terfenadine. This is suggested since terfenadine is metabolized predominantly to fexofenadine. These properties observed at 5- 20 mg/kg p.o. were: 1.↑ Cyclic AMP levels in rat mast cells, 2.↑ Cyclic AMP levels in guinea pig lungs, and 3. ↑ Adenylate cyclase Levels in rat lungs.

The cardiac actions of terfenadine compared with fexofenadine are shown in the following table. The results show that fexofenadine possesses little or no effect on the heart; consequently, the potential for causing Torsades de pointes clinically in little or none at all.

Model	Activity	
	Fexofenadine	Terfenadine
In Vitro Studies		
Blockade of Human Delayed Rectifier K+ Channel, fKH, EC_{50}, μM	214	0.367
Blockade of Delayed Rectifier K+Current in Feline Myocytes, EC_{50}, μM	Inactive at 5	0.17
Blockade of Delayed Rectifier K+Current Using Embryonic Kidney Cells Cloned from Human Heart, Potency	0.0017	1
In Vivo Studies		
Increased QTC Interval in Anesthetized Rabbits, Compound Infused i.v. over 1 h	No effect at 10 mg/kg	23.5% at 1 mg/kg
QTC Interval in Unanesthetized Dogs, Compound given p.o. twice daily for 5 days	No effect at 3 and 10 mg/kg; At 30 mg/kg ↓ QTC	10 mg/kg ↑ the QTC >10% by day 3

In the general pharmacology studies involving the central nervous, cardiovascular, gastrointestinal, coagulating and renal systems, terfenadine possesses no potential clinical adverse effects.

In pharmacokinetics studies, fexofenadine at 30 mg/kg p.o. administered as a solution (98.5% propylene glycol-1.5% glacial acetic acid) to rats showed a 2.9% systemic bioavailability. This was attributed to 2 factors, poor absorption (24%) and high clearance (30 ml/min/kg). In dogs, receiving 8.7 and 27 mg/kg p.o. as a solution the absorption was 53.7 and 47.3%, respectively, showing greater absorption than the rat.

The following table compares the pharmacokinetics of a single dose p.o. fexofenadine in rats, dogs and humans. The dose in the rat (30 mg/kg) was slightly higher than that in the dog (27 mg/kg); both were higher than humans (2.4 mg/kg). In comparing dogs with rats, the dog showed a markedly higher C_{max}, $AUC_{0-\infty}$, elimination half-life (initial and terminal phases) and a

much lower clearance. The t_{max}s and MRTs (mean residence time) were similar. The 17 fold difference in the clearance resulting in longer elimination half lives contributed to higher levels in the dog. With humans, the percent bioavailability fell between that of the dog and rat, and the clearance was much lower than either the rat or dog. When the data was normalized based on mg/kg , the AUC and C_{max} for humans fell between the rat and dog.

Parameter	Rats 30 mg/kg	Dogs 27 mg/kg	Humans 2.4 mg/kg
$C_{max,}$ ng/ml	457	26,640	427
Normalized $C_{max,}$ ng/ml	15	987	178
$T_{max,}$ h	0.5	0.7	1-3
$AUC_{0-\infty}$, ng.h/ml	436	107,505	2682
Normalized $AUC_{0-\infty}$, ng.h/ml	15	3,982	1,118
Elimination Half-Life			
Initial Phase, h	0.4	1.96	
Terminal Phase, h	4.8	33.5	13
Cl_s, ml/min/kg	30	1.75	0.00079
MRT_b, h	3.7	4.0	
% Bioavailability	2.9	47.3-53.7	33

Distribution studies following the administration of 10 mg/kg p.o. fexofenadine were determined in Sprague-Dawley rats. Based on AUC_{0-TF}, fexofenadine was predominantly distributed in the stomach, small intestine, large intestine and to a lesser degree in the liver. In this study 91.7% and 0.87% of the radioactive dose was excreted in the feces and urine, respectively.

Following the administration of 300 mg/kg p.o. of terfenadine to pregnant animals, levels of fexofenadine were determined in the plasma levels of the dams and in the plasma levels of the fetuses. Fexofenadine was found in greater amounts in the plasma of the fetuses of the rabbits (477 ng/ml) than in the fetuses of rats (223 ng/ml); the AUC in the rabbits was approximately 9 x higher than that in the rat showing different pharmacokinetics. The dam/fetal ratio of the plasma levels in the rabbit was higher than rat (52 vs 4.1).

