Table 31.

Geometric Mean AUC (ng•hr/mL) and 95% Confidence Intervals for Rizatriptan by Treatment Day and Gender

	Day 1	Day 1[a]	Day 3	Day 6
Females	66.3 (56.4, 77.9)	66.4 (56.5, 77.9)	198.1 (172.5, 227.3)	198.6 (153.0, 257.8)
Males	58.5 (48.9, 69.9)	58.6 (49.0, 70.0)	190.6 (154.7, 234.9)	194.1 (164.2, 229.4)

[a] $AUC_{(0-\infty)}$. All others, $AUC_{(0-24)}$.

Geometric Mean C_{max} (ng/mL) and 95% Confidence Intervals for Rizatriptan by Treatment Day and Gender

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	Day 1	Day 3	Day 6
Females	19.9 (15.2, 25.9)	34.5 (28.8, 41.2)	38.0 (27.6, 52.1)
Males	18.2 (14.9, 22.1)	35.2 (28.3, 43.7)	32.8 (27.0, 39.8)
Combined	19.0 (16.4, 22.0)	34.8 (30.8, 39.3)	35.3 (29.9, 41.7)

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Geometric Mean AUC (ng•hr/mL) and 95% Confidence Intervals for L-706,248 by Treatment Day and Gender

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	Day 1	Day 1[a]	Day 3	Day 6
Females	8.5 (7.5, 9.7)	8.6 (7.5, 9.7)	24.5 (20.9, 28.6)	26.4 (21.6, 32.2)
Males	8.3 (7.2, 9.6)	8.3 (7.2, 9.6)	22.8 (20.9, 25.0)	25.2 (23.7, 26.8)

[a] $AUC_{(0-\infty)}$. All others, $AUC_{(0-24)}$.

Geometric Mean C_{max} (ng/mL) and 95% Confidence Intervals for L-706,248 by Treatment Day and Gender

	Day 1	Day 3	Day 6
Females	2.1 (1.7, 2.7)	3.5 (2.8, 4.2)	4.1 (3.2, 5.3)
Males	2.1 (1.8, 2.4)	3.2 (2.7, 3.8)	3.2 (2.9, 3.5)

Table 32.

Individual and Mean (± S.D., N = 8) Values of AUC* (ng·hr/ml) of MK-0462 in Healthy Males Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	AUC^{1}_{0-24}	$AUC^{1}_{0-\infty}$	AUC^{3}_{0-24}	AUC^{6}_{0-24}
4				
5				
7				
8				
13				
15				
16				
17				
Mean	59.67	59.75	196.29	197.41
S.D.	13.12	13.11	55.03	37.61

Individual and Mean (± S.D., N = 8) Values of AUC* (ng·hr/ml) of L-706,248 in Healthy Males Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	AUC^{1}_{0-24}	$AUC^{1}_{0-\infty}$	AUC^{3}_{0-24}	AUC^{6}_{0-24}
4				
5				
7				
8				
13				
15				
16				
17				
Mean	8.38	8.44	22.96	25.26
S.D.	1.41	1.44	2.50	1.95

Individual and Mean (± S.D., N = 8) Values of AUC* (ng·hr/ml) of MK-0462 in Healthy Females Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	AUC^{1}_{0-24}	$AUC^{1}_{0-\infty}$	AUC^{3}_{0-24}	AUC^{6}_{0-24}
19				
24				
25				
27				
28				
30				
33				
36				
Mean	67.31	67.37	200.40	206.25
S.D.	11.64	11.61	32.60	54.55

Individual and Mean (± S.D., N = 8) Values of AUC* (ng·hr/ml) of L-706,248 in Healthy Females Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	AUC^{1}_{0-24}	$AUC^{1}_{0-\infty}$	AUC^{3}_{0-24}	AUC^{6}_{0-24}
19				
24				
25				
27				
28				
30				
33				
36				
Mean	8.63	8.65	24.85	27.05
S.D.	1.43	1.43	4.68	6.36

Individual and Mean (± S.D., N = 8) Values of C_{max}* (ng/ml) of MK-0462 and L-706,248 in Healthy Males Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	MK-0462			L-706,248		
	C^{1}_{max}	C^{3}_{max}	C^{6}_{max}	C^{1}_{max}	C^{3}_{max}	C^{6}_{max}
4						
5						
7						
8						
13						
15						
16						
17						
Mean	18.63	36.26	33.50	2.11	3.30	3.20
S.D.	4.40	9.91	6.91	0.41	0.78	0.32

Individual and Mean (± S.D., N = 8) Values of C_{max}* (ng/ml) of MK-0462 and L-706,248 in Healthy Females Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	MK-0462			L-706,248		
	C^{1}_{max}	C^{3}_{max}	C^{6}_{max}	C^{1}_{max}	C^{3}_{max}	C^{6}_{max}
19						
24						
25						
27						
28						
30						
33						
36						
Mean	20.63	35.19	40.47	2.20	3.54	4.30
S.D.	5.45	8.33	16.31	0.56	0.84	1.32

Table 33.

Individual and Mean (± S.D., N = 8) Values of T_{max}^* (hr) of MK-0462 and L-706,248 in Healthy Males Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	MK-0462			L-706,248		
	T_{max}^1	$(T_{max}^3)^*$	$(T_{max}^6)^*$	T_{max}^1	$(T_{max}^3)^*$	$(T_{max}^6)^*$
4						
5						
7						
8						
13						
15						
16						
17						
Mean	1.1	1.0	0.8	1.4	1.3	1.5
S.D.	0.4	0.5	0.4	0.5	0.5	0.5

Individual and Mean (± S.D., N = 8) Values of T_{max}^* (hr) of MK-0462 and L-706,248 in Healthy Females Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	MK-0462			L-706,248		
	T_{max}^1	$(T_{max}^3)^*$	$(T_{max}^6)^*$	T_{max}^1	$(T_{max}^3)^*$	$(T_{max}^6)^*$
19						
24						
25						
27						
28						
30						
33						
36						
Mean	0.7	0.9	1.2	1.6	1.3	1.3
S.D.	0.3	0.5	0.5	0.5	0.5	0.4

Individual and Mean (± S.D., N = 8) Values of Apparent $t_{1/2}^*$ (hr) of MK-0462 and L-706,248 in Healthy Males Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	MK-0462			L-706,248		
	$t_{1/2}^1$	$t_{1/2}^3$	$t_{1/2}^6$	$t_{1/2}^1$	$t_{1/2}^3$	$t_{1/2}^6$
4						
5						
7						
8						
13						
15						
16						
17						
Harmonic Mean	2.16	1.92	2.52	2.35	2.56	3.01

Individual and Mean (± S.D., N = 8) Values of Apparent $t_{1/2}^*$ (hr) of MK-0462 and L-706,248 in Healthy Females Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	MK-0462			L-706,248		
	$t_{1/2}^1$	$t_{1/2}^3$	$t_{1/2}^6$	$t_{1/2}^1$	$t_{1/2}^3$	$t_{1/2}^6$
19						
24						
25						
27						
28						
30						
33						
36						
Harmonic Mean	2.08	1.89	1.76	1.74	2.25	1.83

Individual and Mean (± S.D., N = 8) Values of Percentage of Dose (%) Excreted in Urine as MK-0462 or L-706,248 (U_e^*) in Healthy Males Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	MK-0462			L-706,248		
	U_e^1	U_e^3	U_e^6	U_e^1	U_e^3	U_e^6
4						
5						
7						
8						
13						
15						
16						
17						
Mean	7.14	10.09	5.80	0.60	0.85	0.52
S.D.	2.41	4.43	1.54	0.31	0.47	0.15

Individual and Mean (± S.D., N = 8) Values of Percentage of Dose (%) Excreted in Urine as MK-0462 or L-706,248 (U_e^*) in Healthy Females Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	MK-0462			L-706,248		
	U_e^1	U_e^3	U_e^6	U_e^1	U_e^3	U_e^6
19						
24						
25						
27						
28						
30						
33						
36						
Mean	8.33	10.88	8.19	0.84	0.95	0.78
S.D.	3.29	5.60	3.34	0.23	0.58	0.24

Table 34.

