CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20625

MEDICAL REVIEW(S)

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.
Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**
Sponsor: Hoechst Marion Roussel, Inc.
Date NDA Submitted: July 31, 1995
Material Reviewed: Protocol PJPR0004 from NDA 20-625

Protocol No. PJPR0004 - conducted from August 23, 1993 to December 6, 1993 in Leeds, England

Note: MDL-16,455 is the designation for the acid metabolite of terfenadine; and MDL-16,455A, fexofenadine, is the designation for MDL-16,455 from the synthetic source.

Title
"Multiple Dose Pharmacokinetics and Pharmacodynamics of Terfenadine and Its Major Metabolite."

Objectives
(A) "to determine the effect of multiple dosing of terfenadine and MDL 16,455A on QTc interval";
(B) "to determine the extent and duration of inhibition of skin wheal and skin flare area from terfenadine or MDL 16,455A";
(C) "to characterize the multiple dose plasma and urine pharmacokinetics of terfenadine and MDL 16,455A";
(D) "to determine the steady-state relative bioavailability of plasma MDL 16,455 area under the curve (AUC) after dosing with MDL 16,455A as compared to MDL 16,455 from terfenadine metabolism";
(E) "to determine whether a relationship exists between plasma MDL 16,455 concentrations and changes in QTc interval duration and inhibition of the skin wheal and flare areas."

Study Design
This study was an open-label, randomized, four period (11 days per period with subjects sequestered in clinic for the first 9 days of each period), four-way complete crossover (>13 but <28 day washout) design conducted in 24 healthy males who were between 18 and 55 years of age.

Treatment E:	An oral dose of 60 mg terfenadine (1x60 mg Seldane tablets) every 12 hours for thirteen doses (Days 2-8).
Treatment F:	An oral dose of 180 mg terfenadine (3x60 mg Seldane tablets) every 12 hours for thirteen doses (Days 2-8).
Treatment G:	An oral anhydrous dose of 60 mg MDL 16,455A every 12 hours for thirteen doses (Days 2-8)
Treatment H:	An oral anhydrous dose of 180 mg MDL 16,455A every 12 hours for thirteen doses (Days 2-8)

No drug was administered on Day 1 of each period. MDL 16,455A was administered as an oral

solution of MDL 16,455A in a propylene glycol-acetic acid vehicle. Marketed 60 mg Seldane tablets were used for the terfenadine treatment.

Study Measurements

ECGs:
Serial 12-lead electrocardiograms (ECGs) were obtained for -
-- 72 hours after the final dose on Day 8 (0, 2, 4, 8, 12, 24, 48, 72 hours);
-- 12 hours after treatment on Days 1 and 2 (0, 2, 4, 8, 12 hours);
A single ECG was obtained at -
-- 4 hours after the morning dose on Days 3-7.

Plasma Samples:
-- Serial blood samples were collected for 72 hours (0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 hours) after the last dose on Day 8;
-- trough blood samples were collected prior to the morning dose on Days 6-8;
-- a pre-dose blood sample was obtained on Day 2.

In subjects receiving terfenadine, plasma was quantitated for MDL 16,455 and terfenadine and urine was quantitated for MDL 16,455, terfenadine, MDL 17,523 (alcohol metabolite of terfenadine), and MDL 4,829 (dealkylated metabolite of terfenadine). In subjects receiving MDL 16,455A, plasma and urine was quantitated for MDL 16,455.

Urine Samples:
Urine samples were collected from 0 to 12 hours after the morning treatment administration times on Days 1, 2 and 8.

Wheal and Flare Measurements:
Serial wheal and flare areas were measured for -
-- 72 hours after the final dose on Day 8 (0, 2, 4, 6, 8,12, 24, 48, 72 hours);
-- 12 hours after the treatment administration time on Days 1 and 2 (0, 2, 4, 6, 8, 12 hours).

Safety Measurements:
All subjects were monitored by lead-II telemetry from Day 1 until Day 9. Vital signs were measured three times a day throughout the study. Clinical laboratory measurements were conducted pre- and post-study. Reports of adverse events were collected.

