E. Restrictions:

Before and during each study phase, water may be allowed *ad libitum* except for 1 hour before and after drug administration. The subject should be served standardized meals and beverages at specified times. No alcohol or xanthine- or caffeine-containing foods and beverages should be consumed for 48 hours before each study period and until after the last blood sample is collected.

F. Blood Sampling:

Blood samples should be collected in sufficient volume for analysis of parent drug and active metabolite(s), if any. The sampling times should be such that it should be able to capture the C_{max} and T_{max} during the absorption period. Sampling should be carried out for at least three terminal elimination half-lives for both parent drug and active metabolite(s). Whole blood, plasma, or serum, whichever is appropriate for the analytes, should be harvested promptly and samples should be frozen at -20 °C or -70 °C to maintain sample stability.

G. Analytical Method:

The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery, and stability of the samples under the storage and handling conditions associated with the analytical method.

H. Pharmacokinetic Analysis:

From the plasma drug concentration-time data, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{e1} and $t_{1/2}$ should be estimated.

I. Statistical Analysis:

Analysis of variance appropriate for a crossover design on the pharmacokinetic parameters using the general linear models procedures of SAS or an equivalent program should be performed, with examination of period, sequence, and treatment effects. The 90 percent confidence intervals for the estimates of the difference between the test and reference least squares means for the pharmacokinetic parameters (AUC_{0-t}, AUC_{0-inf}, Cmax) should be calculated, using the two one-sided t-test procedure.

Appendix A

Narrow Therapeutic Range Drugs

Aminophylline Tablets, ER Tablets
Carbamazepine Tablets, Oral Suspension
Clindamycin Hydrochloride Capsules
Clonidine Hydrochloride Tablets
Clonidine Transdermal Patches
Dyphylline Tablets
Disopyramide Phosphate Capsules, ER Capsules
Ethinyl Estradiol/Progestin Oral Contraceptive Tablets
Guanethidine Sulfate Tablets
Isoetharine Mesylate Inhalation Aerosol
Isoproterenol Sulfate Tablets
Lithium Carbonate Capsules, Tablets, ER Tablets
Metaproterenol Sulfate Tablets
Minoxidil Tablets
Oxtriphylline Tablets, DR Tablets, ER Tablets
Phenytoin, Sodium Capsules (Prompt or Extended), Oral Suspension
Prazosin Hydrochloride Capsules
Primidone Tablets, Oral Suspension
Procainamide Hydrochloride, Capsules, Tablets, ER Tablets
Quinidine Sulfate Capsules, Tablets, ER Tablets
Quinidine Gluconate Tablets, ER Tablets
Theophylline Capsules, ER Capsules, Tablets, ER Tablets
Valproic Acid Capsules, Syrup
Divalproex, Sodium DR Capsules, DR Tablets
Warfarin, Sodium Tablets
ER - Extended Release
DR - Delayed Release

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William B. Schultz,

Deputy Commissioner for Policy.

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