Clinical Pharmacology Summary (NDA 20-955 / SE5-006)

Single dose pharmacokinetics were determined after the administration two Ferrlecit doses in pediatric patients with iron deficiency undergoing chronic hemodialysis that were receiving supplemental erythropoietin therapy. Patients determined to be iron-deficient following suspension of their normal iron supplementation for 4 weeks (i.e., at Screening Visit 5), were randomized to a Ferrlecit dose of either 1.5 mg/kg (n = 22) or 3.0 mg/kg (n = 26), infused I.V. by syringe pump over 1 hour, not to exceed 125 mg per dose, during eight consecutive HD sessions over an approximate 22 day period. Blood samples were drawn for determination of Ferrlecit PK at 0 (pre-dose), 0.5, 1, 1.25, 1.5, 2, 3, 4, 6 and 48 hrs.

Table 1. Summary of the PK parameters following administration of 1.5 mg/kg and 3 mg/kg single doses of Ferrlecit to iron-deficient pediatric hemodialysis patients

Pharmacokinetic Parameter	1.5 mg/kg Ferrlecit® (n = 22)	3.0 mg/kg Ferrlecit® (n = 26)
C_{max} (mean ± SD μg/dL)	1287 ± 285	2283 ± 637
AUC_{0-48} (mean±SD μg•hr/dL)	9327 ± 4038	16,830 ± 6526
$AUC_{0-\infty}$ (mean ± SD μg•hr/dL)	9499 ± 4089	17,087 ± 6776
T_{max} (median hrs)	1.0	1.0
$t_{1/2}$ (median hrs)	2.0	2.1
K_{el} (mean ± SD hr-1)	0.43 ± 0.30	0.39 ± 0.27
Cl (mean ± SD L/hr)	0.69 ± 0.50	0.66 ± 0.52
V_d (mean ± SD L)	1.6 ± 0.6	1.9 ± 1.1

Mean serum iron concentrations (total iron and Ferrlecit®-bound iron) increased in a dose-dependent manner that is approximately proportional to the I.V. administered Ferrlecit dose (Table 1).

Table 2. Summary of the mean pediatric and adult PK parameters

Pharmacokinetic Parameter	Pediatric Population N = 22	Adult Population N = 7
C_{max} (mean; μg/dL)	1287	1551
$AUC_{0-\infty}$ (mean; μg•hr/dL)	9499	3772
$t_{1/2}$ (median; hrs)	2.0	-- *
Cl (mean; L/hr)	0.69	3.58
V_d (mean; liters)	1.62	13.4

Cmax values in the pediatric population were comparable to those of adults with similar Ferrlecit doses (125 mg infused over 1 hour). However, mean AUC values were approximately two-fold higher while total systemic clearance was five-fold lower in the pediatric population relative to the adults. In addition, the volume of

distribution (V_d) was around eight-fold lower in pediatric patients relative to adults (Table 2). Based on these data, a single dose of 1.5 mg/kg of Ferrlecit with a total dose of 125 mg per session should not be exceeded in pediatric patients with iron deficiency undergoing chronic hemodialysis that are receiving supplemental erythropoietin therapy.

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