

**Summary Report**

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CEDRA DCN 11-657-T1

Mylan Pharmatceuticals Inc. PRIL-0367

## Summary Report

## Purpose

This was a randomized, single-dose, two-way crossover study designed to compare the rate and extent of absorption of two formulations of omeprazole, 20 mg PRILOSEC OTC Tablets (Procter & Gamble) and 20 mg PRILOSEC Capsules (manufactured for AstraZeneca LP by Merck & Co. Inc.), under fasting conditions.

## Clinical Procedures Summary

Forty-eight healthy adults were enrolled in this two period crossover comparison of two formulations of omeprazole conducted at PRACS Institute, Ltd per Protocol PRIL-0367. Subjects received two separate drug administrations in assigned periods (Period I: October 18 – 19, 2003 and Period II: October 25 – 26, 2003), one treatment per period, according to the randomization schedule. Dosing days were separated by a washout period of 7 days. An equal number of subjects were randomly assigned to each possible sequence of treatments. Drug administration consisted of an oral 20 mg omeprazole dose of the following treatments under fasting conditions:

Test Product:	Procter & Gamble
Treatment A	20 mg PRILOSEC OTC™ Tablets Lot 3242171971 Expiration 03/06
Reference Product:	AstraZeneca LP/ Merck & Co. Inc.
Treatment B	20 mg PRILOSEC® Capsules Lot M7886 Expiration 11-2004

Blood samples were drawn prior to dosing (pre-dose) and at 0.25, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 14, and 16 hours post-dose. The samples were shipped to CEDRA Corporation for analysis.

## Pharmacokinetic Analysis

Concentration-time data obtained during the study were stored in the Watson LIMS system (InnaPhase Corporation, Version 6.4.0.02) and transferred directly to WinNonlin (Pharsight, Enterprise Version 4.0) using the Custom Query Builder. Data for forty-five subjects were included in the pharmacokinetic and statistical analyses.

Pharmacokinetic data were analyzed using noncompartmental methods in WinNonlin. The lower limit of quantitation for the bioanalytical assay of omeprazole in plasma was 1.00 ng/mL. Concentration data that were below the limit of quantitation (BLQ) were excluded from the data

set prior to data summarization and pharmacokinetic analysis. BLQ concentrations at time-zero (pre-dose) were treated as zero in the analysis.

The following pharmacokinetic parameters were calculated for each subject and period: peak concentration in plasma ( $C_{max}$ ), time to peak concentration ( $T_{max}$ ), elimination rate constant ( $\lambda_z$ ), terminal half-life ( $T_{1/2}$ ), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration ( $AUC_{last}$ ), and area under the plasma concentration time curve from time-zero extrapolated to infinity ( $AUC_{inf}$ ).

Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the pharmacokinetic parameters obtained from the noncompartmental analysis,  $C_{max}$ ,  $T_{max}$ ,  $\lambda_z$ ,  $T_{1/2}$ ,  $AUC_{last}$ , and  $AUC_{inf}$ . Natural logarithm ( $\ln$ ) transformations of  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  were included in the statistical analysis. The 90% confidence interval (CI) for the difference between the means of the Test Formulation and the Reference Product was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80%-125%.  $T_{max}$  values of the Test Formulation and the Reference Product were compared using the non-parametric Wilcoxon Signed Rank Test.