Individual and Mean (± S.D., N = 8) Values of CL_r^* (ml/min) of MK-0462 and L-706,248 in Healthy Males Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	MK-0462			L-706,248		
	CL_r^1	CL_r^3	CL_r^6	CL_r^1	CL_r^3	CL_r^6
4						
5						
7						
8						
13						
15						
16						
17						
Mean	198.7	264.6	145.4	130.4	178.2	109.1
S.D.	58.2	144.9	24.5	56.6	83.1	34.1

Individual and Mean (± S.D., N = 8) Values of CL_r^* (ml/min) of MK-0462 and L-706,248 in Healthy Females Receiving Orally a Single Dose of 10 mg MK-0462 on Day 1 and 10 mg MK-0462 Every Two Hours (q2h) for Three Doses on Days 3, 4, 5, and 6

Subject #	MK-0462			L-706,248		
	CL_r^1	CL_r^3	CL_r^6	CL_r^1	CL_r^3	CL_r^6
19						
24						
25						
27						
28						
30						
33						
36						
Mean	206.7	278.2	212.0	171.0	192.2	155.4
S.D.	63.2	165.8	93.5	50.2	108.5	56.3

Summary Statistics for Systolic Blood Pressure Area Under the Curve for Rizatriptan and Placebo

Day	Time Interval	Rizatriptan (n=24)		Placebo (n=12)		p-Value
		Mean	SD	Mean	SD	
1	0-2 Hrs	-1.1	11.5	-5.7	15.8	>0.250
	2-6 Hrs	-6.0	29.4	-20.0	30.4	0.193
	0-6 Hrs	-7.0	37.7	-25.7	45.4	0.200
3	0-2 Hrs	3.6	14.4	-5.1	12.5	0.084
	2-6 Hrs	5.7	31.3	-4.4	30.2	>0.250
	0-6 Hrs	9.3	44.1	-9.5	41.2	0.227
6	0-2 Hrs	5.6	9.5	-0.3	6.2	0.057
	2-6 Hrs	8.9	33.8	-3.0	21.0	>0.250
	0-6 Hrs	14.6	41.8	-3.4	25.0	0.182

Summary Statistics for Diastolic Blood Pressure Area Under the Curve for Rizatriptan and Placebo

Day	Time Interval	Rizatriptan (n=24)		Placebo (n=12)		p-Value
		Mean	SD	Mean	SD	
1	0-2 Hrs	-0.2	10.0	-2.4	9.7	>0.250
	2-6 Hrs	-2.3	23.0	-7.3	23.3	>0.250
	0-6 Hrs	-2.5	31.9	-9.7	31.3	>0.250
3	0-2 Hrs	5.5	11.2	-4.3	6.3	0.002
	2-6 Hrs	11.2	21.7	-7.6	10.1	0.001
	0-6 Hrs	16.7	30.6	-11.9	14.1	0.001
6	0-2 Hrs	3.5	8.7	1.9	8.5	>0.250
	2-6 Hrs	9.9	19.6	-0.04	24.3	0.196
	0-6 Hrs	13.4	25.9	1.8	32.1	>0.250

Table 35.

Individual and Mean (± S. D., N=12) Values of AUC and C_{max} of MK-0462 in Healthy Males Receiving Single Oral Doses of 10-mg MK-0462 RAPIDISC™ and 10-mg MK-0462 Tablet

Subject #	AUC (ng·h/ml)		C_{max} (ng/ml)	
	RAPIDISC™	Tablet	RAPIDISC™	Tablet
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	119	123	33.7	44.3
S.D.	40	44	10.2	19.6

Individual and Mean (± S. D., N=12) Values of T_{max} and $t_{\frac{1}{2}}$ of MK-0462 in Healthy Males Receiving single Oral Doses of 10-mg MK-0462 RAPIDISC™ and 10-mg MK-0462 Tablet

Subject #	T_{max} (h)		$t_{\frac{1}{2}}$ (h)	
	RAPIDISC™	Tablet	RAPIDISC™	Tablet
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	1.5	0.82	2.0*	2.0*
S.D.	0.6	0.19	—	—

Subject Ratings from Taste Questionnaire

Placebo and RAPIDISC™

		Placebo		RAPIDISC™	
		N	Percent	N	Percent
Sweetness	Much Too Sweet	0	0	0	0
	Slightly Too Sweet	5	41.7	4	33.3
	Right Amount of Sweetness	7	58.3	5	41.7
	Needs a Little More Sweetness	0	0	2	16.7
	Needs a Lot More Sweetness	0	0	1	8.3
Flavor	Very Acceptable Flavor	4	33.3	0	0
	Moderately Acceptable Flavor	4	33.3	5	41.7
	Neutral Flavor	3	25.0	0	0
	Moderately Unacceptable Flavor	1	8.3	5	41.7
	Very Unacceptable Flavor	0	0	2	16.7
Bitterness	Extremely Bitter	0	0	0	0
	Very Bitter	0	0	4	33.3
	Slightly Bitter	1	8.3	5	41.7
	Not Very Bitter At All	6	50.0	3	25.0
	Not At All Bitter	5	41.7	0	0
Mintiness	Much Too Minty	0	0	0	0
	Slightly Too Minty	2	16.7	2	16.7
	Has the Right Amount of Mintiness	4	33.3	4	33.3
	Needs a Little More Mintiness	5	41.7	6	50.0
	Needs a Lot More Mintiness	1	8.3	0	0
Taste in Mouth	Very Pleasant	1	8.3	0	0
	Slightly Pleasant	6	50.0	2	16.7
	Neither Pleasant nor Unpleasant	3	25.0	1	8.3
	Slightly Unpleasant	2	16.7	7	58.3
	Extremely Unpleasant	0	0	2	16.7
After Taste	Very Pleasant	1	8.3	1	8.3
	Slightly Pleasant	1	8.3	1	8.3
	Neither Pleasant nor Unpleasant	6	50.0	3	25.0
	Slightly Unpleasant	3	25.0	5	41.7
	Very Unpleasant	0	0	2	16.7
	No After Taste	1	8.3	0	0

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Overall Taste Assessment for Placebo and RAPIDISC™

	Placebo		RAPIDISC™	
	N	Percent	N	Percent
Better Than Average Taste for a Medication	6	50.0	1	8.3
Average Taste for a Medication	6	50.0	7	58.3
Worse Than Average Taste for a Medication	0	0	4	33.3
No Taste	0	0	0	0

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Table 36.

Individual and Mean (± S.D., N = 18) Pharmacokinetic Parameters of MK-0462 in Healthy Male Subjects Receiving Orally a Single Dose of Two MK-0462 5-mg Tablets Used in an Initial Phase I Study

Subject #	$AUC_{0-\infty}$[a] (ng·hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
118							
Mean	50.7	18.0	0.9	1.8[b] 1.9	10.2	345.7	0.40[c] 0.41
S.D.	15.4	5.6	0.4	0.4	3.0	83.7	0.10

Individual and Mean (± S.D., N = 18) Pharmacokinetic Parameters of MK-0462 in Healthy Male Subjects Receiving Orally a Single Dose of One MK-0462 10-mg Tablet (Encapsulated) as Used in the Phase IIb Dose - Finding Study

Subject #	$AUC_{0-\infty}$[a] (ng·hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
118							
Mean	49.5	16.8	1.3	1.6[b] 1.7	10.3	353.3	0.39[c] 0.40
S.D.	14.6	5.5	0.7	0.3	3.0	76.7	0.08

Individual and Mean (± S.D., N = 18) Pharmacokinetic Parameters of MK-0462 in Healthy Male Subjects Receiving Orally a Single Dose of One MK-0462 10-mg Final Market Composition Tablet as Used in Phase III Studies

Subject #	$AUC_{0-\infty}$[a] (ng·hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
118							
Mean	53.2	19.6	1.0	1.7[b] 1.8	10.8	344.9	0.43
S.D.	14.4	6.1	0.6	0.3	2.6	61.0	0.09

Individual and Mean (± S.D., N = 18) Pharmacokinetic Parameters of MK-0462 in Healthy Male Subjects Receiving a Single Dose of 4-mg Intravenous MK-0462 Infusion Over 30 Minutes

Subject #	$AUC_{0-\infty}$ (ng·hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
118					
Mean	49.4	1386.3	1.8[a] 2.0	25.4	353.9
S.D.	8.4	230.3	1.0	5.2	100.0

Table 37.

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of MK-0462 in Healthy Female Subjects Receiving Orally a 5-mg MK-0462 FMC Tablet

Subject #	AUC_0 [a] (ng·hr/ml)	C_{max} [a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
13							
14							
15							
16							
17							
18							
19							
20							
21							
114							
23							
24							
Mean	34.5	10.4	1.0	1.7[b] 1.9	12.7	316.2	0.40[c] 0.41
S.D.	13.0	3.9	0.6	0.4	4.5	65.7	0.080

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of MK-0462 in Healthy Female Subjects Receiving Orally a 5-mg MK-0462 FMC RAPIDISC™

Subject #	AUC_0 [a] (ng·hr/ml)	C_{max} [a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
13							
14							
15							
16							
17							
18							
19							
20							
21							
114							
23							
24							
Mean	33.2	11.1	1.6	1.6[b] 1.7	13.3	347.5	0.42[c] 0.36
S.D.	9.8	4.7	0.8	0.4	3.9	117.0	

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of MK-0462 in Healthy Female Subjects Receiving Orally a 10-mg MK-0462 FMC Tablet

Subject #	AUC_0 [a] (ng·hr/ml)	C_{max} [a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
13							
14							
15							
16							
17							
18							
19							
20							
21							
114							
23							
24							
Mean	73.9	21.3	1.5	1.7[b] 1.8	13.8	320.0	0.45[c] 0.45
S.D.	23.4	6.9	0.8	0.3	3.9	73.2	0.05

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of MK-0462 in Healthy Female Subjects Receiving Orally a 10-mg MK-0462 FMC RAPIDISC™

Subject #	AUC_0 [a] (ng·hr/ml)	C_{max} [a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
13							
14							
15							
16							
17							
18							
19							
20							
21							
114							
23							
24							
Mean	75.9	20.3	2.5	1.7[b] 2.2	15.3	350.7	0.47[c] 0.56
S.D.	24.7	7.9	1.4		3.9	62.2	