Subject Inclusion Criteria

- healthy, nonsmoking males between the ages 18 and 55 years and not more than 15% from the ideal weight and age
- no clinically significant abnormalities before study initiation for the following: clinical laboratory measurements; ECG; medical history, physical exam,
- histamine wheal area must be approximately three times subject's own saline wheal area

Subject Exclusion Criteria

- hypersensitivity reaction to terfenadine or MDL 16,455A
- significant organ abnormality or disease
- treatment with either prescription **or nonprescription (OTC)** medication within 14 days of trial initiation
- hepatic or renal clearance altering agents (eg, erythromycin, cimetidine, barbiturates, phenothiazines, etc) within 30 days of study initiation
- ketoconazole or itraconazole within three months of study initiation
- astemizole (Hismanal®) within six months of study initiation
- QTc interval of greater than 440 msec or with any underlying conditions known to prolong the QTc
- a flare area greater than 2 cm^2 after intradermal injection with normal saline

Results - Patient Accounting

The sponsor reports that 24 subjects were enrolled; 23 subjects received MDL-16,455A 180mg Q12H, terfenadine 60mg Q12H, and terfenadine 180mg Q12H; 22 subjects completed the study. Two subjects were withdrawn due to adverse events prior to completing treatment with MDL-16,455A 60mg Q12H (see discontinuations below).

Results - Pharmacokinetic Parameters

The sponsor summarized the pharmacokinetic results in tabular and figure format, reproduced below. In general the AUCss(0-12 h) following administration of MDL-16,455A was smaller (67%- 60mg; 75%-180mg) than that observed following terfenadine administration. The sponsor reports the following pharmacokinetic results for MDL-16,455A:

A) An 80mg dose of MDL-16,455A Q12H would result in an AUC_{ss}(0-12 h) for MDL-16,455A equivalent to a 60mg dose of terfenadine;

B) Following terfenadine and MDL-16,455A administration, the AUC_{ss}(0-12h), Cmax-ss and Cmin-ss for MDL-16,455 were dose proportional;

C) The Tmax following MDL-16,455A (1-1.2h) was more rapid compared to that for terfenadine (2.3-4 h);

D) The steady state ratio of Cmax to Cmin was greater following MDL-16,455A administration compared to that following terfenadine administration;

E) Steady state for MDL-16,455 is achieved by day 5 following both MDL-16,455A and terfenadine administration;

F) The half-life of MDL-16,455 is somewhat shorter following MDL-16,455A (11.8-14.0 h) administration compared to that following terfenadine administration (17.6-20.1 h).

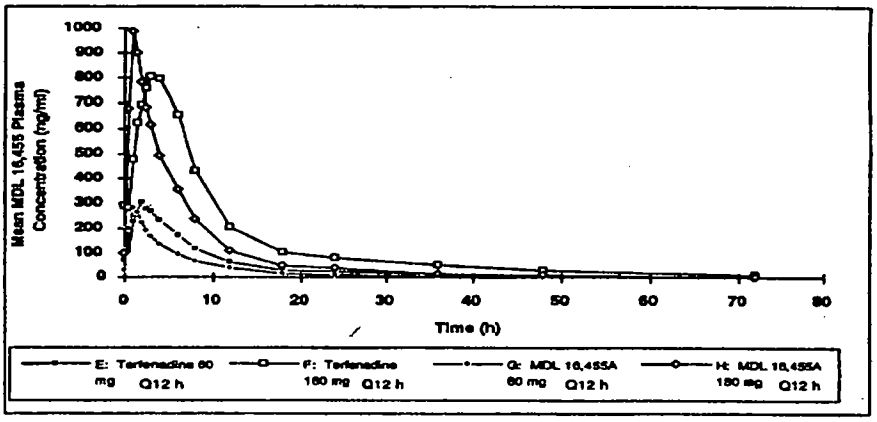

Figure 8-58. Mean Plasma MDL 16,455 Concentration as a Function of Time Following Administration of MDL 16,455A and Terfenadine

