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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-545/S-007

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:20,545 (SCM-007)	**Submission Date:**	September 28, 2001
Drug Name:	Procanbid (procainamide hydrochloride)	
Formulation:	Extended release tablets, 500 and 1000 mg	
Applicant:	King Pharmaceuticals Research and Development	
Submission:	Supplemental NDA: bioequivalence study	
Reviewer:	Elena V. Mishina, Ph.D.	

BACKGROUND:

Procanbid (procainamide hydrochloride) is a group 1A cardiac antiarrhythmic agent that reduces impulse conduction velocity in atria, His-Purkinje fibers, and ventricular muscle and has variable effects on the atrioventricular (AV) node. The drug causes peripheral ganglionic blockade and has weak anticholinergetic action and slight negative inotropic action. Procanbid is indicated for the treatment of documented ventricular arrythmias such as sustained ventricular tachycardia that, in the judgement of the physician, are life-threatening.

Procanbid extended release tablets are produced now at [redacted] A new manufacturing site is at Greenville, North Carolina (GNC). In compliance with SUPAC-MR requirements to the manufacturing site change, the sponsor conducted the comparative biequivalence study in vivo on the 1000 mg tablets. The biowaiver criteria for the same changes being made to lower strength (500 mg) of the Procanbid extended release tablets have been met. Additionally, the sponsor performed an in vitro comparative dissolution study on both 500 mg and 1000 mg tablets in the four prescribed media. With this supplemental NDA 20,545 (SCM 007), the sponsor submitted for review the results of these two studies.

RESULTS:

The study comparing two products, the one manufactured at Greenville, North Carolina (GNC), test, and the other at [redacted], reference, showed that the 2 products were bioequivalent based on the comparison of AUC and Cmax for both parent drug (procainamide) and its metabolite (N-acetylprocaiamide, NAPA).

The main pharmacokinetic parameters are summarized in Table 1 (procainamide) and Table 2 (NAPA).

Table 1. Comparison of Pharmacokinetic Parameters for Procainamide

PK Parameter	Test Treatment A	Reference Treatment B	Ratio (A/B)	90% C.I.
AUCT [ug*hr/mL]	17.3088	17.0580	1.0147	95.69 - 107.25
(Geometric Mean)	16.3972	16.0564	1.0212	
ln AUCT [ug*hr/mL]	2.7971	2.7761	1.0212	95.79 - 108.87
AUCI [ug*hr/mL]	18.3402	18.2196	1.0066	94.18 - 107.14
(Geometric Mean)	17.4069	17.0819	1.0190	
ln AUCI [ug*hr/mL]	2.8569	2.8380	1.0190	94.87 - 109.46
Cmax [ug/mL]	1.3027	1.2115	1.0753	101.36 - 113.70
(Geometric Mean)	1.2561	1.1651	1.0781	
ln Cmax [ug/mL]	0.2280	0.1528	1.0781	102.12 - 113.82

Table 2. Comparison of Pharmacokinetic Parameters for NAPA

PK Parameter	Test Treatment A	Reference Treatment B	Ratio (A/B)	90% C.I.
AUCT [ug*hr/mL]	14.7643	13.9045	1.0618	100.13 - 112.24
(Geometric Mean)	13.4061	12.6990	1.0557	
ln AUCT [ug*hr/mL]	2.5993	2.5449	1.0559	98.52 - 113.18
AUCI [ug*hr/mL]	15.8974	15.1649	1.0483	97.91 - 111.75
(Geometric Mean)	14.5486	13.9312	1.0443	
ln AUCI [ug*hr/mL]	2.6812	2.6371	1.0451	96.76 - 112.87
Cmax [ug/mL]	0.5813	0.5137	1.1316	106.49 - 119.84
(Geometric Mean)	0.5358	0.4806	1.1150	
ln Cmax [ug/mL]	-0.6220	-0.7325	1.1168	105.80 - 117.89

Additionally, the in vitro comparative dissolution study showed that the two products have similar dissolution profiles in the four prescribed media for parent drug. The dissolution profiles of the 1000 mg tablet were similar in the three prescribed media but were not similar in water. The water media is recognized as the least relevant medium for the evaluation of drug dissolution profiles since it does not resemble a biological fluid.