The following table compares the excretion pattern of fexofenadine in rats, dogs and humans. Humans, dogs and rats show similar excretory pattern, i.e., fexofenadine was excreted predominantly in the feces by way of the biliary tract and a small amount in the urine.

Species Dose, mg/kg	% of Dose Excreted	
	Feces	Urine
Rat		
10, p.o.	87.2	1.2
1, i.v	82.4	11.1
1, portal vein	84.5	4.7
Dog		
1, i.v.	78.1	13.1
Human		
	80	11

In the excretion studies no metabolites were found in the rat (feces), dog (feces) and human (urine and feces). In an in vitro study, fexofenadine was incubated with rat microsomes alone, in microsomes from dexamethasone-treated rats to induce P-450 enzymes and in human microsomes. After 1 h incubation a small amount of the N-dealkylated fexofenadine was found. Thus, fexofenadine undergoes oxidative dealkylation in both species at a slow rate. Since this metabolite was not found in the primary excretory route of rats, dogs and humans, fexofenadine undergoes little or no metabolism in rats, dogs and humans.

In binding studies with plasma, the binding of fexofenadine to plasma proteins of rats and humans was similar and slightly lower than the binding to dogs. At concentrations from 0.1-0.8 μg/ml, the binding ranged from 88.4%-89.7% for rats, 88.9%-90.8% for humans and 93.0%-94.3% for dogs.

In toxicity studies fexofenadine was administered p.o. to rats, mice and dogs in single dose studies and in multidose studies up to 1 month in rats and dogs. The results from the reproductive and longer term toxicity studies for terfenadine were acceptable for fexofenadine since 1. terfenadine is predominantly metabolized to fexofenadine which contributes substantially to its antihistaminic activity, and 2. greater exposure to fexofenadine occurred when terfenadine was administered particularly in rats. The systemic bioavailability for fexofenadine in rats following p.o. administration of terfenadine was approximately 10 x higher (29% vs 2.9%) than when fexofenadine was administered.

The following compares the single dose p.o. toxicity studies of fexofenadine and terfenadine in mice and rats. In rats and mice both fexofenadine and terfenadine were similar as their LD_{50}s were > 5000 mg/kg p.o. This may be attributed to poor absorption due to poor aqueous solubility. From this submission, poor systemic bioavailability in rats to fexofenadine also contributed to the low toxicity. Fexofenadine was also not toxic in dogs.

Compound Species	Doses, mg/kg, p.o.	Results
Fexofenadine		
Mice	4310 5146	No toxicity, LD_{50} > 5146 mg/kg p.o.
Rat		
	4310 5146	No toxicity, unabsorbed compound in feces LD_{50} > 5146 mg/kg p.o.
Dogs		
	1000 2000	Ataxia, LD_{50} > 2000 mg/kg p.o.
Terfenadine		
Mice		LD_{50} > 5000 mg/kg p.o.
Rats		LD_{50} > 5000 mg/kg p.o.

The results from multidose studies (10-14 days) in dogs with fexofenadine and terfenadine are summarized in the following table. Terfenadine was administered daily in single and/or divided doses. Terfenadine was more toxic than fexofenadine.

Compound	Doses, mg/kg, p.o.	Results
Fexofenadine	10, 30, 100, 300	No toxicity
Terfenadine	150, 500, 1000	At all doses, emesis, ↓ food consumption, ↓ body weight gained; 1000 mg/kg, pituitary, renal and cardiac changes were seen.

In a 3 month toxicity study in rats terfenadine was 10, 100 and 300 mg/kg were administered by gavage. Pharmacokinetics were not conducted in this study, but for a dose of 150 mg/kg from a 30 day dietary study, the AUC ranged from 9,091-11,618 ng.h/ml for F and M, respectively. This was 3.4-4.3 x the AUC for the clinical therapeutic dose. Thus, the AUC for the 300 mg/kg is higher than 4.3. At all doses the reticulocyte count was increased. The M showed an increase in the absolute and relative weights of the seminal vesicles at the 100 and 300 mg/kg p.o. At 300 mg/kg, there was a decrease in the absolute and relative weights of the heart and prostate. The F showed a dose related increase in the absolute and relative weights of the pituitary and thyroid and adrenal glands. Unabsorbed (?) terfenadine was found in 4 M and 9 F 300 mg/kg treated animals. No histopathology was noted.

No chronic toxicity studies was conducted on terfenadine in rats.