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Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of Intravenously Administered MK-0462 in Healthy Female Subjects Receiving Orally a 5-mg MK-0462 FMC Tablet and a Simultaneous Intravenous Infusion of 1-mg Stable-Labeled MK-0462 Solution Over 50 Minutes

Subject #	$AUC_{0-\infty}$ (ng•hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	MRT (hr)	V_{ss} (L)
13							
14							
15							
16							
17							
18							
19							
20							
21							
114							
23							
24							
Mean	16.6	1050.5	1.8[a]	30.2	313.5	2.0	125.9
S.D.	3.6	224.5	1.9 (0.4)	7.1	82.4	0.4	37.3

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of Intravenously Administered MK-0462 in Healthy Female Subjects Receiving Orally a 10-mg MK-0462 FMC Tablet and a Simultaneous Intravenous Infusion of 1-mg Stable-Labeled MK-0462 Solution Over 50 Minutes

Subject #	$AUC_{0-\infty}$ (ng•hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	MRT (hr)	V_{ss} (L)
13							
14							
15							
16							
17							
18							
19							
20							
21							
114							
23							
24							
Mean	16.2	1081.6	1.6[a]	30.4	323.6	2.0	127.5
S.D.	3.8	239.4	0.3	4.6	65.6	0.3	25.1

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of Intravenously Administered MK-0462 in Healthy Female Subjects Receiving Orally a 5-mg MK-0462 FMC RAPIDISC™ and a Simultaneous Intravenous Infusion of 1-mg Stable-Labeled MK-0462 Solution Over 50 Minutes

Subject #	$AUC_{0-\infty}$ (ng•hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	MRT (hr)	V_{ss} (L)
13							
14							
15							
16							
17							
18							
19							
20							
21							
114							
23							
24							
Mean	15.6	1121.2	1.5[a]	28.5	312.9	1.9	126.0
S.D.	3.5	241.6	1.6 (0.3)	7.4	86.5	0.5	44.9

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of Intravenously Administered MK-0462 in Healthy Female Subjects Receiving Orally a 10-mg MK-0462 FMC RAPIDISC™ and a Simultaneous Intravenous Infusion of 1-mg Stable-Labeled MK-0462 Solution Over 50 Minutes

Subject #	$AUC_{0-\infty}$ (ng•hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	MRT (hr)	V_{ss} (L)
13							
14							
15							
16							
17							
18							
19							
20							
21							
114							
23							
24							
Mean	15.9	1099.3	1.8[a]	31.9	345.2	2.1	134.2
S.D.	3.6	251.7	1.9 (0.5)	4.7	69.7	0.4	28.5

Table 39.

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of MK-0462 in Healthy Male Subjects Receiving Orally a 10-mg MK-0462 FMC RAPIDISC™

Subject #	$AUC_{0-\infty}$[a] (ng·hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12				2.0[b]	12.6	388.8	0.46[c] 0.47
Mean	56.3	16.6	2.5	2.1	2.7	78.7	— 0.41
S.D.	16.9	6.0	0.9	0.7			

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of Intravenously Administered MK-0462 in Healthy Male Subjects Receiving Orally a 10-mg MK-0462 FMC RAPIDISC™ and a Simultaneous Intravenous Infusion of 1-mg Stable-Labeled MK-0462 Solution Over 50 Minutes

Subject #	$AUC_{0-\infty}$ (ng·hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	MRT (hr)	V_{ss} (L)
1							
2							
3							
4							
5							
6							
7							
8							
9							
10				23.4			
11				26.1			
12							
Mean	11.9	1443.4	1.7[a] 1.8	25.6	371.2	1.9	162.4
S.D.	2.0	247.8	0.3	2.9	80.2	0.5	40.9

Table 40.

Individual and Mean (± S.D., N = 6) Pharmacokinetic Parameters of MK-0462 and ^{14}C-Radioactivity in Healthy Males Receiving a Single I.V. Dose of 3 mg of ^{14}C-MK-0462

Subj. No.	MK-0462 AUC (ng·hr/ml)	CL (ml/min)	V_{ss} (l)	CL_r (ml/min)	CL_r/CL	$t_{1/2}$ (hr)	^{14}C-Radioactivity AUC (ng eq·hr/ml)	$t_{1/2}$ (hr)	AUC Ratio[a]
1									
2									
3									
4									
5									
6									
Mean	38.1	1325	154	349	0.26[c]	2.4[b]	125.2	5.8[b]	0.30[c]
S.D.	5.4	195	28	50	–	–	10.8	–	–

[a]Calculated as AUC of MK-0462/AUC of ^{14}C-radioactivity.
[b]Harmonic mean.
[c]Geometric mean.

Individual and Mean (± S.D., N = 6) Pharmacokinetic Parameters of MK-0462 and ^{14}C-Radioactivity in Healthy Males Receiving a Single Oral Dose of 10 mg of ^{14}C-MK-0462

Subj. No.	MK-0462 AUC (ng·hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	CL_r (ml/min)	^{14}C-Radioactivity AUC (ng eq·hr/ml)	C_{max} (ng eq/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC Ratio[a]
1										
2										
3										
4										
5										
6										
Mean	59.8	19.8	1.4	2.2[b]	396	333.8	59.0	1.8	5.6[b]	0.17[c]
S.D.	23.6	9.8	1.4	–	112	43.4	8.2	1.2	–	–

Individual and Mean (± S.D., N = 6) Values of Urinary Recovery of MK-0462 Following Separate I.V. (3 mg) and Oral (10 mg) Administration of ^{14}C-MK-0462

Subject No.	Percent of Dose Excreted in Urine as MK-0462[a] I.V.	P.O.
1		
2		
3		
4		
5		
6		
Mean	26.5	14.3
S.D.	3.4	4.6

[a]Calculated using values from Tables 10 and 12 in Appendix I and the I.v. (Table 5) and capsule (Table 6) dosage fo...

Table 41.

Individual and Mean Values of Pharmacokinetic Parameters of MK-0462 in Patients from Three Groups, Group I (a), Group II (b), and Group III (c), of Renal Insufficiency Following the Administration of a 5-mg Oral Dose of 1 mg/ml MK-0462 Solution

(a)

Subject #	$AUC_{0-\infty}$[a] (ng·hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
1							
2							
4							
5							
6							
7							
8							
Mean	43.8	12.7	0.9	2.1[b]	5.5	110.9	0.56[c]
S.D.	18.1	3.0	0.3	—	2.0	35.9	—

(b)

Subject #	$AUC_{0-\infty}$[a] (ng·hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
9							
10							
11							
12							
14							
Mean	43.9	11.4	0.8	2.1[b]	2.4	47.0	0.53[c]
S.D.	21.5	4.9	0.3	—	1.4	11.9	—

(c)

Subject #	$AUC_{0-\infty}$[a] (ng·hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	F
17					
18					
19					
20					
21					
22					
Mean	51.9	12.5	0.8	2.6[b]	[c]
S.D.	14.3	5.7	0.6	—	—

Individual and Mean Values of Pharmacokinetic Parameters of MK-0462 in Patients from Three Groups, Group I (a), Group II (b), and Group III (c), of Renal Insufficiency Following the Administration of a 2-mg Intravenous Dose of 1 mg/ml MK-0462 Solution

(a)

Subject #	$AUC_{0-\infty}$[a] (ng·hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)
1					
2					
4					
5					
6					
7					
8					
Mean	30.0	1159.1	2.0[b]	9.9	113.4
S.D.	7.0	244.0	—	3.8	44.2

(b)

Subject #	$AUC_{0-\infty}$[a] (ng·hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)
9					
10					
11					
12					
14					
Mean	30.9	1134.4	1.8[b]	3.5	37.3
S.D.	8.3	270.1	—	2.7	25.2

(c)

Subject #	$AUC_{0-\infty}$[a] (ng·hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)
17			
18			
19			
20			
21			
22			
Mean	38.6	912.5	2.5[b]

Table 42.

Individual and Mean (± S.D., N = 3) Pharmacokinetic Parameters for (a) I.V. MK-0462, Oral (b) MK-0462, and (c) L-706,248 in Healthy Male Subjects Receiving Orally a 5-mg MK-0462 Tablet and a Simultaneous I.V. Infusion of 1.0-mg Stable-Labeled MK-0462 Over 50 Minutes (Part 1)

(a) I.V. MK-0462

Subject #	$AUC_{0-\infty}$[a] (ng•hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	MRT (hr)	V_{ss} (L)
4					
5					
6					
Mean	10.1	1667.8	1.5[b]	1.7	174.1
S.D.	1.2	185.4	—	0.4	25.4

(b) Oral MK-0462

Subject #	$AUC_{0-\infty}$[a] (ng•hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	F
4					
5					
6					
Mean	22.7	8.5	0.8	1.5[c]	0.44[c]
S.D.	6.2	1.0	0.3	—	—

(c) L-706,248

Subject #	$AUC_{0-\infty}$[a] (ng•hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$[d] Ratio	C_{max}[d] Ratio
4						
5						
6						
Mean	4.6	1.5	1.4	1.5[b]	0.22[c]	0.18[c]
S.D.	0.8	0.4	0.6	—	—	—

Individual and Mean (± S.D., N = 7 or 3) Pharmacokinetic Parameters for I.V. MK-0462 in Patients with (a) Mild or (b) Moderate Hepatic Insufficiency Receiving Orally a 5-mg MK-0462 Tablet and a Simultaneous I.V. Infusion of 1.0-mg Stable-Labeled MK-0462 Over 50 Minutes (Part 2)

(a) Mild hepatic insufficiency

Subject #	$AUC_{0-\infty}$[a] (ng•hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	MRT (hr)	V_{ss} (L)
7							
8							
9							
13							
14							
15							
16							
Mean	13.6	1297.9	2.1[b]	28.1	358.9	1.9	142.4
S.D.	3.2	338.5	—	8.5	127.3	0.7	61.9

(b) Moderate hepatic insufficiency

Subject #	$AUC_{0-\infty}$[a] (ng•hr/ml)	CL_p (ml/min)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	MRT (hr)	V_{ss} (L)
10							
11							
12							
Mean	12.3	1450.2	1.9[c]	30.1	415.1	2.1	177.5
S.D.	3.8	472.2	—	6.9	34.8	0.6	49.9

Table 43.