RECOMMENDATION

The application is acceptable for meeting the Office of Clinical Pharmacology and Biopharmaceutics requirements and shows that the product manufactued by King Pharmaceuticals at Greenville, North Carolina is bioequivalent to the product manufactured at [redacted] The new manufacture site at Greenville may be approved from a biopharmaceutics point of view.

/S/

Date_____

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

/S/

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

cc list: NDA 20545, MehulM, MishinaE, HFD 110 BIOPHARM

Comparative, Randomized, Single-Dose, Two-Way Crossover Bioavailability Study of King Pharmaceuticals Procainamide HCL (Procanbid) 1000 mg Extended Release Tablets Manufactured at Two Different Sites in Healthy Adult Males and Females under Fasting Conditions

STUDY ID: K772-00-1001 **Volumes:** 3-6

Principal Investigator: [redacted] MD

Sites:

Clinical:

[redacted]

Analytical:

[redacted]

OBJECTIVES:

To compare the single dose bioavailability under fasting conditions of two batches of 1000 mg Procainamide HCL 1000 mg extended release tablets (Procanbid) manufactured at two different sites.

METHODS:

Study Design:

Open label, randomized, two-way crossover study to compare the single dose bioavailability under fasting conditions of 1000 mg Procainamide HCL extended release tablets (Procanbid) manufactured at two sites. Healthy subjects were screened within 21 days of the first dose period. Initially, 26 subjects were enrolled followed by additional 9 subjects a week later. Totally, 32 subjects have completed the study. In Period I, all subjects were randomly assigned to the Treatment A or B. In dosing Period II, subjects received an alternative treatment. The tablets were taken with 240 mL of water after 10 hours of overnight fast. They remained upright for the next 4 hours after the dose.

Formulations:

Treatment A, test product: King Pharmaceuticals 1000 mg Procainamide HCL extended release tablets (Procanbid) manufactured at Greenville, NC, Lot # OK2728, size [redacted]

Treatment B, reference product: King Pharmaceuticals1000 mg Procainamide HCL extended release tablets (Procanbid) manufactured at [redacted] Lot # 881202

Mode of administration. Single oral dose.

Washout period. Each period was separated by at least 7-day wash-out.

Biological Analytes: Blood samples were collected pre-dose and 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48, and 72 hours post-dose.

Assay:

The plasma samples were assayed for procainamide and NAPA using a validated [redacted] method.

Specificity: satisfactory.

Linearity: satisfactory. The assay calibration range was — mcg/mL to — mcg/mL for procainamide and NAPA.

Limit of quantitation was set to — mcg/mL.

Precision and accuracy: satisfactory.

Intra-assay

Procainamide:

At the limit of quantitation:
CV — % Difference from theoretical —%
All other concentrations:
CV between — and —% Difference from theoretical — %.

NAPA:

At the limit of quantitation
CV — % Difference from theoretical —%
All other concentrations
CV between — and — % Difference from theoretical — %.

Inter-assay

Procainamide:

At the limit of quantitation
CV — % Difference from theoretical — %
All other concentrations
CV between — % Difference from theoretical —%.

NAPA:
At the limit of quantitation
CV — % Difference from theoretical — %
All other concentrations
CV between — % Difference from theoretical — %.

Data Analysis: Pharmacokinetic parameters (AUCt and AUCinf) were calculated using noncompartmental methods. Cmax and Tmax values were extracted from raw data. ANOVA model was used to compare the effect of treatment. It included sequence, subject with sequence, treatment and phase. ANOVA was performed on log-transformed parameters.

