OFFICE of CLINICAL PHARMACOLOGY

sNDA:	**19-901 S050**
Brand Name:	**Altace**
Generic Name:	Ramipril
Applicant:	King Pharmaceuticals,™ Inc.
Submission:	Pediatric Supplement
Therapeutic Class:	Angiotensin-converting enzyme inhibitor
Dosage Form & Strength:	PO (capsules) 2.5, 5, 10 mg
Indication:	Hypertension in Pediatric Patients
Dosing Regimen	2.5 mg to 20 mg PO daily
Primary Reviewer:	Elena V. Mishina, Ph.D.

EXECUTIVE SUMMARY

RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed NDA 19-901 and finds the clinical pharmacology and biopharmaceutics sections acceptable.

A single-dose of Ramipril was administered to 33 pediatric patients. Patients were stratified by age (2 to 6 years, 7 to 12 years, and 13 to 16 years) and were randomized to receive either low (0.05 mg/kg) or high (0.2 mg/kg) dose ramipril, up to a maximum dose of 20 mg.

The pharmacokinetics of ramipril and its active metabolite ramiprilat were assessed over a 26-hour period (rich data file). The blood pressure was monitored over a 26-hour period. Only the PK data were analyzed using both non-compartmental and population approaches.
Following low-dose administration, ramipril peak concentrations (Cmax) of 4.9 ng/mL was achieved at 0.5 hours (median) and ramiprilat Cmax of 5.5 ng/mL was achieved at 3 hours.
Following high-dose administration, ramipril Cmax of 27.3 ng/mL was achieved at 0.5 hours (median) and ramiprilat Cmax of 27.0 ng/mL was achieved at 2 hours.
Exposure (Cmax, AUC0-24 and AUC0-∞) to ramipril and ramiprilat increased with dose, but not in a dose-proportional manner. The mean harmonic half-life of ramipril was longer after the low-dose (6.9 hours) than after the high-dose (5.5 hours).

The population PK models were fitted separately to the ramipril and ramiprilat plasma concentration vs. time data. The inter-subject variabilities of CL and V2 were moderate for ramipril (42 and 35%) and they were higher for ramiprilat (65 and 113%). The mean values of ramipril clearance were similar for the high and low doses (4.7 vs. 4.6 L/min) with body weight as the only significant covariate. The ramiprilat clearance was influenced by body weight and treatment group: it was estimated much higher for the high dose group compared to the low dose group (0.58 vs. 0.23 L/min). These results confirm the nonlinearity in the ramiprilat PK at the two studied doses.

The pharmacodynamics (blood pressure and heart rate) data in this study had very high inter-patient variability. The decrease in BP was more pronounced in the high-dose group. The maximal decreases in average SBP and DBP were achieved at 4 hours (5.2 ± 9.8 and 3.6 ± 8.2 mmHg, low dose), at 2 hours (3.4 ± 14.6 and 5.9 ± 11.3 mmHg, high dose) post dose, and for the patients 13-16 years of age received low dose at 8 hours post dose (7.6 ± 3.3 and 8.4 ± 9.0 mmHg). When the data were averaged by age groups, the mean values of SBP and DBP changes were different for each group; however, due to high variability and small number of patients per groups (4-6 patients), the differences were not statistically significant.

The blood pressure lowering effect was not correlated with the ramipril or ramiprilat plasma concentrations.
In the low treatment arm, 2-6-year old children have an increased heart rate (up to 63 bpm) and 7-12 years old children had somewhat lower heart rate (decrease by 6 bpm). In the other groups the fluctuations of the changes in heart rate around the baseline values were random.
When the same doses (normalized by body weight) of ramipril were administered to adults and children, the exposure to ramipril (pro-drug) in children was smaller than in adults, the exposure to ramiprilat (active metabolite) estimated by both Cmax and AUC0-24 was similar in adults and children.

COMMENTS:

Issues not addressed by the sponsor:

1. Pharmacokinetic samples were not obtained in the pivotal study, thus the concentration-response relationship for ramipril and ramiprilat could not be established.

2. In the single dose study, the sponsor measured the blood pressure at the time of the pharmacokinetic samples; however, the sponsor did not attempt to characterize the relationship between the blood pressure changes and ramipril and ramiprilat plasma concentrations. It does not seem that the high dose of ramipril was more effective than the low dose.

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