Individual and Mean (± S.D., N = 7 or 3) Pharmacokinetic Parameters for Oral MK-0462 in Patients with (a) Mild or (b) Moderate Hepatic Insufficiency Receiving Orally a 5-mg MK-0462 Tablet (Part 2)

(a) Mild hepatic insufficiency

Subject #	$AUC_{0-\infty}$[a] (ng•hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
7							
8							
9							
13							
14							
15							
16							
Mean	30.2	10.9	1.1	1.8[b]	11.6	325.4	0.44[c]
S.D.	9.5	2.2	0.4	—	4.9	113.7	—

(b) Moderate hepatic insufficiency

Subject #	$AUC_{0-\infty}$[a] (ng•hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e (%)	CL_r (ml/min)	F
10							
11							
12							
Mean	42.3	14.1	0.9	2.1[b]	17.8	351.6	0.69[c]
S.D.	11.1	3.8	0.5	—	5.0	51.8	—

Individual and Mean (± S.D., N = 7 or 3) Pharmacokinetic Parameters for L-706,248 in Patients with (a) Mild or (b) Moderate Hepatic Insufficiency Receiving Orally a 5-mg MK-0462 Tablet (Part 2)

(a) Mild hepatic insufficiency

Subject #	$AUC_{0-\infty}$[a] (ng•hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e[c] (%)	CL_r (ml/min)	$AUC_{0-\infty}$[c,d] Ratio	C_{max}[c,d] Ratio
7								
8								
9								
13								
14								
15								
16								
Mean	3.1	0.9	1.4	1.6[b]	0.8	213.5	0.11[c]	0.06
S.D.	1.1	0.3	0.5	—	0.3	99.4	—	—

(b) Moderate hepatic insufficiency

Subject #	$AUC_{0-\infty}$[a] (ng•hr/ml)	C_{max}[a] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	U_e[c] (%)	CL_r (ml/min)	$AUC_{0-\infty}$[c,d] Ratio	C_{max}[c,d] Ratio
10								
11								
12								
Mean	2.0	0.4	1.4	2.4[b]	0.4	197.7	0.05[c]	0.03[c]
S.D.	0.3	0.2	0.3	—	0.1	46.6	—	—

Individual and Mean (±S.D., N=8) Values of $AUC_{0-\infty}$ and C_{max} of MK-0462 in Healthy Elderly Female and Male Subjects Receiving Single Oral Doses of a 10-mg MK-0462 Tablet

Sub. No.	$AUC_{0-\infty}$, ng·h/ml	C_{max}, ng/ml	Sub. No.	$AUC_{0-\infty}$, ng·h/ml	C_{max}, ng/ml
Male			Female		
1			12		
2			13		
4			14		
5			15		
6			16		
7			17		
9			19		
10			20		
Mean	75.04	25.59		84.19	24.22
S.D.	20.17	8.29		15.41	16.77

Individual and Mean (±S.D., N=8) Values of T_{max} and $t_{1/2}$ of MK-0462 in Healthy Elderly Female and Male Subjects Receiving Single Oral Doses of a 10-mg MK-0462 Tablet

Subject No.	T_{max}, h	$t_{1/2}$, h	Subject No.	T_{max}, h	$t_{1/2}$, h
Male			Female		
1			12		
2			13		
4			14		
5			15		
6			16		
7			17		
9			19		
10			20		
Mean	1.00	1.79*		1.31	1.78*
S.D.	0.38			0.84	

Individual and Mean (±S.D., N=8) Values of Renal Clearance of MK-0462 (Cl_r) Following a Single Oral Dose of a 10-mg MK-0462 Tablet

Subject No.	Cl_r, ml/min	Subject No.	Cl_r, ml/min
Male		Female	
1			
2		12	
4		13	
5		14	
6		15	
7		16	
9		17	
10		19	
		20	
Mean	209.09	mean	185.10
S.D.	21.08	S.D.	50.93

Individual and Mean (±S.D., N=8) Values of Percentage of Dose Excreted in Urine as MK-0462 (U_e) Following a Single Oral Dose of a 10-mg MK-0462 Tablet

Subject No.	U_e, %Dose	Subject No.	U_e, %Dose
Male		Female	
1			
2		12	
4		13	
5		14	
6		15	
7		16	
9		17	
10		19	
		20	
Mean	9.39	Mean	9.25
S.D.	2.26	S.D.	2.87

Table 45.

Individual and Mean (± S.D., N = 11) Values of Pharmacokinetic Parameters of MK-462 on Day 7 in Healthy Subjects Receiving Orally Placebo q12h for 7.5 Days and 10 mg of MK-0462 on Days 7 and 8.

Subject #	AUC (ng·hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
2				
3				
4				
5				
6				
7				
8				
209				
10				
111				
12				
Mean	93.4	25.6	1.3	2.1[a]
S.D.	32.7	9.4	1.0	–

Individual and Mean (± S.D., N = 11) Values of Pharmacokinetic Parameters of MK-462 on Day 7 in Healthy Subjects Receiving Orally 120 mg of Propranolol q12h for 7.5 Days and 10 mg of MK-0462 on Days 7 and 8

Subject #	AUC (ng·hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
2				
3				
4				
5				
6				
7				
8				
209				
10				
111				
12				
Mean	159	46.8	1.0	2.8[a]
S.D.	59.7	23.6	0.6	–

[a] Harmonic mean

Table 46.

Individual and Mean (±S.D., N=12) Pharmacokinetic Parameters of MK-0462 on Day 4 in Healthy Young Subjects Receiving Orally 150-mg t.i.d Moclobemide (Trt A) or placebo (Trt B) for 4 days and a Single Dose 10-mg MK-0-462 on Day 4.

	Subject	Sex	AUC* (ng·h/ml)		C_{max} (ng/ml)		Tmax (h)		$t_{1/2}$* (h)	
			Trt A	Trt B	Trt A	Trt B	Trt A	Trt B	Trt A	Trt B
	1	Male								
	2	Male								
	3	Male								
	4	Male								
	5	Male								
	6	Male								
		mean	141.59	66.62	30.28	23.16	2.1	1.5	2.26	1.66
		S.D.	32.10	20.27	13.45	11.43	1.2	0.9	0.3	0.2
	7	Female								
	8	Female								
	9	Female								
	10	Female								
	11	Female								
	12	Female								
		mean	174.76	76.21	32.40	22.05	2.8	1.4	2.38	1.77
		S.D.	58.73	13.85	8.24	7.66	0.9	0.7	0.3	0.3
Overall Mean			158.17	71.42	31.34	22.61	2.4	1.5	2.31	1.71
Overall S.D.			48.33	17.29	10.69	9.30	1.0	0.8	0.3	0.3

Individual and Mean (±S.D., N=12) Pharmacokinetic Parameters of Metabolite L-706,248 on Day 4 in Healthy Young Subjects Receiving Orally 150-mg t.i.d Moclobemide (Trt A) or Placebo (Trt B) for 4 Days and a Single Dose 10-mg MK-0-462 on Day 4

Subject	Sex	AUC* (ng·h/ml)		C_{max} (ng/ml)		T_{max} (h)		$t_{1/2}$* (h)	
		Trt A	Trt B	Trt A	Trt B	Trt A	Trt B	Trt A	Trt B
1	Male								
2	Male								
3	Male								
4	Male								
5	Male								
6	Male								
	mean	46.99	9.73	6.39	3.01	3.3	2.0	3.07	1.84
	S.D.	7.65	3.64	0.71	1.49	1.0	0.8	0.4	0.3
7	Female								
8	Female								
9	Female								
10	Female								
11	Female								
12	Female								
	mean	57.93	10.33	7.91	2.65	3.7	1.7	3.14	1.73
	S.D.	9.22	2.28	1.57	0.85	0.8	0.8	0.7	0.3
Overall Mean		52.46	10.03	7.15	2.83	3.5	1.8	3.10	1.59
Overall S.D.		9.89	2.92	1.41	1.17	0.9	0.8	0.6	0.4

Table 47.

Individual and Mean (+S.D., N=12) Cl_R (ml/min) and Percent-Dose Excreted (Ue) in Urine as MK-0462 on Day 4 in Healthy Young Subjects Receiving Orally Moclobemide Plus MK-0462 (Trt A) and Placebo Plus MK-0462 (Trt B).