In a 1 month toxicity study in dogs, fexofenadine was administered 90, 300 and 900 mg/kg daily in 3 divided doses. The C_{max}s and AUCs were dose related, and the F showed higher AUCs than the M. No accumulation or decrease in plasma levels were seen. At 900 mg/kg salivation and emesis were seen; there was a dose related decrease in absolute and relative thymus weights at the MD and HD. No histopathology was seen. The NOEL was 90 mg/kg p.o. Based on the above results in the 10- 14 day studies, these results further support that in the dog fexofenadine was less toxic than terfenadine.

In dogs, the 2 year study with terfenadine was acceptable since terfenadine (80 mg/kg/day, LOEL) resulted in an exposure to fexofenadine based on AUCs that was 8.5-17.4 x the human exposure (2.4 mg/kg/day). In this study 30 and 100 mg/kg were dosed initially. The low dose was well tolerated. After 2-3 weeks due to toxicity, i.e., tremors, convulsions, impaired and death in 2/8 animals, the daily 100 mg/kg dose was reduced to 80 mg/kg after the treatment was temporarily stopped to allow for recovery. At this dose some central nervous system effects and constipation was seen during the latter part of the study; upon histological

examination, 2/2 M showed tubular atrophy in the testes at 80 mg/kg. The NOEL was 30 mg/kg.

In the carcinogenicity studies in mice and rats, 50 and 150 mg/kg of terfenadine were administered in the diet. No neoplasms were seen in the mice. In rats there was some increase in the incidence of adenocarcinomas in the uterus (C, 0/18, 50, 3/22, 150, 2/18) and mammary glands (C, 0/18, 50, 0/22, 150, 3/18) ; these were not considered significant to pursue when reviewed by one reviewer, C. Oberlander. When Dr. Taylor reviewed these data in 1990, two of his recommendation was: 1. to request the historical control data, and to request another carcinogenicity study if there are other findings that warrant this. This reviewer feels that since: 1. the incidence was not statistically significant when analyzed by the Fishers Exact test, 2. the incidence was low, and there was no dose relationship at least with the uterine neoplasm, 3. fexofenadine was not genotoxic, and 4. terfenadine has been on the market for a long period with no reported incidence or any indication of neoplasms, these findings are not considered clinically important. The following table shows that at the 150 mg/kg dose level, the AUC in F mice was twice that of the M while in rats, the AUCs were comparable, and that the ratio of the mice/rat AUC to the clinical dose AUC ranged from 2.1 to 4.3. The AUC for the lower dose was not reported. By today's standard, the MTD was not tested in the mouse. However, the ratios of the AUCs for the 150 mg/kg dose in mice and rats to the AUC for the human clinical exposure were 2.1 and 4.3. The above 4 factors were considered in conceiving this conclusion.

Parameter	Mice 150 A	Rats 150 A	Relative to Human AUC A/B	
			Mice	Rats
$AUC_{24\,h}$, μg.h/ml, M	5.66	11.6	2.1	4.3
F	11.44	9.1	4.3	3.4
Human $AUC_{0-\infty}$ for 2.4 mg/kg dose: 2.682 μg.h/ml, B Single Dose Lj				

3.1333 0-12h Multiple dose Lj Mice 2.7 Rats 3.3

Fexofenadine was not mutagenic in the Salmonella-Escherichia coli/mammalian microsome reverse mutation, the (CHO/HGPRT) forward mutation and the rat lymphocyte chromosomal aberration in vitro assays and in the mouse bone marrow micronucleus in vivo test. This was further supported by studies in which terfenadine was inactive in the mouse bone marrow micronucleus in vivo test at 500, 1000 and 2000 mg/kg.

Based on reproductive toxicity studies with terfenadine in which significant exposure to

fexofenadine was achieved, no teratogenic effects were seen in mice, 50, 100 and 200 mg/kg p.o. by gavage, in rats, 50, 150 and 300 mg/kg p.o. by gavage or dietary administration and in rabbits, 30, 100 and 300 mg/kg p.o. by dietary administration. In rats administration of 50, 150 and 300 mg/kg in the diet did not affect fertility. At 150 and 300 mg/kg there was decreased food consumption and body weight gained in the dams and decreased body weight and survival of the fetuses. No AUC was reported in mice for 200 mg/kg p.o. However, in a month dietary study the AUC for 150 mg/kg the AUC_{24h} was 11,444 ng.h/ml. This was 4.3 x the human therapeutic exposure of 2,682 ng.h/ml for a daily dose of 160 mg. The AUC_{24h}s for the 300 mg/kg p.o. were 11,927 ng.h/ml for the rat and 101,631 ng.h/ml for the rabbit. They were 4.4 and 37.9 times the human therapeutic exposure.

