

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20872**

**PHARMACOLOGY REVIEW**

Dr. J. M. C. H. U.

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**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**  
**Original**

**Reviewer:** Lawrence F. Sancilio, Ph.D.

**DIVISION:** PULMONARY DRUG PRODUCTS, HFD-570

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**Sponsor:** Marion Merrell Dow Inc.  
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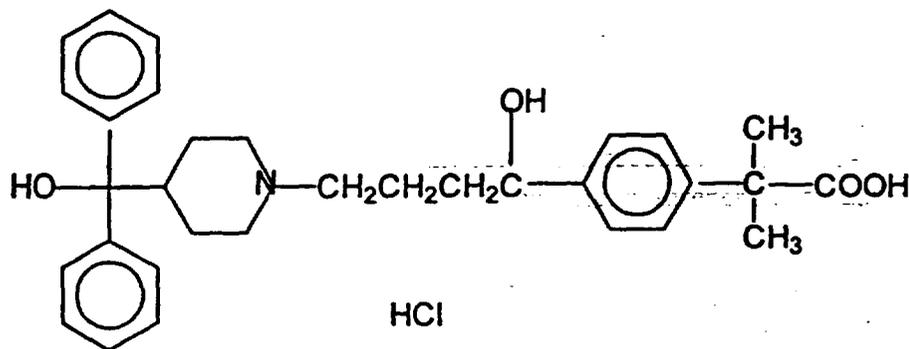
**Drug Name:** Fexofenadine HCl, MDL 16,455A, TAM (terfenadine active metabolite)

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

**CAS Registry No.:** 138452-21-8

**Molecular Weight:** 538.13, C<sub>32</sub>H<sub>39</sub>NO<sub>4</sub>. HCl

**Structure:**



**Relevant NDAs:** 20-625, 19-949

**Pharmacological Class:** H1 receptor antagonist

**Indication:** Treatment of seasonal rhinitis and chronic idiopathic urticaria.

**Clinical Formulation and Components**

Core	Weight, mg/tablet			
	30	60	120	180
✓ Fexofenadine HCl				
✓ Microcrystalline Cellulose Avicel PH101				
✓ Pregelatinized Starch				
✓ Croscarmellose Sodium, intragranular				
✓ Microcrystalline Cellulose Avicel PH102				
✓ Croscarmellose Sodium, extragranular				
✓ Mg Stearate				

**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

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

**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<sub>1</sub> 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 <sup>14</sup>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  $^{14}\text{C}$  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  $^{14}\text{C}$  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  $^{14}\text{C}$  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<sub>2</sub> 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<sub>2</sub> monolayer, K-96-09991-N, vol. 25.

Effect of sodium camphorsulfonate, sodium acetate and ursodeoxycholic acid on the absorption of fexofenadine HCL in the Caco<sub>2</sub> in vitro model, K-96-0366-N, vol. 25.

