NDA#19901

Supplement amendment: SE5-050

Sponsor: King Pharmaceuticals Research and Development, Inc.

Name of Finished Product: ALTACE@ Capsules

Name of Active Ingredient: Ramipril

Proposed indication: essential hypertension in children

EXECUTIVE SUMMARY

Introduction:

Altace@ (ramipril) is approved 1) for the treatment of hypertension, alone or in combination with thiazide diuretics, and 2) patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction.

Conclusion:

There is no indication that the use of ramipril in doses up to 20 mg is efficacious in children with hypertension. There were no unexpected safety events reported in this NDA supplement.

Summary:

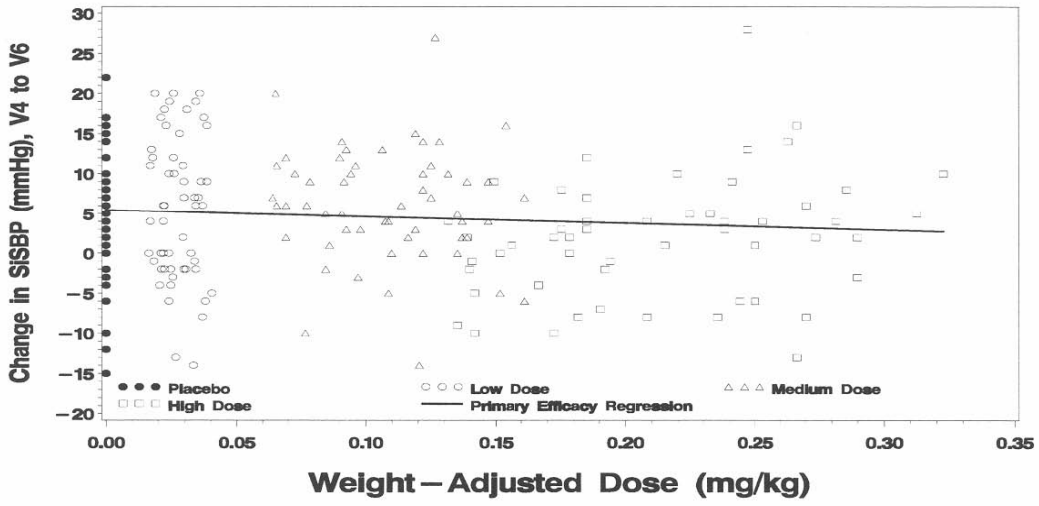
The data base for the use of ramipril in children consists of one efficacy study (Study K726-01-4002) and the 1-year extension, one pharmacokinetic study (K726-01-4001), and published and unpublished literature reviews.

Study K726-01-4002: A Dose-Escalation, Randomized Double-Blind Withdrawal Study of the Efficacy, Dose Response, and Safety of Ramipril for the Treatment of Hypertension in Children and Adolescents. The primary objective was to evaluate the efficacy of ramipril in children ages 6 to 16 years with hypertension. The design was dose-escalation, randomized, double-blind withdrawal. There were 4 phases: screening, dose-escalation (open-label), randomized withdrawal (double-blind), and 1 year follow-up (open-label). Hypertension was defined as a sitting systolic blood pressure (SiSBP) or sitting diastolic blood pressure (SiDBP) $\geq$ the 95th percentile for age, gender, and height, or $\geq$ the 90th percentile for age, gender, and height for subjects with diabetes mellitus or chronic renal insufficiency. Subjects were started on low-dose study drug at Visit 1 (0.625, 1.25, or 2.5 mg, depending on their screening weight). Thereafter, study drug was increased to the next higher dose at 10 - 2 days (2.5, 5, or 10 mg) and at 20 - 2 days (5, 10, or 20 mg). In the randomized withdrawal phase, eligible subjects were randomized within their weight group strata to 1 of 4 blinded dose groups (placebo, low dose, medium dose, and high dose) in a ratio of 1: 1: 1: 1. Treatment was up to 23 days. The subsequent open label follow-up phase continued up to 1 year.

