**Title:** Population pharmacokinetic analysis of perindoprilat in hypertensive paediatric patients

**Authors:** Céline M Laffont* (1), France Mentré (2), Emmanuelle Foos-Gilbert (1)

**Institutions:** (1) Servier Research Group, Courbevoie, France; (2) INSERM U738, Paris, France; Université Paris 7, Paris, France

**Background:** The use of angiotensin-converting enzyme (ACE) inhibitors in the treatment of children suffering from hypertension or congestive heart failure has been widely recognized as useful. However, little is known about the pharmacokinetics of ACE inhibitors in this population of patients.

**Objective:** To develop a population pharmacokinetic model for perindoprilat in paediatric patients using both paediatric and adult data.

**Methods:** An orodispersible formulation of perindopril (prodrug) was developed for paediatric use. This formulation was administered once per day to 59 hypertensive children and adolescents [median age (range) = 6 (2-15) years] in a 4-month Phase II study. It was also given once per day to 24 healthy adult volunteers for one week in a Phase I study. Sparse (n=3-5) or extensive (n=11) blood sampling was performed at steady-state in the Phase II and Phase I studies, respectively. Perindoprilat plasma concentrations in paediatric patients (250 observations) were analyzed together with adult data (263 observations) in order to better evaluate the impact of body weight on perindoprilat pharmacokinetic parameters. The population pharmacokinetic analysis was performed using NONMEM version 5.1.

**Results:** Perindoprilat plasma concentrations were analyzed as the sum of unbound perindoprilat concentrations (i.e. not bound to circulating ACE) and concentrations of perindoprilat bound to circulating ACE. Unbound concentrations were best described by a one-compartment model with first-order formation and lag-time. Perindoprilat binding to ACE was modeled using a Michaelis-Menten relationship, assuming a single saturable binding site. Since it was not possible to estimate perindoprilat binding parameters from the present data, those were fixed to parameter estimates found in a previous population analysis in adults, for which adequate blood sampling was performed. Perindoprilat apparent clearance (CL/F) and volume of distribution (V/F) were related to body weight using general allometric equations (power model). Estimation of power model parameters revealed that CL/F and V/F increased almost proportionally with body weight. Creatinine clearance was estimated from serum creatinine using Schwartz formula. It was found to significantly influence CL/F and V/F, which is consistent with previous findings in adults [1] and the renal elimination of perindoprilat. Altogether, body weight and creatinine clearance explained a large part of the between-subject variability in CL/F and V/F for the paediatric population.

**Conclusions:** This population PK model provides a rationale for the adjustment of the initial therapeutic dose in paediatric patients (which may be further modified based on clinical evaluation). The initial therapeutic dose should be administered on a µg/kg basis, and should be reduced in case of moderate renal impairment in agreement with the recommendations made in adults.

**References:**