Distribution of <sup>14</sup>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  $3 \times 10^{-5}M$  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  $1\mu M$  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  $IC_{50}$ s were  $> 10\mu M$ :  $\alpha_1$  adrenergic,  $\alpha_2$  adrenergic,  $\beta$  adrenergic,  $\alpha_1$  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, 0.8, 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 <sub>2</sub> : 7.62 pA <sub>2</sub> : 7.97
Guinea Pig Trachea	ED <sub>50</sub> : > 3 x 10 <sup>-5</sup> M against the contractions induced by acetylcholine, neurokinin A, substance P, leukotriene, D <sub>4</sub> , antigen challenged sensitized trachea, U46619 (a thromboxane A <sub>2</sub> analog), compound 48/80 and capsaicin. ED <sub>50</sub> against histamine contractions: 2.48 x 10 <sup>-5</sup> M
Pilocarpine-Induced Salivation in Mice	Inactive at 3 mg/kg s.c.
Binding Studies using fexofenadine and terfenadine	Inactive at 1 x 10 <sup>-6</sup> against NK-1 and NK-2 receptors
Binding Studies using fexofenadine, (-) fexofenadine and (+) fexofenadine and cetirizine	Inactive 1 x 10 <sup>-5</sup> against α <sub>1</sub> adrenergic, α <sub>2</sub> adrenergic, β adrenergic, L-type Ca channel, α <sub>1</sub> adrenergic, muscarinic m <sub>1</sub> , muscarinic m <sub>2</sub> , muscarinic m <sub>3</sub> , muscarinic m <sub>4</sub> , 5HT <sub>1A</sub> and 5HT <sub>2A</sub> 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 to 1 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 <sup>b</sup>	0.2	0.7	2.0	7.0	0.1 <sup>b</sup>	0.2	0.7	2.0	7.0
Steady State										
Mean Arterial Blood Pressure	0	0	0	0	0	0	0	0	-19 <sup>a</sup>	ND
Spontaneous Heart Rate	0	0	0	0	0	0	0	0	-6 <sup>c</sup>	ND
Maximum Response										
Mean Arterial Blood Pressure	0	0	0	0	0	0	0	-33 <sup>a</sup>	-61 <sup>a,c</sup>	ND
Spontaneous Heart Rate	0	0	0	0	-4 <sup>c</sup>	0	0	0	0	-13 <sup>c</sup>

<sup>a</sup> P<05 when compared to vehicle dose

<sup>b</sup> Dose, mg/kg, i.v. given to the same animal

<sup>c</sup> 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 <sup>a</sup>	0.2	0.7	2.0	7.0	0.1 <sup>a</sup>	0.2	0.7	2.0	7.0
PR Interval, 325 bpm	0	0	0	0	0	0	0	0	+21 <sup>b</sup>	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 <sup>b</sup>	+19 <sup>b</sup>	ND
350 bpm	0	0	0	0	0	0	0	+11 <sup>b</sup>	+20 <sup>b</sup>	ND

ND, Did not determine

CNP, Could not pace.

<sup>a</sup> Dose, mg/kg, i.v. given to the same animal

<sup>b</sup> 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 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<sub>Kr</sub> HERG, No. C-98-0025-R, vol. 14.**

The ID<sub>50s</sub> for blocking the human cardiac potassium channel I<sub>Kr</sub> HERG (mouse fibroblast) listed in the following table show that fexofenadine was the weakest inhibitor of the 3 compounds tested.

Compound	IC <sub>50</sub> , 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<sub>kr</sub> 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<sub>kr</sub>) and Kv4.3 (I<sub>to</sub>) 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<sub>kr</sub>) and Kv4.3 (I<sub>to</sub>) channel inhibitors relative to terfenadine and astemizole.

Compound	IC <sub>50</sub> , nM	
	HERG (I <sub>kr</sub> )	Kv4.3 (I <sub>to</sub> ) 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<sub>kr</sub>) and Kv4.3 (I<sub>to</sub>) 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<sup>-5</sup>M (the highest concentration tested) neither terfenadine nor fexofenadine affected the APD<sub>90</sub> (action potential duration at 90% duration) and the V<sub>max</sub> (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

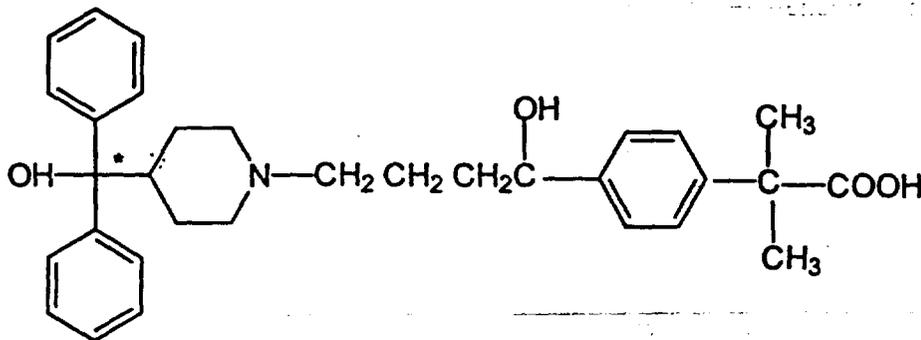
The results are summarized in the following table.