RESULTS:

Procainamide: no statistical sequence and treatment effects were observed. The calculated 90% confidence intervals were (94.87, 109.46), AUCinf, (95.79, 108.87), AUCt, and 102.12, 113.82), Cmax.

NAPA: no statistical sequence and treatment effects were observed. The calculated 90% confidence intervals were (96.76, 112.87), AUCinf, (98.52, 113.18), AUCt, and 105.80, 117.89), Cmax.

The results for procainamide and NAPA are summarized in Tables 1 and 2.

Table 1. Comparison of Pharmacokinetic Parameters for Procainamide

PK Parameter	Test Treatment A	Reference Treatment B	Ratio (A/B)	90% C.I.
AUCT [ug*hr/mL]	17.3088	17.0580	1.0147	95.69 - 107.25
(Geometric Mean)	16.3972	16.0564	1.0212	
ln AUCT [ug*hr/mL]	2.7971	2.7761	1.0212	95.79 - 108.87
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(Geometric Mean)	17.4069	17.0819	1.0190	
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Cmax [ug/mL]	1.3027	1.2115	1.0753	101.36 - 113.70
(Geometric Mean)	1.2561	1.1651	1.0781	
ln Cmax [ug/mL]	0.2280	0.1528	1.0781	102.12 - 113.82

Table 2. Comparison of Pharmacokinetic Parameters for NAPA

PK Parameter	Test Treatment A	Reference Treatment B	Ratio (A/B)	90% C.I.
AUCT [ug*hr/mL]	14.7643	13.9045	1.0618	100.13 - 112.24
(Geometric Mean)	13.4061	12.6990	1.0557	
ln AUCT [ug*hr/mL]	2.5993	2.5449	1.0559	98.52 - 113.18
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Cmax [ug/mL]	0.5813	0.5137	1.1316	106.49 - 119.84
(Geometric Mean)	0.5358	0.4806	1.1150	
ln Cmax [ug/mL]	-0.6220	-0.7325	1.1168	105.80 - 117.89

These results prove that procainamide manufactured at Greenville, NC is bioequivalent to procainamide manufactured

Dissolution:

The dissolution method used apparatus II with 900 mL of media at a paddle speed of 50 rpm (approved dissolution method).

Dissolution profiles of 500 and 1000 mg tablets manufactured at both sites were obtained in four types of media:

0.1 N HCL and 0.05 M pH 7.5 potassium phosphate buffer (approved medium);
Water;
0.1 N HCL;

0.05 M pH 7.5 potassium phosphate buffer.

The mean dissolution profiles in the approved media for 12 single capsules of procainbid for both lots from the two different manufacturing sites are compared in figures 1 and 2 (500 mg and 1000 mg tablets).

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Figure 1. Procainbid 500 mg tablets

