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L0043 Pharmacokinetic Analysis of SUBA(TM)-Itraconazole Capsules Compared to Conventional Itraconazole Capsules for a 3-Day Loading Dose Regimen and After 15 Days of Administration

Stuart Mudge[1], Bruce Burnett*

[1] Mayne Pharma, Inc, Melbourne, Australia

Background: SUBA™-itraconazole (SI), which releases drug in the duodenum compared to conventional itraconazole (CI) in the stomach, was recently approved for treatment of systemic mycoses in the US. Two pharmacokinetic studies, a 3-day loading regimen and a 15-day steady-state, were performed comparing SI to CI to investigate their bioequivalence.

Materials/methods: Both studies were open-label, randomized, two-treatment, two-sequence, two-period, crossover, multiple-dose, oral bioequivalence studies under fed conditions in healthy adults. In the first study, 15 subjects administered SI (2x65mg) and CI (2x100mg) TID for 3 days and once on day 4 were analyzed. Blood samples were collected on days 1-4 prior to administration and over 8 hours post-dose on day 4. In the second study, 16 subjects administered SI (2x65mg) and CI (2x100mg) BID for 14 days and a last dose 30min after a meal on day 15 were analyzed. Blood samples were collected on days 1, 13, 14, and 15 prior to administration and from 0.5 to 12 hours post-dose on day 15. Analysis was by least-squares-geometric means of $C_{max,ss}$, C_{trough} and AUC_{tau}.

Results: In both the loading dose and steady-state studies, $C_{max,ss}$, C_{trough} and AUC_{tau} of itraconazole/hydroxyitraconazole for SI were consistently higher compared to CI (Table). The 90% confidence intervals of the relative mean plasma itraconazole levels of $C_{max,ss}$ and AUC_{tau} for SI, however, were between 80.00 and 125.00% demonstrating bioequivalence to CI. From patient level data, 81% of SI subjects achieved a C_{trough} mean level of >1000ng/mL *vs* 44% for CI at steady-state. When the C_{trough} was corrected for dosage of each formulation [1.18(100mg/65mg)], the relative bioavailability of the SI was 1.82 compared to CI. The study drugs were well-tolerated in both studies. All TEAEs resolved at the end of the studies. One CI subject discontinued due to an AE in the steady-state study. No SAEs were reported.

Conclusions: Total and peak itraconazole exposure was relatively similar between treatments, but SI achieved almost 2x greater relative bioavailability than CI with a similar safety profile. This new, more bioavailable formulation may offer a benefit in the treatment of systemic mycoses by maintaining blood levels of itraconazole in patients.

3-Day Loading Dose Study (N=16 Enrolled, 1 dc'd due to protocol deviation)								
	SI: itraconazole	CI: itraconazole			SI: hydroxy-itraconazole	CI: hydroxy-itraconazole		
Parameter	Geometric Mean	Geometric Mean	SI/CI Ratio (%)	90% Confidence Interval	Geometric Mean	Geometric Mean	SI/CI Ratio (%)	90% Confidence Interval
Cmax,ss (ng/mL)	1055.3	921.3	114.54	103.40-126.88	1691.0	1543.3	109.57	101.45-118.35
Ctrough (ng/mL)	881.1	820.6	107.37	95.58-120.62	1640.8	1508.8	108.75	100.39-117.80
AUCtau (hr*ng/mL)	6881.7	6236.2	110.35	100.10-121.66	12632.7	11317.0	111.63	103.15-120.80
15-Day Steady-State Study (N=24 Enrolled, 7 dc'd due to not receiving all doses, 1 dc'd due to AE)								
Cmax,ss (ng/mL)	1632.2	1457.5	111.99	104.87-119.59	2613.6	2338.9	111.75	105.89-117.93
Ctrough (ng/mL)	1187.4	1004.9	118.16	110.20-126.69	2335	2061.7	113.26	107.39-119.44
AUCtau (hr*ng/mL)	15562.1	14065.1	110.64	104.01-117.70	28143.4	25488.1	110.42	104.28-116.91