Subject #		Ue		Cl_R	
		Trt A	Trt B	Trt A	Trt B
1	Male				
2	Male				
3	Male				
4	Male				
5	Male				
6	Male				
	mean	21.56	10.06	252.17	271.50
	S.D.	6.44	1.43	60.63	78.73
7	Female				
8	Female				
9	Female				
10	Female				
11	Female				
12	Female				
	mean	18.21	10.37	176.80	233.84
	S.D.	9.18	1.72	71.34	52.74
Overall Mean		19.73	10.21	211.06	252.67
Overall S.D.		7.86	1.52	74.60	66.85

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Individual and Mean (+S.D., N=12) CLR (ml/min) and Percent-Dose Excreted (Ue) in Urine as metabolite L-706,248 on Day 4 in Healthy Young Subjects Receiving Orally Moclobemide Plus MK-0462 (Trt A) and Placebo Plus MK-0462 (Trt B).

Subject #		U_e		Cl_R	
		Trt A	Trt B	Trt A	Trt B
1	Male				
2	Male				
3	Male				
4	Male				
5	Male				
6	Male				
	mean	5.58	1.09	186.86	200.84
	S.D.	1.84	0.16	52.72	64.70
7	Female				
8	Female				
9	Female				
10	Female				
11	Female				
12	Female				
	mean	4.49	1.05	127.78	174.23
	S.D.	1.20	0.15	41.31	40.37
Overall Mean		4.99	1.07	154.63	187.54
Overall S.D.		1.55	0.15	54.01	53.26

APPEARS THIS WAY ON ORIGINAL

Table 4S.

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of MK-0462 on Day 7 in Healthy Subjects Receiving Orally 80 mg of Nadolol q12h for 7 Days and a Single 10-mg Dose of MK-0462 on Day 7

Subject #	AUC[a] (ng·hr/ml)	C_{max}[b] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
1				
3				
5				
6				
9				
10				
14				
15				
17				
20				
21				
22				
Mean	65.28	21.39	1.1	1.9[c]
S.D.	19.93	6.86	0.9	—

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of MK-0462 on Day 7 in Healthy Subjects Receiving Orally 100 mg of Metoprolol q12h for 7 Days and a Single 10-mg Dose of MK-0462 on Day 7

Subject #	AUC[a] (ng·hr/ml)	C_{max}[b] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
2				
4				
7				
8				
11				
12				
13				
16				
18				
19				
23				
24				
Mean	70.62	19.63	1.1	1.9[c]
S.D.	20.37	4.63	0.7	—

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of MK-0462 on Day 7 in Healthy Subjects Receiving Orally Placebo (to Match Nadolol) q12h for 7 Days and a Single 10-mg Dose of MK-0462 on Day 7

Subject #	AUC[a] (ng·hr/ml)	C_{max}[b] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
1				
3				
5				
6				
9				
10				
14				
15				
17				
20				
21				
22				
Mean	59.53	18.26	0.8	2.1[c]
S.D.	14.07	5.93	0.4	—

Individual and Mean (± S.D., N = 12) Pharmacokinetic Parameters of MK-0462 on Day 7 in Healthy Subjects Receiving Orally Placebo (to Match Metoprolol) q12h for 7 Days and a Single 10-mg Dose of MK-0462 on Day 7

Subject #	AUC[a] (ng·hr/ml)	C_{max}[b] (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
2				
4				
7				
8				
11				
12				
13				
16				
18				
19				
23				
24				
Mean	65.99	21.65	1.0	1.8[c]
S.D.	20.58	5.99	1.0	—

Table 49.

Healthy Young Subjects Receiving Orally Paroxetine 20-mg (Trt A) or Placebo (Trt B) for 14 days and a Single Dose 10-mg MK-0462 on Day 14

Subjects	Gender	AUC (ng-h/ml) Trt A	AUC (ng-h/ml) Trt B	C_{max} (ng/ml) Trt A	C_{max} (ng/ml) Trt B	T_{max} (h) Trt A	T_{max} (h) Trt B	$t_{1/2}$* (h) Trt A	$t_{1/2}$* (h) Trt B
1	Male								
3	Male								
5	Male								
6	Male								
107	Male								
8	Male								
	Mean	63.57	64.27	17.20	18.64	0.83	0.75	2.35	2.06
	S.D.	22.18	26.20	6.61	10.58	0.41	0.27		
10	Female								
11	Female								
12	Female								
14	Female								
15	Female								
16	Female								
	Mean	81.19	67.15	19.98	16.84	1.08	1.50**	1.88	1.57
	S.D.	26.41	17.10	6.97	4.35	0.74	1.26**		
Overall Mean		72.38	65.71	18.59	17.74	0.96	1.13	2.09	1.78
Overall S.D.		25.01	21.15	6.64	7.77	0.58	0.96		

Individual and Mean (±S.D., N=12) Pharmacokinetic Parameters of Metabolite L-706,248 on Day 14 in Healthy Young Subjects Receiving Orally Paroxetine 20-mg (Trt A) or Placebo (Trt B) for 14 days and a Single Dose 10-mg MK-0462 on Day 14

Subjects	Gender	AUC (ng-h/ml) Trt A	AUC (ng-h/ml) Trt B	C_{max} (ng/ml) Trt A	C_{max} (ng/ml) Trt B	T_{max} (h) Trt A	T_{max} (h) Trt B	$t_{1/2}$* (h) Trt A	$t_{1/2}$* (h) Trt B
1	Male								
3	Male								
5	Male								
6	Male								
107	Male								
8	Male								
	Mean	7.11	7.58	1.55	1.60	1.17	1.33	2.13	2.09
	S.D.	2.36	3.31	0.46	0.49	0.26	0.26		
10	Female								
11	Female								
12	Female								
14	Female								
15	Female								
16	Female								
	Mean	7.50	7.79	1.69	1.72	1.25	1.17	2.07	1.86
	S.D.	2.55	2.31	0.63	0.32	0.61	0.41		
Overall mean		7.31	7.69	1.62	1.66	1.21	1.25	2.10	1.96
Overall S.D.		2.35	2.72	0.53	0.40	0.45	0.34		

MK-0462 on Day 14 in Healthy Young Subjects Receiving Orally Paroxetine Plus MK-0462 (Trt A) and Placebo Plus MK-0462 (Trt B)

Subject No.	Gender	Ue (%) Trt A	Ue (%) Trt B	Cl_R (ml/min) Trt A	Cl_R (ml/min) Trt B
1	Male				
3	Male				
5	Male				
6	Male				
107	Male				
8	Male				
	Mean	12.53	11.54	328.11	354.07
	S.D.	6.04	3.72	87.85	65.70
10	Female				
11	Female				
12	Female				
14	Female				
15	Female				
16	Female				
	Mean	15.13	13.04	325.00	327.30
	S.D.	5.34	4.24	95.59	67.62
Overall Mean		13.83	12.36	326.56	340.68
Overall S.D.		5.60	3.89	87.55	65.08

Individual and Mean (±S.D., N=12) Cl_R (ml/min) and Percent Dose Excreted (U_e) in Urine as Metabolite L-706,248 on Day 14 in Healthy Young Subjects Receiving Orally Paroxetine Plus MK-0462 (Trt A) and Placebo Plus MK-0462 (Trt B)

Subject No.	Gender	Ue (%) Trt A	Ue (%) Trt B	Cl_R (ml/min) Trt A	Cl_R (ml/min) Trt B
1	Male				
3	Male				
5	Male				
6	Male				
107	Male				
8	Male				
	Mean	0.99	0.94	239.04	250.82
	S.D.	0.42	0.32	64.90	73.05
10	Female				
11	Female				
12	Female				
14	Female				
15	Female				
16	Female				
	Mean	1.01	1.11	228.29	251.12
	S.D.	0.31	0.27	58.95	63.97
Overall Mean		1.00	1.03	233.66	250.97
Overall S.D.		0.35	0.29	59.38	65.47

Table 30

Individual AUC_{∞} (ng/h/ml) in Patients Receiving a 5-mg Tablet of MK-0462 and 5 mg of MK-A462 in an Intranasal Solution (100 µl) During and Between Migraine Attacks

Subject	Tablet		Intranasal	
	During	Between	During	Between
S003				
S004				
S005				
S007				
S008				
S009				
S111				
S012				
S013				
S014				
S016				
S018				
S020				
S021				
S102				
S113				
S119				
S122				
Mean	58.9	54.4	52.6 (47.7*)	33.6 (34.4*)
S.D.	37.7	32.5	26.9	14.8

Individual AUC_{∞} Ratio (Relative Bioavailability) in Patients Receiving a 5-mg Tablet of MK-0462 and 5 mg of MK-A462 in an Intranasal Solution (100 µl) During and Between Migraine Attacks

Subject	Tablet During/Between	Intranasal During/Between	During Intranasal/Tablet	Between Intranasal/Tablet
S003				
S004				
S005				
S007				
S008				
S009				
S111				
S012				
S013				
S014				
S016				
S018				
S020				
S021				
S102				
S113				
S119				
S122				
Geo. Mean	1.05	1.28	0.85 (0.77*)	0.69 (0.65*)

