Population Pharmacokinetic and Exposure–Response Models of Once-Weekly Exenatide

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Objectives: Exenatide, a glucagon-like peptide-1 receptor agonist for the treatment of type 2 diabetes, was developed for once-weekly (QW) subcutaneous dosing. Exenatide-containing microspheres are delivered as suspensions in either aqueous (exenatide QW) or nonaqueous diluents (exenatide QWS suspension [QWS]). This analysis aimed to develop a population pharmacokinetic (PPK) model describing the average steady-state plasma exenatide concentration ($C_{ss,av}$) along with an exposure–response model linking exenatide $C_{ss,av}$ to glycated hemoglobin (A1C) for both formulations.

Methods: Pharmacokinetic and efficacy data were collected from 11 phase 2 and 3 clinical studies of exenatide QW (n=8) and exenatide QWS (n=3) with treatment periods of 12–28 weeks. Relationships between exenatide dose, $C_{ss,av}$, and A1C were described with a nonlinear mixed-effects regression model accounting for within- and between-patient variability and estimated using NONMEM Ver7.3.0.

Results: The exenatide models adequately described $C_{ss,av}$ data. Covariates retained in the final PPK model included baseline renal function (estimated glomerular filtration rate), manufacturing scale, ideal body weight, and anti-exenatide antibody titer. Baseline A1C and anti-exenatide antibody titer were significant predictors of A1C reduction in the exposure–response model. After accounting for other population covariates, exenatide QWS for autoinjection (AI) displayed approximately 10% lower $C_{ss,av}$ than exenatide QW. At steady state, the predicted difference in efficacy between exenatide QWS-AI and exenatide QW due to the exposure difference in a typical patient is ≤0.1%. A subgroup analysis using only data from the phase 3 studies with commercially available formulations and devices showed that exposure from the 2 products is not significantly different. The phase 2 and noncommercial batch studies that were excluded from the subgroup analysis had somewhat higher exposures than studies with the commercial product.

Conclusions: Modeling results support the conclusion that exenatide QW and exenatide QWS-AI yield comparable exenatide exposures and that robust efficacy is achieved regardless of age, race, sex, ideal body weight, renal function, or anti-exenatide antibody titer.