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 cumulative doses of 1 mg/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 $C_{max}$ s 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 $\mu$ M, 0.0004 as potent as ebastine 0.013 as potent as loratidine
HERG $I_{Kr}$ Channel (mouse fibroblast L cell line)	$IC_{50}$ : 30 $\mu$ M, 0.001 as potent as terfenadine .
Kv4.3 ( $I_{to}$ ) Channel (mouse fibroblast L cell line)	$IC_{50}$ : 112 $\mu$ M, 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 method. The limits of quantitation ranged from 0.5-1 to 100 ng/ml. 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<sup>14</sup> \* 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 <sub>0-inf</sub> , 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: \_\_\_\_\_ and, Nonclinical  
Pharmacokinetics Pharmacodynamics Dept., Hoechst Marion Roussel, Kansas City, Mo.

### 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

Parameter	Dose, mg/kg p.o.	
	300	1500
C <sub>max</sub> , µg/ml	6.5	17.4
T <sub>max</sub> , h	1	2
AUC <sub>0-4h</sub> , µg.h/ml	37.4 <sup>a</sup>	174.4

<sup>a</sup> 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 ester), 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-β-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.
C <sub>max</sub> , ng/ml	201	11.3	266
T <sub>max</sub> , h	0.01	0.88	1.1
AUC <sub>0-inf</sub> , ng.h/ml	288	48.3	1393
T <sub>1/2</sub> , h	4.0	3.3	4.1
MRT, h	4.5	4.8	5.2
CL, ml/min/kg	53.1	NA	NA
V <sub>ss</sub> , 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
C <sub>max</sub> , ng/ml	217	172	3544
T <sub>max</sub> , h	2.5	1.8	2.4
AUC <sub>0-inf</sub> , ng.h/ml	1643	1282	21,183
T <sub>1/2</sub> , h	10.1	14.6	18.1
MRT, h	9.2	11.5	6.8

The C<sub>max</sub> and AUC observed for fexofenadine following the administration of 13.5 mg/kg p.o. of MDL 46,619 was approximately 1/2 that observed under similar conditions for 8.7 mg/kg p.o. of fexofenadine (AUC<sub>0-inf</sub>, 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 by 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  $^{14}\text{C}$  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  $\text{C}^{14}$  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 < 1 $\mu\text{g}$ equivalent/g
0.5 h	small intestines, urinary bladder, kidney, liver; concentrations > 0.3 $\mu\text{g}$ equivalent/g: myocardium, salivary glands, skeletal muscle, lung, pancreas and thyroid
2 h	intestines, urinary bladder, liver; concentrations > 0.1 $\mu\text{g}$ equivalent/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  $^{14}\text{C}$  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  $\text{C}^{14}$  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 at the level of the kidney, adrenal, eye, brain and thyroid.

### 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 $\mu\text{g}$ equiv./g), esophagus
2.0 h	liver (1.3 $\mu\text{g}$ equiv./g), esophagus, intestines
24 h.	liver (0.082 $\mu\text{g}$ equiv./g)
72 h	no radioactivity

### Conclusion

Following p.o. of 10 mg/kg twice a day for 4.5 days of  $\text{C}^{14}$  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  $^{14}\text{C}$  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  $\text{C}^{14}$  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 at the level of the kidney, adrenal, eye, brain and thyroid. Immediately after killing each dam, 1 fetus was examined separately.

## 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
<b>Day 18 of Pregnancy</b>	
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
<b>Day 12 of Pregnancy</b>	
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<sup>14</sup> 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	Fccs
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
MDI. 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 <sup>14</sup>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.



