CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-021

MEDICAL REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 7, 2007

FROM: Abraham Karkowsky, M.D., Ph.D., Acting Deputy Director, Division of Cardiovascular and Renal Products HFD-110

TO: Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products HFD-110

SUBJECT: Approvability of Altace tablets (Cobalt Pharmaceuticals, Inc.; NDA 22-021)

This memo supports the approvable recommendation for the use of Ramipril tablets (Altace, Cobalt pharmaceuticals). The indications covered by this approvable recommendation are all the currently approved INDICATIONS for Altace capsules. Despite a modest food effect on Ramipril concentrations and a smaller effect on the more active Ramiprilat concentrations, for the tablet compared to the approved capsule, I did not recommend any limitations on dosing relative to food.

Approval of Altace tablets awaits the several additional pieces of information:

- The assignment of an appropriate expiration date for the drug product. The expiration date for the drug product will be assigned pending the application of the Division's recommended dissolution specifications to current and future stability assessments.

  With respect to dissolution specification, the Agency recommended the following solutions, apparatus and conditions. These conditions differed from the sponsor's original proposal.

Apparatus	Paddle method
Medium	0.1N HCl, pH 1.2
Rpm	50 rpm
Volume	500 ml

  Q= ————————

- Also pending is a complete review of the drug substance from the new API (active pharmaceutical ingredient) supplier, ———————— The sponsor has yet

to submit the "Letter-of-Authorization", allowing FDA to access its Drug Master File.

Cobalt pharmaceutics was given the right to reference the entire NDA 19-901 (Altace capsules). The current submission, therefore, is reviewed as a (b) (1) submission and INDICATIONS for Altace capsules can be claimed by Altace tablets. Any pediatric studies that would be required are also covered by the above NDA. The labeling of Ramipril tablets will largely be defined by the current approved Altace capsule labeling.

The pivotal new information was reviewed by C. Noory (Division of Clinical Pharmacology) and P. Shiromani (Office of drug Quality Assessment). There were no new clinical or pharmacology studies submitted. Dr. Resnick's recommended that the preclinical information contained in the King Altace capsule be used for the tablet.

Housekeeping issues:

- The agency considered the CMC inspections as satisfactory.
- DSI inspected the three biopharmaceutic studies (see below).
- A waiver for the performance of an environmental assessment was granted.
- A DDMAC consult on Drug labeling from Lisa Hubbard, R. Ph., was based on the initial patent certification that precluded use of patents covering heart failure. Since, however King pharmaceuticals allowed complete right to reference for the entire NDA19-901, all of the capsule INDICATIONS can be applied to the Tablets.
- Form 3454 was supplied indicating no financial arrangements between the sponsor and the ———— who performed each of the ———— ———— were submitted.

Chemistry:

P. Shiromani recommended approval of the Ramipril tablet at doses of 1.25, 2.5, 5 and 10 mg. There were no deficiencies noted.

DSI review:

The DSI report (by Martin K. Yau, Ph.D; dated 22 November 2006) summarized the results of the inspection of all three biopharmaceutic studies for both the clinical and analytic integrity. A form 483 was issued was issued for the analytic portion of the study.

In several runs a few of a patients' Ramiprilat values (predominantly two subjects # 26 and #27) failed to meet the acceptability criteria. The Ramipril concentrations, however, were found to be acceptably measured. Upon subsequent runs to re-assay for Ramiprilat, the corresponding Ramipril measurement, during those runs for the same individuals differed substantially from those initially measured. These re-measured Ramipril values were not included in the calculation of the pharmacokinetic constants.

DSI recommended excluding the results for two subjects (#26 and #27) in study #2835 and subject #11 in study #2970. DSI also recommended excluding the results of selected time points for other subjects.

The results with the recommended DSI exclusions did not materially alter the results or conclusions of the study. Ms Noory recalculated the pharmacokinetic parameters with and without these subjects. The values are considered in tables 1-4 and labeled as (recalculated).

The DSI reviewer also noted substantial carry-over concentrations of Ramiprilat at baseline of the period 2 measurements. The magnitude of these effects corresponded to > 5% of the concentrations measured for that individual at Cmax. Although the washout period between treatments was a week, the duration was apparently not sufficiently long to washout all of the Ramiprilat. Since the effect of the carryover Ramiprilat would only serve to increase the variance, the successful study findings can be relied upon.

Clinical Pharmacology review:

Dr. Noory reviewed three biopharmaceutic studies.

- Study #2835, a cross-over bioequivalence study comparing the approved Ramipril capsule (Altace) to the proposed tablet formulation at a 10 mg dose.
- Study # 2836 was a crossover, bioequivalence study comparing fed pharmacokinetics comparing Ramipril 10 mg tablets to Altace 10 mg capsules.
- Study # 2970 was a crossover bioequivalence study under fasting conditions, comparing the 1.25 mg dose of Ramipril tablets to Altace 1.25 mg capsules.