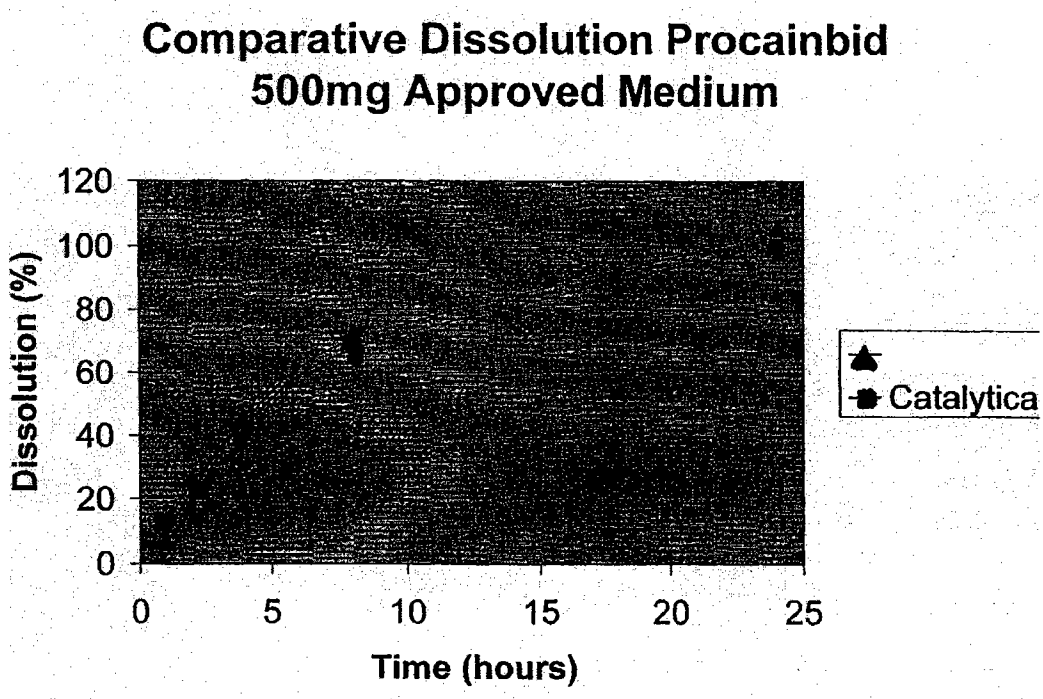
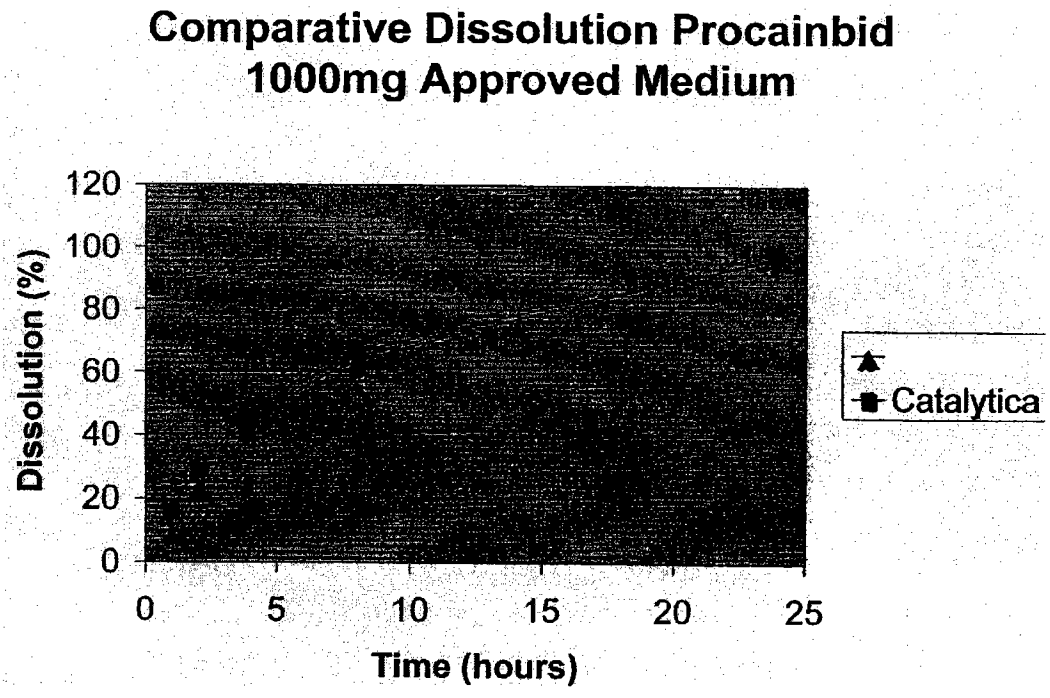


Figure 2. Procainbid 1000 mg tablets



Multi-point dissolution profile data are shown in Table 3 (500 mg tablet) and Table 4 (1000 mg tablet).

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COMMENTS:

The results of bioequivalence study and in vitro comparative dissolution study show that the procanbid tablets manufactured at Greenville, NC are bioequivalent to procainamide tablets manufactured at [redacted]

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