## Results

Fexofenadine (2.5  $\mu$ M to 100  $\mu$ M) 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  $\mu$ M 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 ( $\pm$ ) -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	( $\pm$ ) - Fexofenadine	
	(-)	(+)	(-)	(+)
Auc <sub>0-24</sub> (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	C <sub>max</sub> ng/ml	T <sub>max</sub> h	AUC µg.h/ml	F %	T <sub>1/2</sub> h
<b>Mouse</b>					
Single Dose, mg/kg					
30 p.o.	0.28	0.5	1.59 <sup>a</sup>	19	
5000 p.o.	5.19	0.5	30.22 <sup>a</sup>	2.1	
1, i.v.	923		0.283		
<b>Pregnant Rabbit</b>					
Day 19 of Gestation					
300 mg/kg p.o. <sup>c</sup>	6.5	1.0	37.4 <sup>b</sup>		
1500 mg/kg p.o. <sup>c</sup>	17.4	2.0	174.4 <sup>b</sup>		
<b>Dog</b>					
1.35 mg/kg p.o.	11.3	0.9	0.048	12.4	3.3

<sup>a</sup> AUC was 0-inf

<sup>b</sup> AUC was 0-48h

<sup>c</sup> 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: \_\_\_\_\_

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  $\geq 50$  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<sub>50</sub> 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<sub>0-24h</sub>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 <sub>0-24h</sub> 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 1/2 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: \_\_\_\_\_

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 <sub>0-8h</sub> , µg.h/ml				MDL46,619 <sup>a</sup> C <sub>max</sub> , 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

<sup>a</sup> 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:

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 <sub>0-12 h</sub> , 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  $\geq 50$  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  $\frac{1}{2}$  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, mesenteric	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 patch 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.

**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 a patch 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.

Induction Group and Number	No. of Animals		Challenging Agent
	M	F	
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 9<sup>th</sup> 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.

### Conclusion

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<sub>1</sub> 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. that was withdrawn from the market since it tended to produce 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 to inhibit the IKr channel in the heart leading to the cardiac irregularity. Under normal conditions, was immediately metabolized to fexofenadine. Since this biotransformation involved the hepatic cytochrome P-450 enzyme, CYP3A4, patients

taking 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<sub>1</sub> 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 its enantiomers had affinity to the following receptors: NK-1, NK-2,  $\alpha_1$  adrenergic,  $\alpha_2$  adrenergic,  $\beta$  adrenergic, L-type Ca channel,  $\alpha_1$  adrenergic, muscarinic m<sub>1</sub>, muscarinic m<sub>2</sub>, muscarinic m<sub>3</sub>, muscarinic m<sub>4</sub>, 5HT<sub>1A</sub> and 5HT<sub>2A</sub>.

Fexofenadine did not prolong the QTc interval in dogs and rabbits and it was relatively very weak or inactive in blocking the K<sup>+</sup> channels in vitro or affect the APD<sub>90</sub> 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 findings 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  $\geq 50$  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 seen 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  $AUC_{0-24h}$  for the 80 mg/kg dose of terfenadine was approximately 35  $\mu\text{g}\cdot\text{h}/\text{ml}$  and that for 100 mg/kg of fexofenadine was approximately 44  $\mu\text{g}\cdot\text{h}/\text{ml}$  (Sancilio, 1/12/94 review of IND p 23). Extrapolating the AUC (35  $\mu\text{g}\cdot\text{h}/\text{ml}$ ) of fexofenadine from 80 mg/kg of terfenadine to that for 100 mg/kg of terfenadine, the AUC for fexofenadine would be approximately 44  $\mu\text{g}\cdot\text{h}/\text{ml}$ . 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 p.o. 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 p.o. 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.