Individual Overall C_{max} (ng/ml) in patients receiving a 5-mg Tablet of MK-0462 and 5-mg of MK-A462 in an Intranasal Solution (100 µl) During and Between Migraine Attacks

Subject	Tablet		Intranasal	
	During	Between	During	Between
S003				
S004				
S005				
S007				
S008				
S009				
S111				
S012				
S013				
S014				
S016				
S018				
S020				
S021				
S102				
S113				
S119				
S122				
Mean	21.6	15.7	11.8 (11.6*)	8.2 (8.2*)
S.D.	19.9	8.8	7.5	4.3

Individual C_{max} Ratio in patients receiving a 5-mg Tablet of MK-0462 and 5 mg of MK-A462 in an Intranasal Solution (100 µl) During and Between Migraine Attacks

Subject	Tablet During/Between	Intranasal During/Between	During Intranasal/Tablet	Between Intranasal/Tablet
S003				
S004				
S005				
S007				
S008				
S009				
S111				
S012				
S013				
S014				
S016				
S018				
S020				
S021				
S102				
S113				
S119				
S122				
Geo. Mean	1.20	1.46	0.52(0.50*)	0.49(0.43*)

Individual Initial t_{max} (hour) in Patients Receiving a 5-mg Tablet of MK-0462 and 5-mg of MK-A462 in an Intranasal Solution (100 µl) During and Between Migraine Attacks

Subject	Tablet		Intranasal	
	During	Between	During	Between
S003				
S004				
S005				
S007				
S008				
S009				
S111				
S012				
S013				
S014				
S016				
S018				
S020				
S021				
S102				
S113				
S119				
S122				
Mean	1.0	0.9	0.8 (0.8*)	0.9 (0.9*)
S.D.	0.4	0.5	0.3	0.3

Individual Plasma Half-life (hour) in Patients Receiving a 5-mg Tablet of MK-0462 and 5 mg of MK-A462 in an Intranasal Solution (100 µl) During and Between Migraine Attacks

Subject	Tablet		Intranasal	
	During	Between	During	Between
S003				
S004				
S005				
S007				
S008				
S009				
S111				
S012				
S013				
S014				
S016				
S018				
S020				
S021				
S102				
S113				
S119				
S122				
Harmonic Mean	1.9	2.0	2.5 (2.5*)	2.3 (2.4*)

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20864/20865

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Dennis M. Erb, Ph.D.
Director
Regulatory Affairs

June 4, 1998

DUPLICATE

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not desk copies.

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Paul D. Leber, M.D., Director
Division of Neuropharmacological
Drug Products, HFD-120, Rm. 4037
Office of Drug Evaluation I
Center for Drug Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852-1448

CENTER FOR DRUG EVALUATION AND RESEARCH

JUN 05 1998

RECEIVED HFD-120

MERCK
Research Laboratories

NDA 20-864: MAXALT® (rizatriptan benzoate) Tablets
AMENDMENT TO A PENDING APPLICATION

Dear Dr. Leber:

Reference is made to the subject pending New Drug Application (NDA); trade package component labeling for MAXALT® Tablets submitted on February 11, 1998; and a phone conversation between Ms. Lana Chen, Project Manager, FDA and Dr. Dennis Erb, Merck Research Laboratories (MRL) on May 20, 1998 regarding package component labeling for sample packages.

As agreed in the aforementioned teleconference, we are submitting with this letter package component labeling for samples of MAXALT® 5 and 10 mg tablets. This labeling is a derivative of the package component labeling for trade packages.

If you have any questions or need additional information, please contact Dennis M. Erb, Ph.D. (610/397-7597) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

10 June 98
O.K. for CMC
/S/

OK /S/ 6/12/98

Sincerely,

Dennis M. Erb

Dennis M. Erb, Ph.D.
Director
Regulatory Affairs

Attachments
Federal Express # 1

Desk Copy: Ms. Lana Chen, HFD-120, Room 4031 (Letter only) Federal Express # 2

q/ligi/letters/fda235

NDA: 20-864
Rizatriptan
Item 13: Patent Information

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1.	Active Ingredient	Rizatriptan
2.	Strengths	5 mg and 10 mg
3.	Trade Name	MAXALT
4.	Dosage form Route of Administration	Tablet Oral
5.	Applicant Firm Name	Merck Research Laboratories
6.	NDA Number	20-864
7.	Approval Date	---
8.	Exclusivity-Date First ANDA Could be Submitted	5 years from NDA approval date
9.	Applicable Patent Number*	5,298,520 Expires: Jan. 28, 2012

**Patent expiration dates determined by 35 USC 154(C) enacted pursuant to the General Agreement of Tariffs and Trade (GATT), [Pub. L. No. 103-465 (H.R. 5110), signed December 8, 1994, effective January 1, 1995].*

NDA 20-864: MAXALT 5 mg and 10mg Tablets
(RIZATRIPTAN)

Patent No.	*Patent Claim*	*Exp Date*	*Owned By*	*Licensee-Address*	*Licensee US Contact-Address*
5,298,520	active ingredient	1/28/12	Merck, Sharp & Dohme, Ltd..	Merck & Co., Inc. One Merck Dr. Box 100 Whitehouse Station, NJ 08889-0100	Robert J. North Merck & Co., Inc. 126 E. Lincoln Ave. RY60-30 Rahway, NJ 07065-0900 908-594-7262

NDA: 20-865
Rizatriptan
Item 13: Patent Information

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1.	Active Ingredient	Rizatriptan
2.	Strengths	5 mg and 10 mg
3.	Trade Name	MAXALT
4.	Dosage form Route of Administration	Rapidly Dissolving Wafer Oral
5.	Applicant Firm Name	Merck Research Laboratories
6.	NDA Number	20-865
7.	Approval Date	---
8.	Exclusivity-Date First ANDA Could be Submitted	5 years from NDA approval date
9.	Applicable Patent Number*	5,298,520 Expires: Jan. 28, 2012 4,371,516 Expires: Feb. 01, 2000 4,305,502 Expires: Dec. 15, 1998 4,758,598 Expires: Dec. 15, 1998

APPEARS THIS WAY
ON ORIGINAL

**Patent expiration dates determined by 35 USC 154(C) enacted pursuant to the General Agreement of Tariffs and Trade (GATT), [Pub. L. No. 103-465 (H.R. 5110), signed December 8, 1994, effective January 1, 1995].*

APPEARS THIS WAY
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NDA 20-865: MAXALT RPD 5 mg and 10mg Wafers
(RIZATRIPTAN)

Patent No.	*Patent Claim*	*Exp Date*	*Owned By*	*Licensee-Address*	*Licensee US Contact-Address*
5,298,520	active ingredient	1/28/12	Merck, Sharp & Dohme, Ltd..	Merck & Co., Inc. One Merck Dr. Box 100 Whitehouse Station, NJ 08889-0100	Robert J. North Merck & Co., Inc. 126 E. Lincoln Ave. RY60-30 Rahway, NJ 07065-0900 908-594-7262
4,758,598	dosage form product	12/15/98	John Wyeth and Brother, Ltd.	RP Scherer Frankland Road Blagrove, Swindon Wiltshire, UK SN58RU	Joe Mitchell 2075 West Beaver Road Suite 700 Troy, MI 48084 248-649-0900
4,371,516	dosage form product	2/1/00	John Wyeth and Brother, Ltd.	RP Scherer Frankland Road Blagrove, Swindon Wiltshire, UK SN58RU	Joe Mitchell 2075 West Beaver Road Suite 700 Troy, MI 48084 248-649-0900
4,305,502	dosage form packaged product	12/15/98	John Wyeth and Brother, Ltd.	RP Scherer Frankland Road Blagrove, Swindon Wiltshire, UK SN58RU	Joe Mitchell 2075 West Beaver Road Suite 700 Troy, MI 48084 248-649-0900

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ON ORIGINAL

May 9, 1997

Re: MAXALT Tablets
Rizatriptan
NDA 20-864
Information required in accordance with 21 USC § 355 (b)(1)

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 USC 355(b)(1), attached hereto please find patent information for the above-identified application.

Attached item 13 lists one patent. The undersigned declares that U.S. Patent No. 5,298,520, covers the drug substance, drug product and method of use of the product, which is the subject of this application for which approval is being sought.

Specifically, the undersigned declares that U.S. Patent No. 5,298,520, having an expiration date of January 28, 2012, and owned by Merck Sharp & Dohme Ltd., claims the drug substance, drug product and method of use, which is the subject of this application.

A claim of patent infringement could be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product of this application for which approval is sought.

