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APPLICATION NUMBER:

21-742

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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9/17/07

Pharmacometrics Review
Office of Clinical Pharmacology

NDA:	**21-742**
Compound:	**Nebivolol**
Submission Dates:	**May 31, 2007**
Applicant:	**Mylan Bertek**
Type of submission:	**2nd cycle review (Standard)**
Pharmacometrics Reviewer:	**Yaning Wang, Ph.D.**
Secondary Reviewer:	**Jogarao Gobburu, Ph.D.**

Is higher exposure of nebivolol, e.g. observed in poor metabolizers (PM), associated with more suppression of adrenal function, luteinizing hormone, or testosterone levels in male?

No. Exposure response analyses were performed for nebivolol based on data from Study NEB-PK-03 (Effects of Nebivolol on Adrenal Function, Luteinizing Hormone, and Testosterone Levels in Healthy Male Volunteers). Detailed study design is referred to Dr. Keren Hicks' review. Nine safety endpoints were measured in Study NEB-PK-03, which included area under the curve from time zero to 120 minutes (AUC0-120 min) of ACTH-stimulated (IV dose of 250 µg) serum cortisol levels, AUC0-120 min of serum aldosterone levels after the IV administration of ACTH (250 µg), sex hormone binding globulin, total testosterone level, free testosterone level, mean luetinizing hormone value, peak post-ACTH cortisol level, peak post-ACTH aldosterone above basal level, and peak post-ACTH cortisol above basal level. Under nebivolol 10 mg QD regimen, steady state trough concentration for either l-nebivolol or d-nebivolol was not found to be related to change in any of the 9 safety endpoint after 7 weeks of treatment in healthy male volunteers despite that 4 poor metabolizers achieved significantly higher exposure of l-nebivolol or d-nebivolol (Table 1, Figure 1 and Figure 2). The exposure of l-nebivolol or d-nebivolol was set to be zero for subjects taking placebo. No significant difference was observed between placebo and nebivolol groups in terms of change from baseline for any of the 9 endpoints (Table 2). The only endpoint suggesting a relationship with nebivolol exposure is free testosterone level as indicated by the marginal significant p-values in both regression analysis and t-test. However, the direction of this relationship is opposite of hormone suppression, which is highly influenced by one outlier observation in nebivolol group (patient 59038 with 18 unit increase in free testosterone level at the end of study). The same influence was also observed for total testosterone level. Four poor metabolizers had higher peak post-ACTH aldosterone above basal level compared to either extensive metabolizers (EM) or placebo subjects (Table 3). Overall, these results do not support the observation from animal data which suggested suppression of male hormone by nebivolol.

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Endpoint	Group	N	Mean	Lower	Upper	P-value
Area Under Curve (0-120 min) Aldosterone	Nebivolol	42	-0.58	-2.87	1.72	
	Placebo	48	1.01	-0.30	2.33	
	Difference (Nebivolol-Placebo)		-1.59	-4.12	0.94	0.21
Area Under Curve (0-120 min) Cortisol	Nebivolol	42	0.44	-0.93	1.80	
	Placebo	48	0.77	-0.54	2.07	
	Difference (Nebivolol-Placebo)		-0.33	-2.19	1.53	0.73
Free Testosterone Level	Nebivolol	42	1.00	-0.10	2.10	
	Placebo	48	-0.25	-1.10	0.60	
	Difference (Nebivolol-Placebo)		1.25	-0.10	2.60	0.07
Free Testosterone Level*	Nebivolol	41	0.59	-0.14	1.32	
	Placebo	48	-0.25	-1.10	0.60	
	Difference (Nebivolol-Placebo)		0.84	-0.29	1.97	0.14
Mean Luetinizing Hormone Value	Nebivolol	42	0.04	-0.44	0.52	
	Placebo	48	0.11	-0.23	0.45	
	Difference (Nebivolol-Placebo)		-0.07	-0.64	0.49	0.80
Peak Post-ACTH Aldosterone Above Basal	Nebivolol	42	-0.20	-1.77	1.37	
	Placebo	48	-0.32	-1.68	1.05	
	Difference (Nebivolol-Placebo)		0.12	-1.93	2.16	0.91
Peak Post-ACTH Cortisol	Nebivolol	42	0.20	-0.56	0.96	
	Placebo	48	0.28	-0.40	0.96	
	Difference (Nebivolol-Placebo)		-0.08	-1.08	0.92	0.87
Peak Post-ACTH Cortisol Above Basal	Nebivolol	42	0.11	-1.41	1.64	
	Placebo	48	-1.08	-2.41	0.24	
	Difference (Nebivolol-Placebo)		1.20	-0.79	3.18	0.23
Sex Hormone Binding Globulin	Nebivolol	42	-0.57	-1.93	0.80	
	Placebo	48	0.60	-0.50	1.70	
	Difference (Nebivolol-Placebo)		-1.17	-2.88	0.54	0.18
Testosterone, Total	Nebivolol	42	26.64	-6.66	59.95	
	Placebo	48	-2.90	-31.74	25.95	
	Difference (Nebivolol-Placebo)		29.54	-13.67	72.75	0.18

* Without an influential point in nebivolol group

Table 3. ANOVA comparison results for peak post-ACTH aldosterone above basal level

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Group	Estimate	N	95% CI Lower	95% CI Upper	P-value*
Nebivolol (PM)	6.90	4	2.30	11.50	
Nebivolol (EM)	-0.94	38	-2.44	0.55	
Placebo	-0.31	48	-1.64	1.01	
Difference (PM-Placebo)	7.21		2.43	12.00	0.004
Difference (PM-EM)	7.84		3.01	12.68	0.002
Difference (EM-Placebo)	-0.63		-2.63	1.37	0.532

* Not adjusted for multiple comparisons; PM, poor metabolizers; EM, extensive metabolizers.

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