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pages of trade

secret and/or

confidential

commercial

information

LSI

7/6/99

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

LSI  
- 0 -

July 7, 1999

cc. /Division File, 20-872  
/AWorobec, HFD-570  
/MHimmel, HFD-570  
/C.S.O., HFD-570  
/LFSancilio, HFD-570

cobbs

MAR 12 1999

**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY  
DATA  
Chemistry Consult**

**Reviewer:** Lawrence F. Sancilio, Ph.D.

**Date of Consultation Request:** 1/22/99

**DIVISION:** PULMONARY DRUG PRODUCTS, HFD-570

**Reviewer Completion Date:** 3/12/99

**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

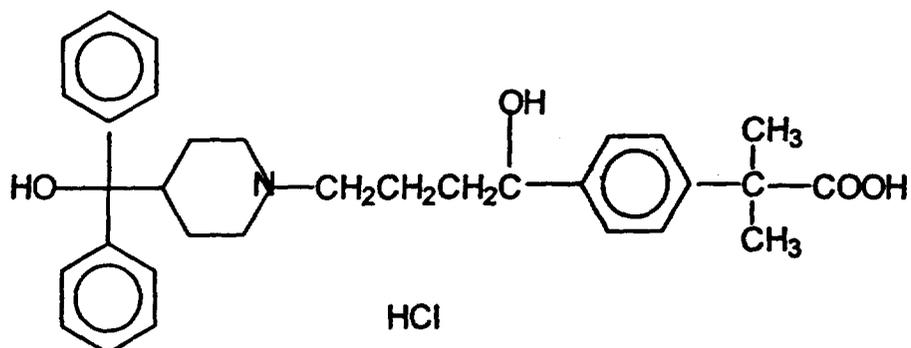
**Drug Name:** Fexofenadine HCl, MDL 16,455A, TAM (terfenadine active metabolite)

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

**CAS Registry No.:** 138452-21-8

**Molecular Weight:** 538.13, C<sub>32</sub>H<sub>39</sub>NO<sub>4</sub>. HCl

**Structure:**



**Pharmacological Class:** H1 receptor antagonist

**Indication:** Treatment of seasonal rhinitis and chronic idiopathic urticaria.

**Formulation:** Tablets, 30, 60, and 180 mg

**Dose and Route of Administration:** 60 mg twice daily or 180 mg once daily.

### **Background**

Fexofenadine HCl is the active metabolite of terfenadine, a marketed H<sub>1</sub> receptor blocker with little or no sedative properties. It is currently being marketed as a capsule. This NDA addresses the marketing of fexofenadine HCl as a tablet.

### **Response to Chemistry Consult regarding the acceptability for the proposed specifications of the three impurities in the drug substance as requested by Hossein Khorshidi, Ph.D.**

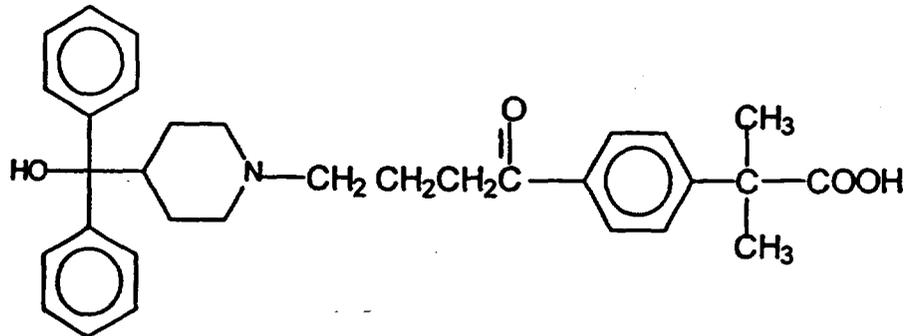
The sponsor proposed that the following impurities each at a specification of % be acceptable for the drug substance: MDL 46, 016, MDL 46, 619 and MDL 102,038. Their structures are listed on the following page.

The ICH Guidelines indicate that in general the specification for each impurity should be < 0.1% without qualification. Impurities ≥ 0.1% require qualification. In an attempt to qualify these impurities, a list of completed toxicity studies was requested from the sponsor of those batches that contained these impurities. Batch No. 69756 contained % MDL 102,038 and % MDL 46,016 and Batch No. 71701 contained % MDL 102,038 and % MDL 46,016. Qualification was not achieved since the duration of the studies was not adequate. The duration of the studies should be ≥ 3 months. The longest study was a 1-month gavage study in dogs with Batch No. 71701.