Recommendation

Based on the preclinical data, there is no objection to approval of fexofenadine.

Comments for further studies: None.

Labeling

Changes were recommended in the submitted label. They are listed in **BOLD** under the Clinical Pharmacology (page 2), Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy and Overdosage Sections of the label which is appended.

Lawrence F. Sancilio 6/24/96

Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

June 24, 1996

cc. /Division File, NDA 20-625
/MSevka, HFD-570
/MHimmel, HFD-570
/C.S.O., HFD-570
/LFSancilio, HFD-570
/ JSun, HFD-570

N:\NDA\20-625\Pharm\95-7-31.REV

Amendments:

NDA ~~18~~ 18.949, Terfenadine, C. G. Oberlander, 4/28/83
Comments on carcinogenic studies with terfenadine, A. C. Taylor, Ph.D., 4/19/90

b(4)

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

/s/

Lawrence Sancilio
5/21/2007 11:15:43 AM
PHARMACOLOGIST

Joseph Sun
5/21/2007 11:59:54 AM
PHARMACOLOGIST
I concur.

NDA Pharmacology Fileability Check List

NDA No: 21-909

Date of submission: 9/28/06

Date of Fileability meeting: 11/17/06

Information to Sponsor: Yes ( ) No (X)

Date of check list: 11/14/06

(1) On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review? Yes (X) No ( ) NA ( ). Reference was made to the information in NDAs 20-625 and NDA 20-872

(2) On its face, is the Pharm/Tox section of the NDA legible for review?
Yes (X) No ( ) NA ( ). Reference was made to the information in NDAs 20-625 and NDA 20-872

(3) Are final reports of all required and requested preclinical studies submitted in this NDA? Yes (X) No ( ) NA ( ) Reference was made to the information in NDAs 20-625 and NDA 20-872.

	Yes	No	NA
Pharmacology	(X)	( )	( )
ADME	(X)	( )	( )
Toxicology (duration, route of administration and species specified)			
acute	(X)	( )	( )
subchronic and chronic studies	(X)	( )	( )
reproductive studies	(X)	( )	( )
carcinogenicity studies	(X)	( )	( )
mutagenicity studies	(X)	( )	( )
special studies	(X)	( )	( )
others	(X)	( )	( )

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, is repeating or bridging the studies necessary? Yes ( ) No (X) NA ( )

If no, state why not? The oral formulation contains acceptable excipients.

If yes, has the applicant made an appropriate effort to repeat the studies using the to be marketed product, to bridge the studies or to explain why such repetition or bridging should not be required? Yes ( ) No ( ) NA ( ).

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) appropriate (including human dose multiples expressed in either mg/m^2 or comparative systemic exposure levels) and in accordance with 201.57? Yes (X) No ( ).

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion? Yes ( ) No ( ) NA (X)

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route? Yes (X) No ( ) NA ( )

If not, has the applicant submitted a rationale to justify the alternative route?
Yes ( ) No ( ) NA ( )

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? Yes (X) No ( ) NA ( ) The studies were reviewed in NDAs 20-625 and NDA 20-872.

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? Yes ( ) No ( ) NA (X)

(10) Are there any outstanding preclinical issues? Yes ( ) No (X)
If yes, identify those below.

(11) From a preclinical perspective, is this NDA fileable? Yes (X) No ( ).
If no, state below why it is not.

(12) Should any additional information/data be requested? Yes ( ) No (X)

NDA Planning Timeline

NDA No.: 21-909

Date of planning timeline:	11/14/06
PDUFA Due Date:	7/29/07
Projected review completion date:	6/1/07
	Milestone Dates
Pharmacology and ADME Toxicology	6/1/07
General toxicity studies Carcinogenicity studies and mutagenicity studies a. Statistical consult request for CA studies b. Submission of CA studies for CAC concurrence Reproductive studies Special studies and others	6/1/07
Labeling	6/1/07

Signatures (optional):

Reviewer Signature _____
Lawrence F. Sancilio, Ph.D.

Supervisor Signature _____
C. Joseph Sun, Ph.D.

Concurrence Yes ___ No ___

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

/s/

Lawrence Sancilio
11/16/2006 03:39:50 PM
PHARMACOLOGIST

Joseph Sun
11/22/2006 01:24:39 PM
PHARMACOLOGIST
I concur.