Population Pharmacokinetic Model for Oral Endoxifen in Patients with Breast or Gynecologic Cancers

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Objectives: To develop a population pharmacokinetic (PK) model to describe variability in the pharmacokinetics of oral endoxifen, evaluate PK linearity over dose and time, and to guide dosing and future trial design.

Methods: Two Phase-I dose-escalation trials (NCT01273168, NCT01327781) were conducted in breast or gynecologic cancer patients receiving flat oral doses of 20-300 mg (Z)-endoxifen HCl daily, on 28-day cycles. Intensive sampling occurred on days 1 and 28, and troughs on days 7 and 14. 1087 cycle-1 concentrations in 63 patients (median weight 68.9 kg) were available. Numerical values were retained for concentrations below the lower limit of quantification (10 samples), and values below the limit of detection were entered as concentration zero (4 of these 10 samples). Nonlinear mixed-effects modeling was performed using NONMEM and Pirana software. The model was evaluated with goodness-of-fit plots and visual predictive check.

Results: A 2-compartment model with first-order elimination, first-order absorption, and an absorption lag adequately described the data; a combined proportional and additive residual error was used. The typical (% RSE) oral apparent clearance (CL/F), apparent volume of central compartment (V2/F), apparent volume of peripheral compartment (V3/F), apparent intercompartmental clearance (Q/F), absorption rate constant (ka), and absorption lag time were 4.63 L/hr (5%), 253 L (7%), 88.1 L (19%), 15.1 L/hr (32%), 0.984 hr⁻¹ (14%), and 0.418 hr (3%), respectively. Between subject variability (% RSE) for CL/F, V2/F, V3/F and ka were 39% (9%), 37% (15%), 48% (24%) and 99% (13%), respectively. BSV on Q/F could not be estimated. All shrinkages were below 10%, except 53% on V3/F. GOF and VPC plots were deemed to be adequate.

Conclusions: A population pharmacokinetic model was identified that demonstrated endoxifen PK parameters were linear in the dosing range of 20-300 mg, and were unchanged over 28 days of dosing.