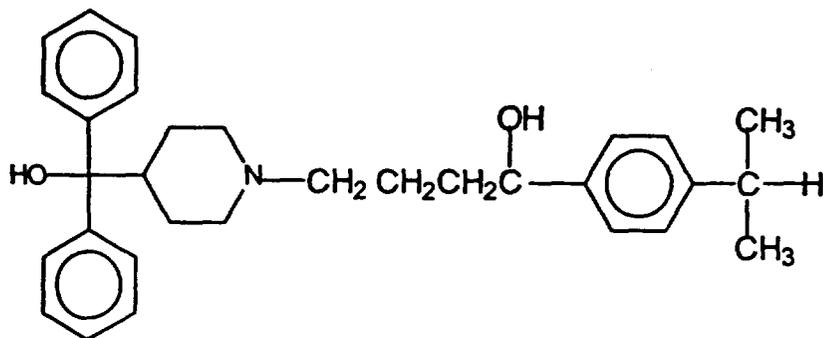
The sponsor recently submitted a 1 month study with a fexofenadine batch that contained % MDL 46, 619, the methyl ester derivative (Report No. K-96-0489 submitted in NDA 20-872). Again, the duration of the study was not adequate to meet the requirement for qualification.

Impurities for specifications % were acceptable if the following was applicable. The impurities were structurally related to the parent compound, and there were no indication that they will be genotoxic or possess a toxicity profile different from the parent compound. MDL 46, 619 is the methyl ester of fexofenadine; in dogs MDL 46, 619 is converted to fexofenadine (Report No. K-97-0521 submitted in NDA 20-872). Both MDL 102,038 and MDL 46,016 are structurally very similar to fexofenadine, as they are the keto and decarboxylated derivatives, respectively. Further, these impurities do not possess components that are structural alerts for potential mutagenicity. Therefore, the proposed specification of % for each of the 3 above impurities in the fexofenadine drug substance was acceptable with no requirement for qualification. This specification for each of these 3 impurities was acceptable in the drug substance and drug product for fexofenadine capsules (NDA 20-625).

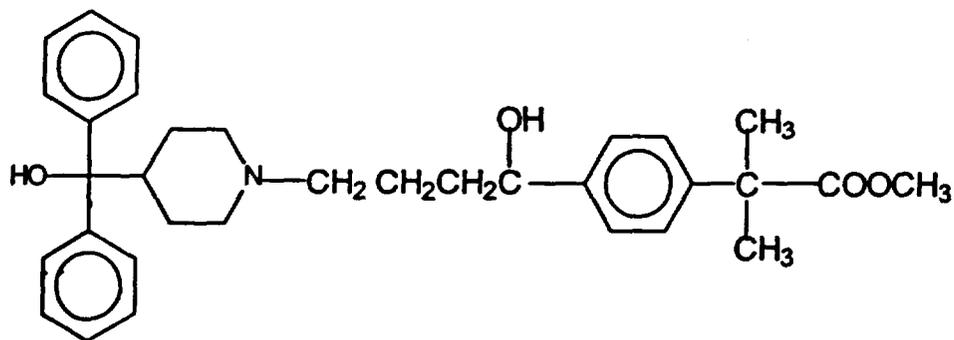
MDL 102,038



MDL 46,016



MDL 46,619



### Recommendation

The proposed % concentration for each of the three impurities (MDL 46, 016, MDL 46, 619 and MDL 102,038) in the fexofenadine drug substance was acceptable. No qualification was needed.

JSI

3/12/99

Lawrence F. Sancilio, Ph.D.

JSI

March 12, 1999

cc: Orig. NDA20-872  
HFD-570/Division File  
HFD-570/LSancilio  
HFD-570/HKhorshidi  
HFD-570/CSO/Cobbs

Approved by Dr. J. Sun