Results: A total of 219 subjects were randomized: 55 to placebo, 54 to low-dose ramipril, 55 to medium-dose ramipril, and 55 to high-dose ramipril. The mean age was 11.8 years with 56% $\leq$ 12 years. The percent of male subjects was 57%, 29% were white, 42% were black, and 17% hispanic. Mean body weight index was 28.9 kg/m2 and 64% of subjects weighed more than 60 kg. The percent with Tanner stage 2 or less was 47%. Most subjects had been previously diagnosed as hypertensive.

The primary efficacy endpoint was the change in the SiSBP between randomization (Visit 4) and the end of the randomized withdrawal phase (Visit 6). The primary analysis of the linear dose response on the change in SiSBP during the withdrawal phase was not statistically significant (p=0.148). No other prospective analyses of SiSBP or SiDBP for the randomized withdrawal phase revealed significant results.

Figure 11-1 Dose-Response to Ramipril by Dose Group–SiSBP (ITT Withdrawal Population)



During the randomized withdrawal phase, there were no deaths, no reports of serious adverse events, and no study discontinuations because of an adverse event.

The cognitive development assessment by parents/guardians and by aggregate report card assessment indicated that the majority of subjects remained unchanged from baseline.

Follow up extension trial (completed)

There were 273 subjects in the 1-year open label safety follow up. There were no deaths. A total of 30 serious adverse events were reported and there were 4 discontinuations because of an adverse event.

Study K726-01-4001 (completed)

This was a randomized, open label, single dose pharmacokinetic study. The objective was to determine the pharmacokinetics of ramipril and its active metabolite, ramiprilat, in children and adolescents from 2 to 16 years of age. The pharmacokinetic results were reviewed by Elena Mishina, PhD. She concluded that “the exposure to ramipril (prodrug) in children was smaller than in adults, [and] the exposure to ramiprilat (active metabolite) estimated by both Cmax and AUC0-24 was similar in adults and children.”

Safety: There were 30 subjects in the safety population. There were no deaths, serious adverse events, or drop outs because of an adverse event.

ESCAPE (ongoing)

This is an uncontrolled, parallel group, randomized, open label study. Subjects are at least 2 years of age and suffer from progressive renal disease. The 2 treatment groups are 1) conventional blood pressure control group and 2) intensive blood pressure control group. The purpose of the trial is to investigate whether the use of vigorous antihypertensive treatment to achieve target blood pressure below the 50th percentile is beneficial for reducing the progression of chronic renal failure in children.

Unpublished safety data

These data were obtained by the sponsor review of post marketing safety information and from a physician survey of heathcare delivery to pediatric population.

The search of the sanofi aventis and King safety databases for spontaneous reports of adverse events involving children receiving ramipril yielded 8 cases. There were no deaths. There was one serious adverse event: acute pancreatitis (ramipril was discontinued and the patient recovered). There were 2 reports of accidental ingestion; there were no adverse events cited with either report.

The pediatrician survey yielded no reports of deaths. There is no indication from this survey that ramipril in children has a different safety profile from the one in adults.

Literature search

The objective of this search was to identify all published reports of ramipril use in children with hypertension. A search strategy was devised to identify all published studies that reported ramipril use in a hypertensive pediatric population. The sponsor collaborated with the International Pediatric Hypertension Association (IPHA) to query (via e-mail) clinicians treating pediatric patients. If the clinician had treated a child less than 18 years of age with ramipril for hypertension, but not as part of a research protocol, they contacted IPHA for a case report form. The clinician recorded demographic, dosing, and safety data on a case report form for each patient that met the criteria. Any serious adverse events that were judged to be associated with the use of ramipril were reported immediately to the sponsor who then contacted the clinician directly for further information and determined the need for further regulatory reporting.

There were 5 articles found that were published in a peer reviewed journal involving the use of ramipril in children with hypertension. All studies were uncontrolled, unblinded case series in roughly 440 patients with chronic kidney disease. The safety reports pertained to the initiation of dialysis, the progression to end stage renal disease, or expected safety associated with the use of ramipril. Hyperkalemia resulted in the discontinuation of one patient. There were reports of mild decreases in hematology values.

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