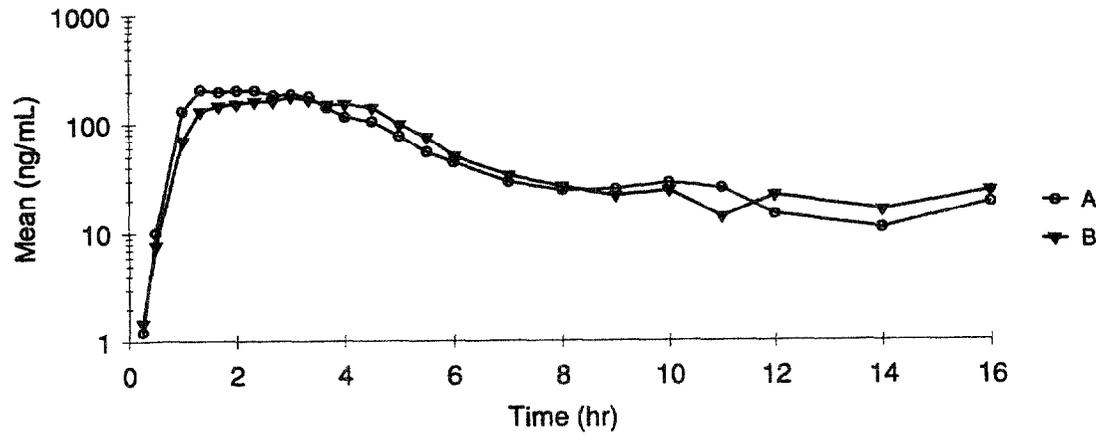
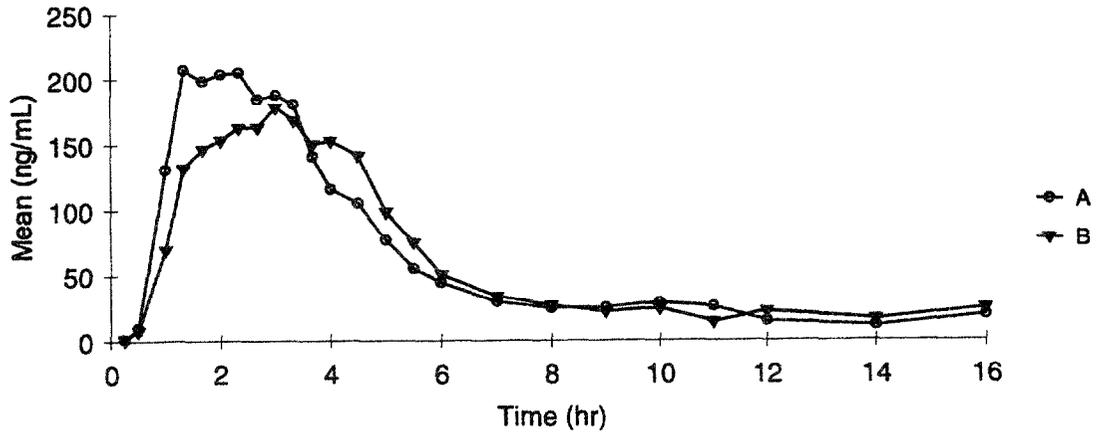
## Results

Forty-five subjects completed the study and were included in the pharmacokinetic and statistical analyses. Subjects 6, 17, and 46 did not complete the study and samples for these subjects were not assayed. Data and results are summarized in the following figure and tables. Mean concentration-time data are shown in Table S1 and Figure S1. Results of the pharmacokinetic and statistical analyses are shown in Tables S2 through S5.

## Conclusions

For comparisons of PRILOSEC OTC tablets to PRILOSEC capsules, statistical analysis of the data reveals that 90% confidence intervals are within the acceptable bioequivalent range of 80% and 125%, for the natural log transformed parameters  $\ln(AUC_{last})$  and  $\ln(AUC_{inf})$ . The 90% confidence intervals for the natural log transformed parameter  $\ln(C_{max})$  were 117% - 146%. Therefore, this study demonstrates that PRILOSEC OTC tablets, 20 mg, distributed by Proctor & Gamble are not bioequivalent to PRILOSEC capsules, 20 mg, manufactured for AstraZeneca LP by Merck & Co. Inc., following a single, oral 20 mg (1 × 20 mg) dose administered under fasting conditions.

**Figure S1: Mean Omeprazole Concentration vs Time Plots for PRILOSEC OTC Tablets (Treatment A) and PRILOSEC Capsules (Treatment B) under Fasting Conditions**



A = PRILOSEC OTC Tablets, B = PRILOSEC Capsules

**Table S1: Concentration-Time Data after the Administration of Two Formulations of Omeprazole**

Time (hr)	Treatment A: PRILOSEC OTC Tablets			Treatment B: PRILOSEC Capsules				
	n	Mean (ng/mL)	SD (ng/mL)	CV (%)	n	Mean (ng/mL)	SD (ng/mL)	CV (%)
0.00	0	BLQ	NC	NC	0	BLQ	NC	NC
0.25	1	1.21	NC	NC	1	1.49	NC	NC
0.50	12	10.1	12.8	127	19	7.75	11.00	142
1.00	31	131	168	129	35	69.8	97.9	140
1.33	37	207	269	130	41	132	206	157
1.67	40	199	248	125	43	147	200	136
2.00	41	204	218	107	43	153	189	123
2.33	43	205	216	105	41	163	188	116
2.67	43	185	175	94.7	43	163	185	114
3.00	44	188	235	125	44	178	238	133
3.33	44	181	287	159	45	169	232	138
3.67	44	141	237	168	45	150	213	142
4.00	44	116	217	187	45	153	244	159
4.50	45	105	188	179	45	142	215	152
5.00	45	77.2	156.5	203	45	98.7	163.0	165
5.50	42	55.2	115.9	210	45	75.3	163.4	217
6.00	40	44.4	96.4	217	44	50.6	102.9	203
7.00	34	29.3	66.6	227	39	33.7	76.7	228
8.00	25	24.5	52.5	214	30	26.5	58.4	220
9.00	16	25.1	41.8	167	24	21.9	45.5	208
10.00	10	28.7	34.5	120	15	24.4	40.8	167
11.00	7	25.7	24.2	94.1	13	13.9	24.7	177
12.00	6	14.7	14.9	101	6	22.1	22.2	101
14.00	5	11.0	9.5	86.4	5	16.1	13.1	81.8
16.00	3	18.9	16.1	85.1	4	24.2	26.9	111

n = Number of quantifiable concentrations at each scheduled time

BLQ = All concentrations below limit of quantification (1.00 ng/mL)