Supporting Data:	*Page*
Appendix A1: Plasma	*S8-V1.156-P107*

Table 8-141. Mean MDL 16,455 Pharmacokinetic Parameters and Treatment Comparisons Following Administration of MDL 16,455A and Terfenadine

Parameter	Trt	Mean	%CV	Adjusted Mean*	Pairwise Comparisons: Pair	Ratio (%)	90% CI	P value
AUC_{ss}(0–12 h) h-ng/ml	E	1972.25	19.39	1934.06				
	F	6265.92	20.81	2042.66	F/E	105.62	(94.5,118.0)	0.414
	G	1367.06	27.91	1305.93	G/E	67.52	(60.3, 75.6)	<0.001
	H	4839.71	27.02	1547.87	H/G	118.53	(105.9,132.7)	0.014
					H/F	75.78	(67.8, 84.7)	<0.001
$C_{max,ss}$ ng/ml	E	341.06	39.28	323.73				
	F	870.92	21.69	283.42	F/E	87.55	(75.5,101.5)	0.138
	G	299.42	37.94	275.31	G/E	85.04	(73.2, 98.8)	0.077
	H	1023.39	39.74	316.61	H/G	115	(99.0,133.6)	0.125
					H/F	111.71	(96.4,129.5)	0.216
$C_{min,ss}$ ng/ml	E	59.02	37.62	55.83				
	F	193.39	31.64	61.24	F/E	109.67	(97.3,123.6)	0.203
	G	28.97	27.67	27.46	G/E	49.18	(43.5, 55.5)	<0.001
	H	90.80	43.22	28.30	H/G	103.07	(91.3,116.4)	0.679
					H/F	46.22	(41.0, 52.1)	<0.001
$t_{1/2}$ h	E	20.16	28.17	19.46				
	F	17.62	18.3	17.54	F/E	90.14	(81.2,100.1)	0.102
	G	14.05	22.07	13.81	G/E	70.97	(63.9, 78.8)	<0.001
	H	11.88	29.3	11.47	H/G	83.06	(74.8, 92.2)	0.004
					H/F	65.39	(58.9, 72.6)	<0.001
$t_{max,ss}$ h	E	2.30	43.76	2.18				
	F	4.02	51.33	3.70	F/E	171.37	(142.8,205.6)	<0.001
	G	1.05	32.7	1.00	G/E	46.09	(38.3, 55.5)	<0.001
	H	1.20	39.35	1.11	H/G	111.61	(92.8,134.3)	0.325
					H/F	30.02	(25.0, 36.0)	<0.001
$CL_{po,ss}$ L/h	E	N/A	N/A					
	F	N/A	N/A					
	G	44.61	35.35					
	H	38.25	39.71					
$C_{max,ss}/C_{min,ss}$	E	6.14	34.52					
	F	4.84	32.93					
	G	11.19	48.40					
	H	12.79	47.02					

E = Terfenadine 60 mg Q12 h (N=23)
F = Terfenadine 180 Q12 h (N=23)
G = MDL 16,455A 60 mg Q12 h (N=22)
H = MDL 16,455A 180 mg Q12 h (N=23)
* = Adjusted mean and statistical comparisons are based on data normalized to the 60 mg dose for AUC_{ss}(0–12 h), $C_{max,ss}$, and $C_{min,ss}$.

Supporting Data:	Page
Appendix A1: Plasma	S8-V1.156-P107
Appendix B2: MDL 16,455 Pharmacokinetic Parameters, Treatment Comparisons,	S8-V1.158-P6

The sponsor also reports pharmacokinetic results for terfenadine (see table and figure reproduced below) and notes that as the dose of terfenadine was increased from 60mg to 180mg, the AUCss(0-12 h) increased by 96%, the Cmax-ss by 40% and the Cmin-ss by 125%; and the half-life was the same (60mg - 16.4 h; 180mg - 16.6 h).