

Bioequivalence Summary Clozapine Tablets, 25 mg

Study Dates:

Fasting: January - March 1996

Contract Firms:

LeeCoast Research Center, Inc.
Fort Myers, Florida

Wisconsin Analytical & Research Services
Madison, Wisconsin

Bioassay Laboratory Inc.
Round Rock, Texas

Test Products:

Clozapine Tablets, 25 mg, manufactured by IVAX
Pharmaceuticals, Inc. and distributed by TEVA
Pharmaceuticals USA, Lot # ND-234.

Reference Products:

CLOZARIL® Tablets, 25 mg, manufactured and
distributed by Novartis, Lot # 081U 4750.

Study Design:

Fasting Study

A randomized, two-way, single-dose, open-label, cross-over fasting study was conducted to compare the relative bioavailability of Clozapine Tablets, 25 mg, manufactured by IVAX Pharmaceuticals, Inc. and distributed by TEVA Pharmaceuticals USA and CLOZARIL® Tablets, 25 mg, manufactured and distributed by Novartis. Forty (40) subjects were enrolled in the study; however after twenty-four (24) subjects were enrolled the study was discontinued for safety reasons. Nineteen (19) subjects completed the study. Subjects were admitted to the clinical facility at least twelve (12) hours prior to dosing and were confined until 24 hours post-dose. Following an overnight fast of at least 10 hours, subjects were administered a single, oral 12.5 mg (1/2X25 mg tablet) dose of test or reference product in each study period according to the study randomization. Subjects were required to continue fasting for an additional 4 hours after dosing. Blood samples were obtained prior to dosing and at scheduled intervals for 72 hours after dosing for the assay of clozapine and normethylclozapine plasma concentrations. Subjects

underwent a one-week drug-free "washout" period between dosing periods.

Summary of Comparative Data:

Table 1 below shows the comparative AUC (Area Under the Curve) and Cmax (Maximum Observed Plasma Concentration) values of clozapine and normethylclozapine for the test and reference formulations for the fasting study. Figure 1 shows the comparative mean plasma levels for the formulations during the fasting study.

CLOZARIL® is a registered trademark of Novartis.
See accompanying prescribing information for Clozapine Tablets.

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Table 1	Comparative AUC (Area Under the Curve) and C _{max} (Maximum Observed Plasma Concentration) Values. Fasting 25 mg Study (N=19)	
	InAUC _{inf} (Test/Reference) [90% Confidence Interval]	InC _{max} (Test/Reference) [90% Confidence Interval]
Clozapine	102 [93.8;111]	96.0 [80.3;115]
Normethylclozapine	103 [95.2;111]	98.8 [87.0;112]

Conclusion:

A review of the pharmacokinetic data demonstrates that Clozapine Tablets, 25 mg, manufactured by IVAX Pharmaceuticals, Inc. and distributed by TEVA Pharmaceuticals USA are bioequivalent to CLOZARIL[®] Tablets, 25 mg, manufactured and distributed by Novartis.

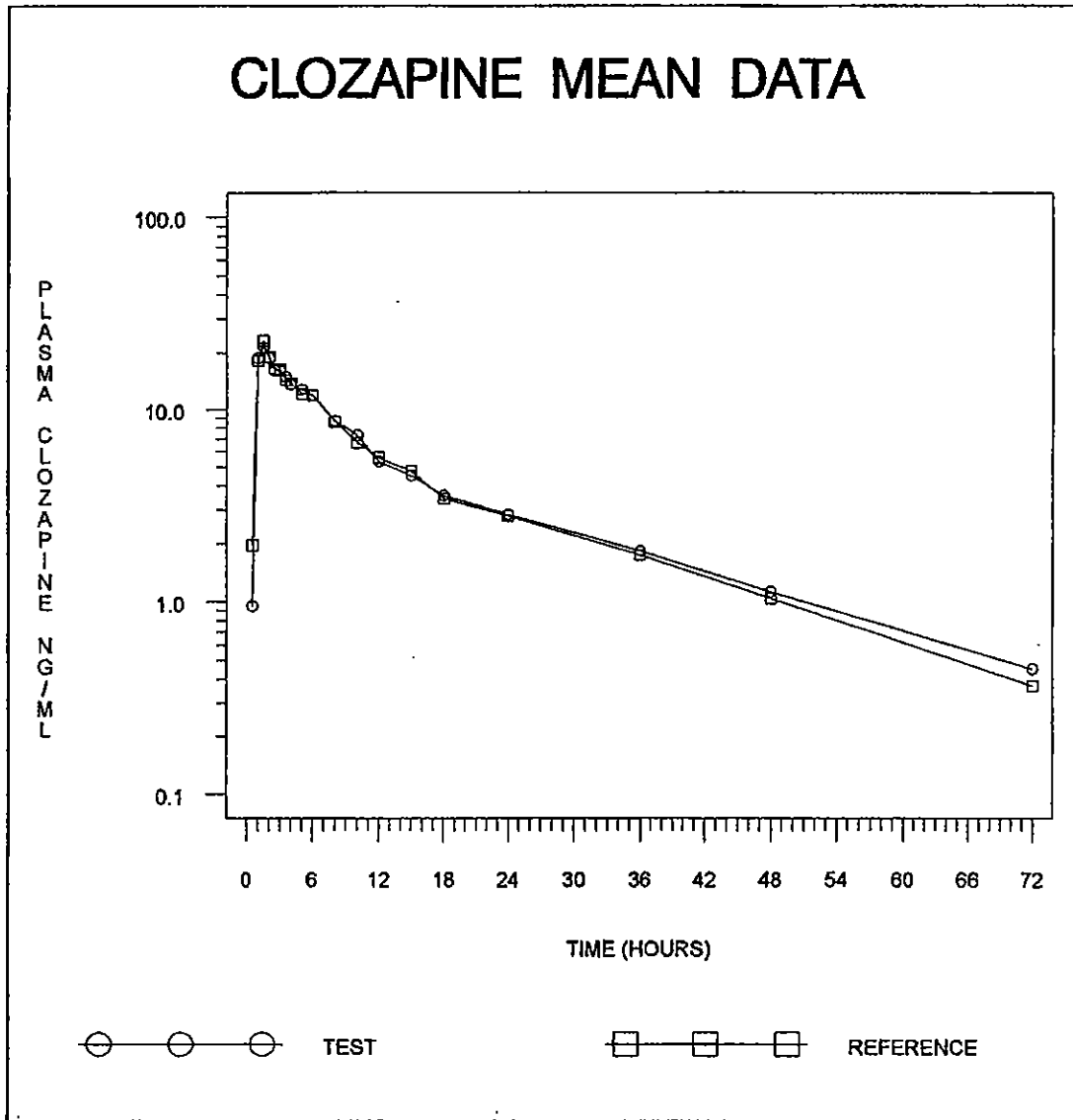
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CLOZAPINE 25 MG TABLET STUDY

Figure 1



CLOZAPINE 25 MG TABLET STUDY

Figure 2