Very truly yours,

Robert J. North
Assistant Patent Counsel

APPEARS THIS WAY
ON ORIGINAL

NDA:	**20-864**
Trade Name:	**Maxalt Tablet**
Generic Name:	**rizatriptan benzoate**
Applicant Name:	**Merck**
Division:	**HFD-120**
Project Manager:	**Lana Y. Chen, R.Ph.**
Approval Date:	June 29, 1998

PART I

IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a. Is it an original NDA? **Yes**

   b. Is it an effectiveness supplement? **No**
   If yes, what type? (SE1, SE2, etc.)

   c. Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") **Yes**

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study. **N/A**

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: **N/A**

   d. Did the applicant request exclusivity? **Yes**

   If the answer "yes," how many years of exclusivity did the applicant request? **5 yrs**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? No

If yes, what is NDA number

If yes, what is Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade? No

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

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PART II

FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product. **No**

   Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

   If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product. **N/A**

   If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

   If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

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PART III

THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a. In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

b. Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

1) If yes, explain:

2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

If yes, explain:

If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:

Investigation #2, Study #:

Investigation #3, Study #:

APPEARS THIS WAY
ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

   a. For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

      Investigation #1

      Investigation #2

      Investigation #3

      If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

      NDA: Study:

      NDA: Study:

      NDA: Study:

   b. For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

      Investigation #1

      Investigation #2

      Investigation #3

      If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

      NDA: Study:

      NDA: Study:

NDA: Study:

c. If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #: Study #:

Investigation #: Study #:

Investigation #: Study #:

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND#: Explain:

Investigation #2
IND#: Explain:

Investigation #2
IND#: Explain:

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
Explain:

Investigation #2
Explain:

Investigation #3
Explain:

Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

If yes, explain:

/S/

Lana Y. Chen, R.Ph.
Project Manager
DNDP, HFD-120

APPEARS THIS WAY
ON ORIGINAL

/S/ 6/18/98

Paul Leber, M.D.
Director
DNDP, HFD-120

c:\wpfiles\max_tab.nda\ap\exclusiv.sum
Final: May 29, 1998

cc:
Original NDA
Division File
HFD-120/Chen
HFD-85/Holovac

APPEARS THIS WAY
ON ORIGINAL

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-864 Trade (generic) names Maxalt (rizatriptan) Tablets

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 and #4 below as appropriate.)

✔ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

✔ a. The applicant has committed to doing such studies as will be required.

✔ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

_____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

APPEARS THIS WAY
ON ORIGINAL

/S/
Signature of Preparer

6/10/98
Date

cc:
Orig NDA
HFD-120 Division File
NDA Action Package

APPEARS THIS WAY
ON ORIGINAL

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-865 Trade (generic) names Maxalt (rizatriptan) MLT

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126© for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 and #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

✔ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

The Sponsor is currently awaiting the results of their adolescent study for the tablet formulation (NDA 20-864) prior to inititating pediatric studies for Maxalt-MLT.

APPEARS THIS WAY
ON ORIGINAL

/S/

Signature of Preparer

6/16/98

Date

cc:
Orig NDA
HFD-120 Division File
NDA Action Package

APPEARS THIS WAY
ON ORIGINAL

NDA 20-864: MAXALT® (rizatriptan benzoate) Tablets

APPEARS THIS WAY
ON ORIGINAL

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc., did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL

NDA 20-865: MAXALT (rizatriptan benzoate) in RAPIDISC®

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc., did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL

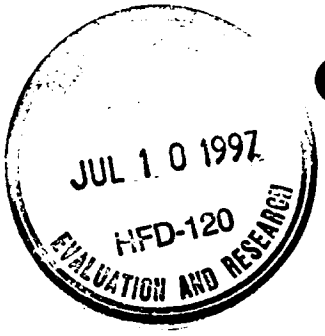
Dennis M. Erb, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7597
215 652 5000

These copies are OFFICIAL FDA Copies
not desk copies.

July 9, 1997

Ms. Lana Chen, CSO
Division of Neuropharmacological
Drug Products HFD-120
Office of Drug Evaluation I (CDER)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852-1448



MERCK
Research Laboratories

DUPLICATE

NEW CORRE

Dear Ms. Chen:

NDA 20-864: MAXALT™ (Rizatriptan Benzoate) Tablets
NDA 20-865: MAXALT™ (Rizatriptan Benzoate) in RAPIDISC™

Please refer to the above-referenced New Drug Applications submitted June 30, 1997 and to a telephone request on July 7, 1997.

Per your request, enclosed are the following:

APPEARS THIS WAY
ON ORIGINAL

- Twelve (12) additional copies of Volumes 1.1 and 1.2 of both NDAs;
- One (1) additional copy of the Environmental Assessment Report (Volume 1.4) of both NDAs;
- One (1) additional copy of the Table of All Investigators (attached to this letter).

As discussed in the aforementioned telephone conversation, Sections A, C, F, G and H of the Synopsis of the Application (Volume 1.2) are identical in both submissions. Section B contains the identical Proposed Text of Labeling in both submission, except for the Patient Package Insert, which is specific to each dosage form.

Please direct questions or need for additional information to Dennis Erb, Ph.D. (610/397-7597) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

Dennis M. Erb, Ph.D.
Director
Regulatory Affairs

Attachments
Enclosure

Federal Express #1
q\robinson\mchugh\maxalt

Chen

Dennis M. Erb, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7597
215 652 5000

DESK COPY

May 13, 1998

MERCK
Research Laboratories

Paul D. Leber, M.D., Director
Division of Neuropharmacological
Drug Products, HFD-120, Rm. 4037
Office of Drug Evaluation I
Center for Drug Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852-1448

NDA 20-865: MAXALT® (rizatriptan benzoate) in RAPIDISC™
GENERAL CORRESPONDENCE

Dear Dr. Leber:

APPEARS THIS WAY
ON ORIGINAL

Reference is made to the above subject New Drug Application, telephone conversations with Dr. Bob Seevers, Team Leader Chemistry, FDA, on April 30, 1998 and May 1, 1998 and Ms. Lana Chen, Project Manager, FDA, on May 4, 1998 with Dr. Dennis Erb, Merck Research Laboratories (MRL), concerning the dosage form descriptor for the oral dosage form, which As discussed in the aforementioned conversations, FDA has reached consensus on the use of With this letter we are providing our understanding of the actions to be taken by FDA and MRL in regards to implementation of the new dosage form descriptor.

Specifically, FDA will require all companies to comply with this new terminology for the ZYDIS® formulation, including products already approved for market. Based on this understanding, it was agreed that Merck will revise the formulation descriptor for MAXALT® RPD™ by direct substitution of the word "orally" for "rapidly". Thus the formulation descriptor for MAXALT® RPD™ will be "Orally Disintegrating Tablet".

We trust that this letter accurately reflects the Agency's position and agreements reached in the aforementioned teleconferences.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions or need additional information, please contact Dennis M Erb, Ph.D. (610/397-7597) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Dennis M. Erb

Dennis M. Erb, Ph.D.
Director
Regulatory Affairs

Federal Express # 1

Desk Copies: Dr. Robert Seevers, HFD-510, Room 14B18 Federal Express# 2
Dr. Eric Sheinin, HFD-830, Room N112 Federal Express# 3
Dr. Randy Levin, HFD-120, Room 4047 Federal Express # 4
Ms. Lana Chen, HFD-120, Room 4037 Federal Express # 4

q/ligi/letters/223

APPEARS THIS WAY
ON ORIGINAL

Consult #858 (HFD-120)

MAXALT rizatriptan benzoate tablet

The following look-alike/sound-alike conflicts were noted: MAXAIR, MAXAQUIN and PAXIL. The Committee does not believe that these have significant potential for confusion. There were no misleading aspects found.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 11/1/97, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR TRADEMARK REVIEW

859

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

RECEIVED DEC 04 1997

From: Division of Neuropharmacological Drug Products Paul Leber, MD /S/ 7/30/97 X	**HFD-120**
Attention: Lana Chen	**Phone:** (301) 594-2850
Date: July 30, 1997	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Maxalt : RPD	**NDA/ANDA#** NDA 20-865
Established name, including dosage form: Rizatriptan Benzoate WAFER	
Other trademarks by the same firm for companion products: Maxalt Tablet	
Indications for Use (may be a summary if proposed statement is lengthy): Migraine	
Initial Comments from the submitter (concerns, observations, etc.): None	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NFA 20-865; HFD-120/division file; HFD-120/L.Chen; HFD-120/Bates

Rev. December 95

APPEARS THIS WAY
ON ORIGINAL

Consult #859 (HFD-120)

MAXALT RPD rizatriptan benzoate wafer

The following look-alike/sound-alike conflicts were noted: MAXAIR, MAXAQUIN and PAXIL. The Committee does not believe that these have significant potential for confusion.

The Committee is concerned about the use of RPD to denote Rapidisc since it may give the impression of being therapeutically rapid rather than rapidly dissolving.

Furthermore, the Committee recommends that the established name (rizatriptan benzoate rapidly disintegrating tablet) be used to be consistent with previous approvals that have used the same technology. Additionally, the term "wafer" is not a recognized dosage form descriptor used by the USP for monograph titles.

Overall, the Committee finds the proposed proprietary name acceptable and the established name unacceptable.