The results of these studies established bioequivalence of the low (1.25) and high dose (10 mg) Ramipril tablet relative to Altace capsules under fasting conditions. The two intermediate doses of the tablets were granted biopharmaceutic waivers, based on formulation proportionality to the bioequivalent tablet strength. In addition, the two intermediate tablet doses demonstrated similarity of dissolution profiles to the Ramipril tablet that was utilized in the pharmacokinetic studies.

The formulations were not bioequivalent under fed conditions, predominantly based on the higher Cmax for the Ramipril. Ramipril is approximately 1/6 as active as the de-esterified ramiprilat with respect ACE-I. The extent of absorption under fed conditions for ramipril, however, was not substantially different for the two formulations. For ramiprilat, under fed conditions, the extent of absorption was bioequivalent (AUC measurements), Cmax for ramiprilat was outside the generall accepted allowed upper bioequivalence boundary. The lower estimate did not include 1.

Study # 2835 compared the 10 mg Altace capsules compared to 10 mg Altace tablets (N=34 enrolled). Bold values are the robustness assessments based on the recommendations of the DSI reviewer (see previous).

Table 1: Pharmacokinetic constants, study #2835, 10 mg Altace capsules compared to the tablets:

	Ramipril		Ramiprilat	
	Ramipril Tablet	Altace capsule	Ramipril Tablet	Altace capsule
AUC (0-t) ng x hr/ml **recalculated**	16.8 ± 5.5 **16.4 ± 5.4**	16.4 ± 5.3 **16.1 ± 5.2**	236.7 ± 54.3 **238.5 ± 56.7**	229.4 ± 61.7 **232.8 ± 62.7**
AUC 0-∞ ng x hr/ml **recalculated**	17.3 ± 5.4 (n=28) **16.9 ± 5.3 (n=26)**	17.4 ± 4.9 (n=29) **17.3 ± 4.7 (n=27)**		
Cmax ng/ml **recalculated**	27.6 ± 9.2 **26.7 ± 8.6**	25.1 ± 8.5 **25.6 ± 8.9**	23.7 ± 2.0 **23.9 ± 13.2**	23.2 ± 13.3 **23.7 ± 13.6**
Tmax hr **recalculated**	0.5 **0.5**	0.5 (n=29) **0.6 (n=27)**	3.5 (n=29) **2.2 (n=27)**	2.0 (n=29) **2.3 (n=27)**
T1/2	2.7 ± 1.6 (n=29)	3.1 ± 4.5 (n=18)	105 ±38	109 ± 16 (n=28)
Kel (hr-1)	0.37 ± 0.2	0.37 ± 0.2 (n=28)	0.0073 ± 0.002	0.0064 ± 0.0009

N=34 unless otherwise specified for the initial evaluation. N=32 for the recalculated analysis

Table 2: 90% CI for pharmacokinetic parameters, study #2835, 10 mg capsules versus tablets, fasting:

Parameter↓	90% CI		Intra-subject variation	
	Ramipril	Ramiprilat	Ramipril	Ramiprilat
AUC (0-t) ng x hr/ml **recalculated**	95 to 109 **94 to 110**	98 to 110 **88 to 99**	16%	13%
AUC 0-∞ ng x hr/ml **recalculated**	89 to 106 **87 to 108**	-------- **95 to 107**	15%	------
Cmax ng/ml **recalculated**	98 to 122 **93 to 118**	92 to 116 **91 to 116**	25%	26%

N=34 unless otherwise specified for the initial evaluation. N=32 for the recalculated analysis.

Study # 2970 compared the 1.25 mg Altace capsules compared to 1.25 mg Altace tablets (N=34 enrolled). Bold values are the robustness assessments based on the recommendations of the DSI reviewer (see previous).

Table 3: Pharmacokinetic constants study #2970 1.25 mg Altace capsules compared to the tablets:

	Ramipril		Ramiprilat	
	Ramipril Tablet	Altace capsule	Ramipril Tablet	Altace capsule
AUC (0-t) ng x hr/ml **recalculated**	1.8 ± 0.9 1.8 ± 0.9	1.8 ± 0.8 1.8 ± 0.8	70.4 ± 21 69.8 ± 19.1	75.4 ±20 74.0 ± 20.2
AUC 0-∞ ng x hr/ml **recalculated**	1.8 ± 1.0 (n=29) 1.9 ± 1.0 (n=28)	1.8 ± 0.9 (n=29) 1.8 ± 0.9 (n=28)	177 ± 97 171 ± 95 (n=28)	166 ± 53 163 ± 52 (n=28)
Cmax ng/ml **recalculated**	2.6 ± 1.2 **2.7 ± 1.2**	2.5 ± 1.3 **2.6 ± 1.3**	1.1 ± 0.5 **1.1 ± 0.4**	1.2 ± 0.4 **1.1 ± 0.4**
Tmax hr **recalculated**	0.5 **0.5**	0.5 **0.6**	3.5 **4.0**	3.3 **3.6**
T1/2	0.7 ± 0.8 (n=29)	0.8 ± 1.2 (n=29)	201 ±113 (n=29)	179 ± 79 (n=28)
Kel (hr-1)	0.16 ± 0.7	0.2 ± 0.6 (n=28)	0.0044 ± 0.002 (n=28)	0.0044 ± 0.001 (n=28)

N=34 unless otherwise specified for the initial evaluation. N=32 for the recalculated analysis.

Table 4: 90% CI for pharmacokinetic parameters study #2970 1.25 mg capsules versus tablets, fasting:

Parameter↓	90% CI		Intra-subject variation	
	Ramipril	Ramiprilat	Ramipril	Ramiprilat
AUC (0-t) ng x hr/ml **recalculated**	96 to 110 **95 to 111**	88 to 99 **87 to 99**	16%	14%
AUC 0-∞ ng x hr/ml **recalculated**	95 to 110 **95 to 117**	90 to 120 **89 to 121**	16%	28%
Cmax ng/ml **recalculated**	97 to 116 **96 to 118**	91 to 103 **90 to 101**	21%	14 %

Study #2836 evaluated the pharmacokinetics of a 10 mg dose of Altace capsules versus tablets under fed conditions. There were 32 subjects enrolled in this cross-over study. The model independent pharmacokinetic constants are tabulated in Tables 5 and the 90% CI shown in table 6. The Ramipril and Ramiprilat concentrations in this study are graphed in Figures 1 and 2.

The inactive parent drug, Ramipril clearly differs in its Cmax concentration when comparing the fed capsule to that of the tablet. The AUC values, however for Ramipril are within specifications for bioequivalence. With respect to the active Ramiprilat moiety, the tablet relative to that of the capsule is bioequivalent considering either AUC (0-t) or AUC 0-∞. Cmax measurements had a 90% CI that exceeded the standard boundary that defines bioequivalence. In addition, the lower boundary of the Cmax values does not include 1. The difference between the capsule and tablet for Ramipril shows up as a large intra-subject variability.

Table 5: Pharmacokinetic constants, study #2836, 10 mg Altace capsules compared to the tablets: fed conditions

	Ramipril		Ramiprilat	
N=32	Ramipril Tablet	Altace capsule	Ramipril Tablet	Altace capsule
AUC (0-t) ng x hr/ml	19.2 ± 7.3	16.2 ± 5.8	226.9 ± 59.7	217.7 ± 50.4
AUC 0-∞ ng x hr/ml	19.4 ± 7.3	16.6 ± 5.6 (n=29)	329 ± 91 (n=28)	313 ± 73
Cmax ng/ml	25.1 ± 8.5	6.6 ± 2.8	19.2 ± 10.1	15.7 ± 6.3
Tmax hr	1.0	0.9 (n=29)	3.5	4.9 ± 1.0
T1/2	1.0 ± 0.4	0.9 ± 0.3	120 ±36 (n=28)	122 ± 38 (n=29)
Kel (hr-1)	0.76 ± 0.2	0.84 ± 0.3 (n=28)	0.0062 ± 0.002	0.0062 ± 0.001

Table 6: 90% CI for pharmacokinetic parameters study #2836 10 mg capsules versus tablets, fed conditions:

Parameter↓	90% CI		Intra-subject variation	
N=32	Ramipril	Ramiprilat	Ramipril	Ramiprilat
AUC (0-t) ng x hr/ml	112 to 125	101 to 108	13%	8%
AUC 0-∞ ng x hr/ml	111 to 123	95 to 107	12%	13%
Cmax ng/ml	171 to 262	106 to 128	49%	22%

Figure 1: Ramipril concentrations linear scale, Altace capsules compared to Altace tablets under fed conditions.

