Simulated Exenatide Plasma Concentrations in Human Subjects Following Late, Shifted, or Missed Dosing of Exenatide Once-Weekly Suspension

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Objective: To characterize exenatide plasma exposure if a patient misses, delays, or shifts a regularly scheduled dose of exenatide once weekly suspension (QWS).

Methods: Using nonparametric superpositioning, multiple dose exenatide plasma concentrations ($C_{\text{exenatide}}$) were predicted for exenatide QWS 2 mg using pharmacokinetic data from healthy subjects given a single dose of exenatide QWS 10 mg (N=24). To assess scenarios involving a missed regularly scheduled exenatide QWS dose taken 3–6 days late before returning to the previous dose schedule or shifting the dose schedule by ≤3 days, $C_{\text{exenatide}}$ were simulated for weekly dosing and for perturbed dose timings. Complete discontinuation of a subject from regular dosing was also simulated.

Results: Simulated $C_{\text{exenatide}}$ following the initiation of regular dosing is shown in the Figure (left). The impact of perturbed dosing was greatest 6–7 weeks later, when the bulk of exenatide from that particular dose was to be released. For dosing delays ≤6 days or shifts in regular dosing ≤3 days, the impact on $C_{\text{exenatide}}$ was minor (<15%). A single missed dose led to a transient 30% decrease in $C_{\text{exenatide}}$ 6–7 weeks later. Discontinuation of exenatide QWS led to a minimal decline in $C_{\text{exenatide}}$ for 6 weeks followed by a decrease to undetectable concentrations by 10 weeks (Figure, right).

Conclusions: Given the small changes in $C_{\text{exenatide}}$ when exenatide QWS dosing is perturbed, no consequences for efficacy, safety, or tolerability are expected. The slight effects of perturbed dosing on $C_{\text{exenatide}}$ are minimized when patients take their regularly scheduled dose as soon as possible and return to their usual dose schedule. Patients may also shift their regular dosing day of the week by up to 3 days without concern. Patients discontinuing exenatide may retain its therapeutic effect for up to 8 weeks. Those beginning new therapy should be considered treated with both medications for up to 8 weeks.