/S/ 11/3/97, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR TRADEMARK REVIEW

859

RECEIVED DEC 4 1997

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Neuropharmacological Drug Products Paul Leber, ~~MD~~ /S/ x	**HFD-120** 7/31/97
Attention: Lana Chen	**Phone:** (301) 594-2850
Date: July 30, 1997	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Maxalt	**NDA/ANDA#** NDA 20-864
Established name, including dosage form: Rizatriptan Benzoate	TABLET
Other trademarks by the same firm for companion products: Maxalt	RPD
Indications for Use (may be a summary if proposed statement is lengthy): Migraine	
Initial Comments from the submitter (concerns, observations, etc.): None	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NFA 20-864; HFD-120/division file; HFD-120/L.Chen; HFD-120/Bates

Rev. December 95

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

NDA / IND #:	NDA 20-865
DATE:	10 September 1997
PRODUCT NAME:	MAXALT™ (rizatriptan benzoate) RPD
FIRM NAME:	Merck Research Laboratories
Conversation With:	Dennis Erb, Ph.D.
Telephone #:	610.397.7597

(TELECON): Dr. Erb called with information / inquiries on the following points:

(1) Merck is interested in the acceptability of their proposed term "wafer" for the RPD dosage form. This term is used in their proposed labeling for both MAXALT™ and the enalapril maleate RPD, and The Division of Cardio-Renal Drugs has indicated that the term, "orally disintegrating tablet" would be preferred. It was unclear to Merck whether this represents an Agency-wide position at this time; if it does not, they would request reconsideration of the term "wafer" for their product.

(2) In conjunction with item (1), the firm would appreciate, if possible, receiving early feedback on the acceptability of their proposed blister backing and sachet labeling for this product. This is requested by some time in November, because of the necessity of ordering preprinted stock for the manufacture of launch supplies.

(3) The firm proposes submitting a global stability update in December, 1997, rather than piecemeal updates in November and December.

I addressed these points as follows:

(1) I agreed to look into the scope and status of this request (it is pertinent to the review, and although I did not tell Dr. Erb this, is a matter I had previously identified as needing resolution).

(2) The firm's position with regard to this request is reasonable and defensible. I agreed to provide information in November, if at all possible. [(1) has a potential impact on this.]

(3) The firm's proposal is maximally efficient for all concerned and I agreed to it.

(COMMENT): I have confirmed the following facts related to (1):

-The request from Cardio-Renal was issued in a CMC deficiencies letter 02APR97. The term, "orally disintegrating tablet" was requested at that time.

-The Nomenclature Committee has expressed a preference for "rapidly disintegrating tablet" but also notes that USP appears to prefer the term "orally disintegrating tablet".

I am in contact with the Chair of the CDER Labeling and Nomenclature Committee to determine the present situation. A subsequent memorandum to the file will note further details.

/S/

Doris J. Bates, Ph.D., Review Chemist
ONDC Division 1 / Neuropharm
filename: TCON.001

CC: NDA 20-865
HFD-120/Division file
HFD-120/MGuzewska /S/ 9.11.97
HFD-120/DJBates
[redacted]

Original New Drug Application: NDA 20-864 -

MAXALT™ Tablets
(rizatriptan benzoate)

STATEMENT OF ORGANIZATION

This application is formatted as required in 21 CFR 314.50. It consists of a complete "archival" copy (Blue Binders), comprising 123 volumes, and "review" copies of the six (6) technical sections as follows:

ITEM	DESCRIPTION	BINDER COLOR	TOTAL VOLUMES
3	Chemistry, Manufacturing and Control Documentation	Red	4
4	Samples, Methods Validation and Labeling	Red	1
5	Nonclinical Pharmacology and Toxicology Documentation	Yellow	27
6	Human Pharmacokinetics and Bioavailability Documentation	Orange	28
8	Clinical Documentation	Light Brown	46
10	Statistical Documentation	Green	14

In addition to the specific technical item, each review copy also includes, in the appropriate color binder, Volumes 1.1, containing Item 1 (the overall Index to the Contents of the Application) and Volume 1.2, containing Item 2 (Synopsis of the Application), which is the overall summary provided for in 21 CFR 314.50(c). Thus, the total number of volumes in this submission is 253 volumes.

Two additional copies of Item 4 are included with the archival copy but are not included in the total volume count. Items 11 and 12 are provided in electronic format only as previously agreed.

Pursuant to 21 CFR 314.50(k)(3), a complete field copy of the revised Chemistry, Manufacturing and Controls technical section (Item 3) has been submitted to the FDA Philadelphia District Office. This copy is a true copy of Item 3 as contained in the archival and review copies of this application.

MEMORANDUM

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

DATE: June 12, 1998

FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-864 and 20-865
Maxalt® tablets and Maxalt® RPD™ orally disintegrating tablets, rizatriptan benzoate
5 and 10 mg tablets
Sponsor: Merck & Co., Inc.

SUBJECT: Recommendation for approval for Pharmacology and Toxicology

---

The pharmacology and toxicology studies submitted to these NDA's for Maxalt, indicated for the treatment of acute migraine attacks with or without aura in adults, have been summarized in the 4/20/98 review by Dr. Thomas Steele and are adequate to support its approval for the acute treatment of migraine attacks with or without aura in adults. There are no outstanding issues.

Maxalt is another of the triptans and, like sumatriptan, zolmitriptan and naratriptan, it theoretically exerts its anti-migraine activity through its effects as an agonist at the 5-hydroxytryptamine $_{1B/1D}$ receptor.

The toxicological profile of Maxalt is relatively "clean" compared to the other triptans (see the table on page 106 of Dr. Steele's review). There were no serious toxicities in the one year rat and dog toxicology studies, no positive results in the genetic toxicology battery, and no drug related increase in tumors in the mouse and rat carcinogenicity studies. There was some evidence for developmental toxicity in the "definitive" reproduction studies (discussed below).

The major problem with the toxicology package is that maximum tolerated doses were not used in most of the studies. The sponsor seems to have followed a pattern of conducting dose ranging studies and then selecting high doses for the definitive studies that were not associated with a desireable level of toxicity. This is not an issue for the carcinogenicity studies because they were not designed to achieve a maximum tolerated dose. Dosage selection in those studies was based on multiples of human exposure, as allowed for non-genotoxic compounds (ICH guideline: Dose Selection for

Carcinogenicity Studies of Pharmaceuticals) and those studies are eonsidered to be adequate (see CAC-EC report).

The use of doses that were too low is particularly evident in the dog one year study, the *in vivo* clastogenicity assay (mouse micronucleus) and the reproductive toxicity battery. The dog study is the weakest of the studies, which used doses that did not produce noticeable toxicity other than minimal evidence for increased liver weights and which were not substantially higher than clinical doses in terms of exposure. The high dose in that study was associated with AUC values that were approximately 6-fold higher than the AUC's in humans receiving the maximum daily dose of 30 mg. While it would have been desirable to study higher doses, this study qualifies as a marginally adequate chronic non-rodent study for NDA approval.

The mouse micronucleus assay did not conform to OECD guidelines in several respects. For example, the high dose was too low to produce an acceptable degree of inhibition of mitotic index, and the correct number of cells per animal was not evaluated. However, there was evidence for exposure that was 200 times the maximum human exposure, the other assays were all clearly negative, and there were no tumor findings in the lifetime bioassays. Therefore, a repeat study using higher doses is not considered necessary.

The definitive studies in the reproductive toxicology battery also used doses that should have been higher to adequately characterize the toxic potential of Maxalt. However, 100 mg/kg/day (32 times the maximum daily human dose on a surface area basis), a dose which was not associated with maternal toxicity, was associated with some effects (decreased birth weights and postnatal growth) in the offspring of rats dosed through gestation and lactation. In the absence of maternal toxicity these effects indicate a direct effect of drug on the fetus. The middle dose in that study, at which no adverse effects on the fetus were seen, was only 10 mg/kg/day. In the dose ranging study which was conducted to select doses for the definitive study, pup deaths were increased between days 1 and 3 at 250 and 500 mg/kg/day, but not at 100 mg/kg/day (% pup deaths were: controls = 2, 100 mg/kg = 3, 250 mg/kg = 7, 500 mg/kg = 18). We would have had a study which examined the risk to the fetus more comprehensively if 250 mg/kg, a dose associated with minimal maternal toxicity (20% decrease in weight gain), had been chosen as a high dose for the definitive study. There was no evidence in the rat for embryolethality, which has been observed with related drugs, although there was an increase in resorptions and dead fetuses in the rabbit dose ranging study at maternally toxic doses; there was no evidence for teratogenicity in either species. Although Maxalt may have less serious fetotoxic effects than the other triptans, the potential has not been evaluated in well designed studies, that is, studies in which maternal toxicity was achieved. Even so, the decreased pup weights and increased pup mortality provide evidence for risk to the fetus. We have therefore assigned a Pregnancy Category C label to reflect the "adverse effects on the fetus".

The sponsor's primary objection to our proposed labeling is that they believe they should have a Pregnancy Category B. For the reasons noted above we disagree with

their conclusion since there were adverse effects on the fetus in the absence of maternal toxicity and pup deaths in the presence of minimal maternal toxicity. They also have objected to several minor aspects of our proposed labeling, originally faxed to them on April 30, 1998. We responded to their revisions of May 14 (see my memo of May 29) and have continued to negotiate wording. Dr. Levin's recommendations section of his June 9 memo (page 20) summarizes the remaining issues, which are now resolved, and the June 9 version of labeling should be considered the final recommended labeling.

Recommendations:

The pharmacology and toxicology studies submitted to this NDA support its approval with the labeling as finalized on June 9, 1998.

/S/

APPEARS THIS WAY
ON ORIGINAL

Glenna G. Fitzgerald, Ph.D.

NDA 20864, 20865
c.c. Div File
/Leber/Levin/Oliva/Steele/Fitzgerald/Chen

M:\DOS\WPFILES\MAXALTME.WPD

APPEARS THIS WAY
ON ORIGINAL