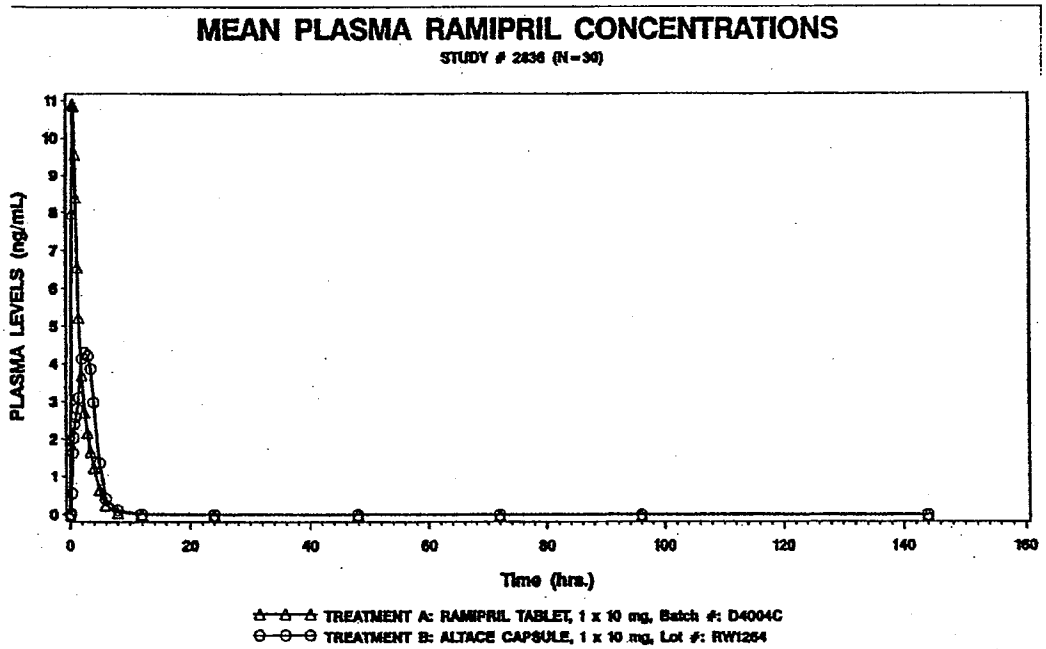
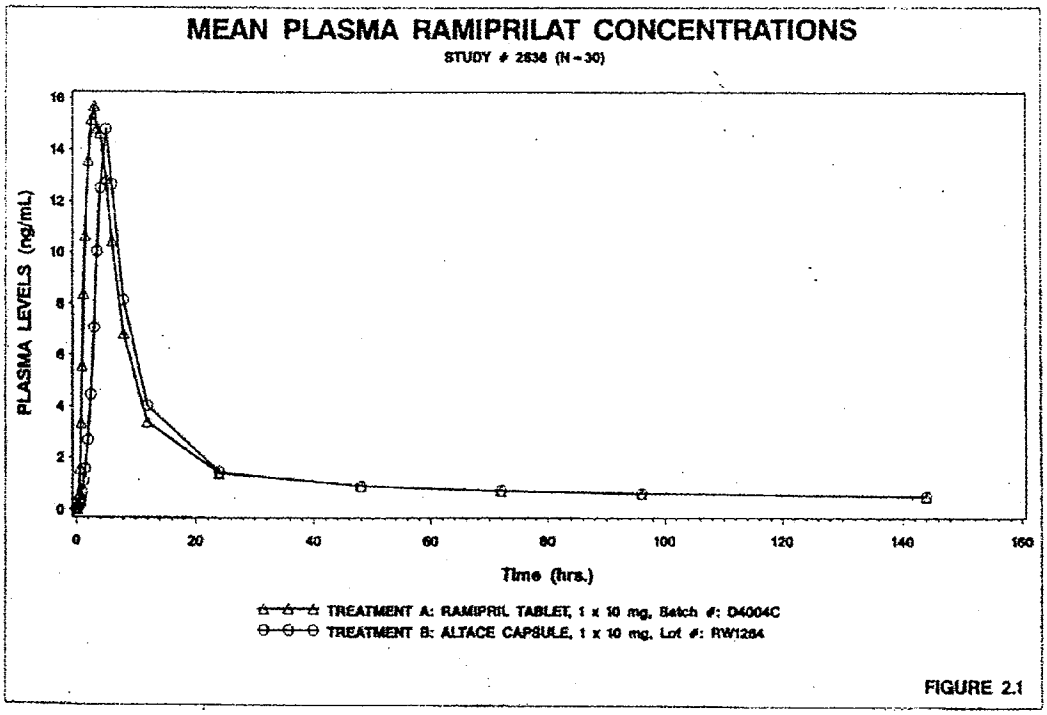


Figure 2: Ramiprilat concentrations linear scale, Altace capsules compared to Altace tablets under fed conditions.



Despite the small disparity in Cmax of the active Ramiprilat moiety, I am recommending that no specific limitations on dosing with respect to food be included within labeling.

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/s/

Abraham Karkowsky
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MEDICAL OFFICER