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Comparative Bioavailability Study of a Fixed Dose Combination of Amlodipine and Enalapril

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Background: A fixed dose combination (FDC) of amlodipine and enalapril is undergoing development to provide an alternative treatment option to simplify treatment regimens and potentially improve compliance in patients who are already taking these medicines individually for hypertension. This pilot study was designed to evaluate the relative bioavailability of a prototype FDC formulation compared to the individual products of amlodipine and enalapril given concurrently as separate tablets.

Methods: This was an open-label, randomised, single dose, two-way crossover study (Study ANE116798) conducted in 15 healthy male (n=9) and female (n=6) subjects aged 18–65 years. The two treatments, 1 x 5 mg amlodipine besilate tablet and 1 x 20 mg enalapril maleate tablet or 1 x amlodipine besilate/enalapril maleate 5 mg/20 mg tablet, were administered orally after an overnight fast. There was a washout period of 14 days between dosing sessions. Blood samples were collected up to 144 hours post-dose for measurement of plasma concentrations of amlodipine, enalapril, and enalaprilat (the active metabolite of enalapril) by validated high performance liquid chromatography mass spectrometry. Following $\log_e$-transformation, area under the plasma concentration-time curve from time zero extrapolated to infinite time ($AUC_{0\text{-}inf}$) (defaulting to the time of last quantifiable concentration, $AUC_{0\text{-}t}$, if $AUC_{0\text{-}inf}$ could not be consistently determined) and maximum plasma concentration (C_{max}) of the analytes were separately analysed using a mixed effects model with fixed effect terms for treatment and period, and subject as a random effect. The study was funded by GlaxoSmithKline.

Results: The 90% confidence intervals for the geometric mean ratios for AUC and C_{max} for amlodipine, enalapril and enalaprilat for the FDC compared with the reference coadministered tablets were within the accepted bioequivalence range of 0.80 to 1.25. Adverse events (AEs) were reported by 7 (47%) and 12 (80%) subjects following administration of the FDC and reference, respectively. The most common AE was headache. No subject had a serious AE or an AE leading to withdrawal.

Analyte	Parameter	Geometric LS Mean				Ratio (FDC:Ref)	90% CI of ratio	%CVw
		n	Ref	n	FDC			
Amlodipine	AUC_{0-t}	15	119.55	15	113.23	0.95	0.88, 1.02	12.0
	AUC_{0-inf}	10	123.10	7	128.01	1.04	0.87, 1.24	20.8
	C_{max}	15	3.65	15	3.97	1.09	1.00, 1.19	13.2
Enalapril	AUC_{0-t}	15	190.50	15	206.67	1.08	0.98, 1.20	16.2
	AUC_{0-inf}	15	191.98	13	206.68	1.08	0.95, 1.22	17.5
	C_{max}	15	132.84	15	130.90	0.99	0.85, 1.14	23.3
Enalaprilat	AUC_{0-t}	15	529.31	15	581.27	1.10	1.01, 1.20	13.6
	C_{max}	15	63.13	15	68.96	1.09	0.96, 1.24	19.6

Units are ng/mL for C_{max} and ng.h//mL for AUC_{0-t} and AUC_{0-inf}.
LS = least squares; CVw = within-subject coefficient of variation.

Conclusion: The prototype FDC of amlodipine besilate and enalapril maleate had comparable bioavailability and tolerability to the reference coadministered tablets.