NC = Not calculated

**Table S2: Pharmacokinetic Parameters for Omeprazole After Oral Administration**

Parameter	<b>Treatment A:</b> PRILOSEC OTC Tablets				<b>Treatment B:</b> PRILOSEC Capsules			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T <sub>max</sub> (hr)	45	2.50	1.19	47.62	45	2.73	1.19	43.35
C <sub>max</sub> (ng/mL)	45	431	303	70.45	45	351	296	84.14
AUC <sub>last</sub> (hr*ng/mL)	45	772.9	907.8	117.47	45	767.9	991.1	129.07
AUC <sub>inf</sub> (hr*ng/mL)	45	778.3	920.9	118.33	45	777.8	1017	130.73
AUC <sub>Extrap</sub> (%)	45	0.44	0.43	97.96	45	0.82	1.33	162.67
λ <sub>z</sub> (hr <sup>-1</sup> )	45	0.9265	0.2971	32.07	45	0.8107	0.2977	36.73
T <sub>1/2</sub> (hr)	45	0.85	0.37	43.23	45	1.19	1.51	127.17
T <sub>last</sub> (hr)	45	8.44	2.90	34.37	45	9.29	2.81	30.21
C <sub>last</sub> (ng/mL)	45	2.71	5.58	206.17	45	3.74	9.57	255.65

**Table S3: Statistical Analysis of the Non-Transformed Pharmacokinetic Parameters of Omeprazole**

Dependent Variable	<b>Least Squares Mean</b>		Difference	Ratio [% Ref]	<b>90% Confidence Interval</b>		Power
	Test	Reference			Lower	Upper	
C <sub>max</sub> (ng/mL)	431.0224	352.1361	78.8863	122.40	111.03	133.78	0.8955
AUC <sub>last</sub> (hr*ng/mL)	771.8263	766.1323	5.6940	100.74	95.53	105.96	1.0000
AUC <sub>inf</sub> (hr*ng/mL)	777.1932	775.8925	1.3007	100.17	94.76	105.58	1.0000
T <sub>max</sub> (hr)	2.5053	2.7333	-0.2280	91.66	81.77	101.55	0.9535
λ <sub>z</sub> (hr <sup>-1</sup> )	0.9257	0.8121	0.1136	113.99	105.98	122.00	0.9922
T <sub>1/2</sub> (hr)	0.8488	1.1801	-0.3313	71.92	40.59	103.26	0.2774

Statistical analysis based on n = 45

Test = PRILOSEC OTC Tablets, Reference = PRILOSEC Capsules

**Table S4: Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of Omeprazole**

Dependent Variable	LS Mean <sup>a</sup>		Geometric Mean <sup>b</sup>		Diff <sup>c</sup>	Ratio (%Ref)	90% CI <sup>d</sup>		Power	ANOVA CV%
	Test	Ref	Test	Ref			Lower	Upper		
ln(C <sub>max</sub> )	5.8736	5.6078	355.5146	272.5349	0.2658	130.45	116.91	145.55	0.9558	31.65
ln(AUC <sub>last</sub> )	6.3105	6.2617	550.3056	524.1326	0.0487	104.99	100.65	109.52	1.0000	11.95
ln(AUC <sub>inf</sub> )	6.3148	6.2700	552.7085	528.4631	0.0449	104.59	100.31	109.05	1.0000	11.82

<sup>a</sup> Least Squares Mean for the Test Formulation (Test) and Reference Product (Ref)

<sup>b</sup> Geometric Mean based on Least Squares Mean (LSM) of ln-transformed values

<sup>c</sup> Difference = LS Mean (Test) – LS Mean (Ref)

<sup>d</sup> 90% Confidence Interval

Statistical analysis based on n = 45

Test = PRILOSEC OTC Tablets, Reference = PRILOSEC Capsules

**Table S5: Wilcoxon Signed Rank Test Comparing T<sub>max</sub> Values of Two Omeprazole Formulations**

Dependent Variable	Median		Range		Signed Rank Test	p-value
	Test	Reference	Test	Reference		
T <sub>max</sub> (hr)	2.33	2.67	1.00 - 6.00	1.00 - 5.50	-103	0.1365

Test = PRILOSEC OTC Tablets, Reference = PRILOSEC Capsules

Statistical analysis based on n = 45